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Formulation Design for Solubility and Dissolution rate enhancement of Aripiprazole using Spherical Agglomeration technique
Running Title: Aripiprazole Solubility and Dissolution enhancement by Spherical Agglomeration

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ABSTRACT:
Purpose: The objective of the present work was to develop spherical agglomerates (SA) of Aripiprazole (APZ), a second-generation atypical antipsychotic drug, which conceptualizes a specific technology based on principles of quasi emulsion solvent diffusion method, to improve the dissolution rate of drug and micromeritic properties. Spherical agglomerate were developed by using three solvents, DMSO, Water and Chloroform as good solvent, poor solvent and bridging liquid respectively. Spherical agglomeration method that transforms crystalline drugs directly into a compacted spherical form for improving the flowability, solubility and dissolution rate. Results show that by solvent system, Concentration of Polymer and stirring speed were the most effective factors that increase solubility and Dissolution rate. The surface morphology of Agglomerates were also characterized by SEM study.
Key Words: Aripiprazole, Spherical Agglomerate, Solubility, Dissolution rate, Solvent system

I. INTRODUCTION

Solubility in different solvent is an intrinsic property for defined molecule. To achieve a pharmacological activity, is must that molecule exhibit certain solubility in physiological gastro-intestinal fluids and to be present in dissolved state at the site of absorption[1]. more than 40% of new chemical entities having low aqueous solubility means they are poorly soluble in water ,which leads to pharmacokinetic variability after oral administration and thereby exhibits poor bioavailability[2]. Therefore improve water solubility or dissolution of these types of drug molecules is great challenge for scientist to formulate or to design a delivery system which provides required oral bioavailability.[3,4]

Spherical crystallization can be defined as "An agglomeration process that transforms crystalline drugs directly into a compacted spherical form for improving the flowability, solubility and compactability"[5,6] A novel particulate technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform the fine crystals directly into compacted spherical form[7]. Kawashima suggested obtaining the size enlargement of particles during the crystallization step by controlling crystal agglomeration with controlled properties[8,9]. He introduced this technique into pharmaceutical manufacturing and showed that spherically dense agglomerates which improve the bioavailability[10], dissolution rate[11], wettability of poorly soluble drug and hence the micromeritic properties are enhanced[12]

Psychiatric practice was revolutionized following the introduction of antipsychotic agents (D2 receptor antagonists) in the 1950s, beginning with chlorpromazine. Additional classes of the dopamine receptor blocking agents were subsequently developed, but side effects such as akathisia, acute dystonic reactions, drug-induced Parkinsonism, and hyperprolactinemia continue to be limiting factors[13]. The prototype atypical agent, clozapine, is highly efficacious, but has the potential to cause serious side effects such as agranulocytosis and seizures. Clozapine and the

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other atypical agents are associated with different side-effect liabilities that include weight gain, somnolence, and possibly metabolic disturbances[14]. Hence, there is an ongoing need to develop new compounds with a side-effect profile that is "patient friendly" yet not compromising efficacy so as to further the field. Aripiprazole is a novel agent with a unique pharmacologic profile that acts as a potent partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at 5-HT2A receptors[15]. Aripiprazole is used for the treatment of schizophrenia, bipolar disorder, major depressive disorder, autism, and Tourette's syndrome[16]. Aripiprazole is a poorly soluble and poorly permeable compound with BCS class IV. It is weak alkaline drug which thus imparts pH-dependent solubility[17].

Penjuri et al (2018) had prepared spherical agglomerates of Ibuprofen which is an anti-inflammatory drug, characterized by poor water solubility, which limits its pharmacologic effects. Marabathuni J. P. et al (2018) had developed simvastatin spherical agglomerates to improve its solubility and dissolution characteristics by spherical agglomeration method.Gyulai O et al (2017) had compared various spherical crystallization techniques to investigate their applicability for ambroxol hydrochloride. Production of spherical crystals with an appropriate particle size is an important objective for active agents dedicated to direct tablet making. Prasanthi D et.al (2018) had studied solubilisation property of Aripiprazole by Solid-Self Emulsifying Drug Delivery Systems technique.Sahoo S. et al (2018) had developed formulation and assess bioavailability of Aripiprazole using Self-Nanoemulsifying Drug Delivery Systems to enhance solubility of Aripiprazole.

Recently Solubilty of Aripiprazole was increased by different method. In this study we increase their dissolution rate, Bioavailability as well as also micromeritic properties by Spherical agglomeration method.

II. MATERIALS AND METHODS

1.1 MATERIALS

Aripiprazole was obtained as a gift sample from Alembic Pharmaceutical Ltd, Poloxamer 108 was obtained from Ozone International, Mumbai (India); Chloroform and DMSO were obtainted from Chemdyes Corporation, Rajkot and RFCL limited, Ankleshwar respectively. All other chemicals and reagents were used of Research grade.

1.2 METHODS

1.2.1 Drug Characterization and Compatibility with Excipients

Drug characterization can be done by UV spectroscopy and identification of Aripiprazole was carried out using FTIR study. For this, the FTIR spectra of plain drug were recorded in FTIR-8400 S Shimadzu spectrophotometer. The pure Aripipraole drug was mixed thoroughly with potassium bromide. Then the scans were obtained at a resolution of 4000-400 cm^{-1}. Compatibility of Aripiprazole with the respective polymer that is Poloxamer 108 was established by Infrared Absorption Spectral Analysis (FTIR). Any changes in the chemical composition after combining with the excipients were investigated with IR spectral analysis[18,19]

1.2.2 Selection of solvent

Various solvents i.e. Tween 80, DMF, Cyclohexane, Triethanolamine, acetone, methanol, dichloromethane, isopropyl alcohol, dimethyl sulfoxide, polyethylene glycol 400, polyethylene glycol 200, chloroform and water were screen with different polarity for selection of good solvent, poor solvent and bridging liquid. An excess amount of Aripiprazole was added to each selected solvent (5ml) and all saturate solution was kept for 24 hr at constant room temperature on shaker bath with constant stirring speed at 120 RPM. Then the each solvent were filtered, diluted with methanol and concentration of drug in each solvent was determined by UV-Visible spectrophotometer at 255 nm against methanol as blank[20,21]

1.2.3 Selection of Polymer

Polymers were selected by i.e. HPMC E5LV, polyethylene glycol 4000, polyethylene glycol 6000, PVP 40,000, β-cyclodextrin, poloxamer 407 and 108. Polymers dissolved in water for formation of different concentration 0.5% and 2% w/v. While Selection of polymer, other processing condition like stirring speed (800 rpm) and ratio of solvent system were kept constant. After selection of polymer, spherical agglomerates were prepared by using different concentration i.e. 0.5%, 1.0%, 1.5%, 2.0% and 2.5% w/v of selected polymer for selection of level of concentration of polymer.

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1.2.4 Spherical Agglomeration(SA) of Aripiprazole

Quasi emulsion solvent diffusion was use to prepare spherical agglomerates of Aripiprazole[22]. The schematic flow for preparation of spherical Agglomerates of Aripiprazole is shown in Figure 1.

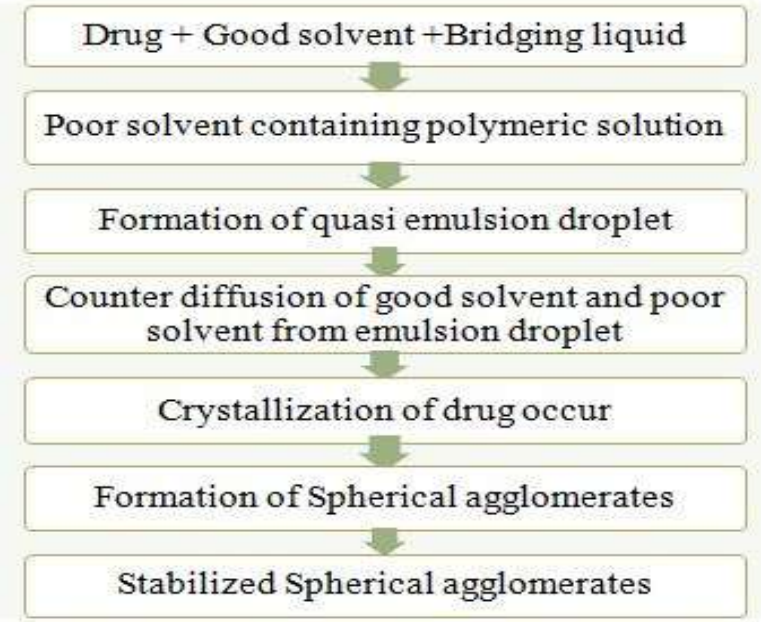

Figure 1: Preparation Process of Aripiprazole SA

1.2.5 Evaluation of Spherical Agglomerates

1.2.5.1 Flow characteristics

Flow characteristics of prepared spherical agglomerates were evaluated by determining angle of repose using fixed funnel method[23]. Carr's Index[24] and Hausner's ratio[25] were measured after tapping fixed amount of agglomerates using bulk density apparatus (Electrolab, Mumbai, India). Average of three readings was recorded.

1.2.5.2 Solubility Study:

Equilibrium solubility studies was carried out by adding excess amount of drug in purified water in glass flasks of 50 ml capacity. The weight amount of sufficient Aripiprazole was added to 10 ml of media and shaking was performed on a shaker for 72 hours with agitation of 150 rpm at 37^{o}C. After attaining equilibrium stage, samples were filter and diluted with respected media. The absorbance of drug was calculated by UV-Visible spectrophotometer at maximum absorbance wavelength and solubility value was calculated using calibration curve of Aripiprazole in water[26].

1.2.5.3 In vitro dissolution studies

In vitro dissolution study of spherical agglomerates of Aripiprazole was carried out by maintained the following conditions or parameter[27].

Instrument: USP dissolution apparatus (TDT-06 model, Electrolab, Mumbai)

Apparatus: USP dissolution Type II (paddle) apparatus

Media: 0.1N HCl

Volume: 900mL

RPM: 50 RPM

Sample withdrawal time: 10, 20 and 30min.

5 ml of sample withdrawn at 10 min time interval and replaced with 5 ml of fresh medium, sample withdrawn was filtered through whatman filter paper. Appropriate dilutions were made using fresh medium to get the absorbance in linearity range of medium. The absorbance of the samples was determined at maximum wavelength at 255 nm by using UV- Visible spectrophotometer against 0.1N HCl as a blank[28,29].

1.2.5.4 Scanning electron microscopy

The surface morphology and shape of both drug and optimized spherical agglomerates was determined by using scanning electron microscopy. The sample was fixed onto metal stub using double

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side conductive tape and agglomerates were observed by scanning electron microscope (JSM-5610) at various scale bars with an acceleration voltage of 15kV in order to analyze the effect of additives on surface morphology and agglomeration efficiency[30,31]

1.2.5.5 Particle size measurement

The size of pure drug particles and Prepared batch spherical agglomerates was measure by Stage micrometer[32].

1.2.6 Preparation of solid dosage form

The optimized Spherical agglomerates, equivalent to 50 mg of Aripiprazole were taking with pharmaceutical excipients like diluent, Superdisintegrant, lubricant and glidant. Mixed whole ingredients for five minuteand directly compress into tablet by using rotator tablet machine[33].

1.2.6.1 Evaluation of Solid-oral dosage form

Weight variation, Hardness, Thickness, Diameter, Disintegration time, Friability, and Drug content was measured with according to Standard IP limit. In-vitro Drug release of prepared tablet was compared with marketed product as well as pure drug[34].

1.2.7 Accelerated stability study

The accelerated stability study was carried out of optimized formulation. The tablet sample was wrapped in the laminated aluminium foil and placed in the stability chamber at 40 ± 2°C/75 ± 5 % relative humidity. Sampling was done as a predetermined time interval of 0, 15 and 30 days. The tablets were evaluated for different physicochemical parameter[35].

III. RESULT

1.3 Selection of Solvent System

Selection of good solvent, poor solvent and bridging liquid various solvents were screened on the basis of the solubility of drug in individual solvents. As shown in above Figure 2 Aripiprazole has lowest solubility in water comparison to other solvents. According to Chow and Leung (1996) principles, Aripiprazole show high solubility in DMSO and lowest solubility in water, so DMSO selected as good solvent, water as poor solvent and Chloroform as bridging liquid as the Chloroform has good wettability with the drug and immiscible with the water. Table 1 shows different ratios of solvent system with combination.

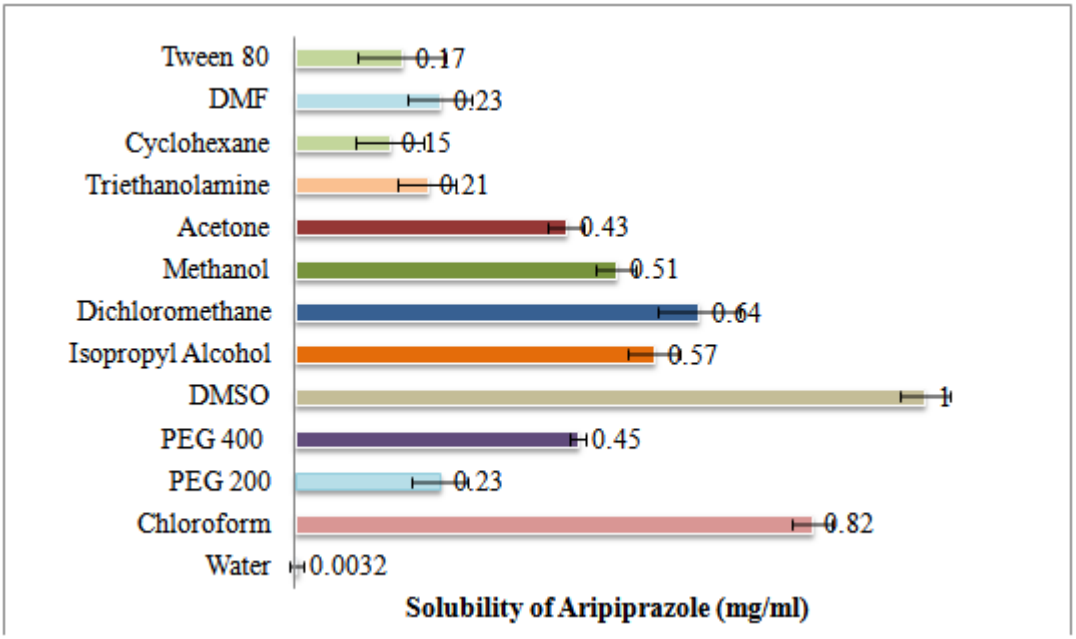

Figure 2: Solubiity of APZ in Various solvent

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Table 1: Selection of Solvent System

Trials	Solvent system	Ratio of Solvents	Saturated Solubility(mg/ml)	Partical Size (µm)	Angle of repose(°)
T1	Chloroform:Acetone:Water	0.2	0.28±0.03	28.28±0.32	39.73±0.28
T2		0.5	0.36±0.005	25.36±0.14	35.37±0.47
T3	DMSO:Chloroform:Water	0.2	0.27±0.003	63.36±0.21	39.27±0.01
T4		0.3	0.75±0.007	78.58±0.43	36.75±0.04
T5		0.5	1.06±0.08	115.21±0.17	22.64±0.08
T6		0.7	1.39±0.001	101.72±0.29	22.89±0.05
T7		1	1.13±0.05	93.33±0.26	23.75±0.03
T8	DCM:IPA:Water	0.2	0.48±0.08	22.48±0.36	33.89±0.35
T9		0.5	0.16±0.01	48.16±0.19	29.62±0.16
T10	Acetone:DCM:Water	0.2	1.53±0.13	33.53±0.07	39.86±0.34
T11		0.3	0.61±0.32	77.61±0.29	36.50±0.27
T12		0.4	0.85±0.11	45±0.16	26.37±0.19
T13		0.5	0.62±0.01	18.5±0.21	30.41±0.01

1.4 Selection of Polymer

Aripiprazole was carried out by utilizing different polymer i.e. HPMC E5LV, polyethylene glycol 4000, polyethylene glycol 6000, PVP 40,000, β-cyclodextrin,poloxamer 407 and poloxamer 108 at different concentration(**Table 2**).Spherical agglomeration was attempt with HPMC E5LV and β-cyclodextrin the flowability of agglomerates were not much improved, furthermore an agglomeration carried out with Poloxamer 407 (batch T_3 to T_6) and Poloxamer 108 (batch T_9 to T_{12}) the flowability of agglomerates were greatly improved and as the concentration of Carrier get increased the rate of dissolution were also improved.Whenever the agglomerates prepared by utilizing Poloxamer 108 (batch T_{10}, T_{11}& T_{12}) showed much improved in flowability, compressibility, and dissolution compare to Poloxamer 407. Poloxamer 108 between 0.5 to 1.5% concentrations (batch T_9, T_{10}& T_{11}) imparts better flowability, compressibility and drug release to the agglomerates. Hence, Poloxamer 108 was selected in concentration between 0.5 to 2 % w/v for agglomeration of Aripiprazole.

Table 2.Selection of Polymer

Trials	Polymer	Concentration of Carrier (%W/V)	Saturated Solubility(mg/ml)	Partical Size (µm)	Angle of repose(°)
T1	**HPMC E5LV**	**0.5**	0.24±0.03	18.28±0.32	39.73±0.28
T2		**1.0**	1.31±0.005	23.36±0.14	35.37±0.47
T3	**POLOXAMER 407**	**0.5**	1.33±0.13	31.53±0.07	39.86±0.34
T4		**1.0**	0.71±0.32	28.61±0.29	36.50±0.27

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T5		**1.5**	0.25±0.11	55±0.16	26.37±0.19
T6		**2**	0.09±0.01	38.5±0.21	30.41±0.01
T7	**β-CYCLO DEXTRIN**	**0.5**	1.78±0.08	32.48±0.36	33.89±0.35
T8		**1.0**	0.06±0.01	58.16±0.19	29.62±0.16
T9	**POLOXAMER 108**	**0.5**	0.80±0.03	123.47±0.31	26.39±0.28
T10		**1.0**	3.82±0.006	278.68±0.05	24.01±0.33
T11		**1.5**	4.96±0.21	344.35±0.14	25.84±0.24
T12		**2.0**	2.42±0.37	141.61±0.23	26.73±0.07
T13	**PEG 4000**	**0.5**	0.83±0.24	38.28±0.05	35.21±0.46
T14		**1.0**	0.57±0.31	65.36±0.09	28.18±0.01
T15	**PEG 6000**	**0.5**	0.16±0.09	43.53±0.14	26.18±0.56
T16		**1.0**	1.05±0.19	67.61±0.02	25.0±0.61
T17		**1.5**	0.03±0.37	65.2±0.21	24.17±0.44
T18		**2**	0.004±0.29	38.5±0.07	31.22±0.28
T19	**PVP 40,000**	**0.5**	0.01±0.13	22.48±0.05	39.61±0.71
T20		**1.0**	0.006±0.28	37.16±0.03	35.61±0.48
T21		**1.5**	0.002±0.16	43.54±0.17	38.03±0.52

1.5 Evaluation of Spherical Agglomerates

Aripiprazole Spherical agglomerates was prepared and evaluated in different batches. The data of evalution parameters were sown in table 3.

Table 3: Evaluation of Spherical Agglomerates batches

Exp. Batch	Drug content	% Yield	Angle of repose(°)	Bulk Density	Tapped density	Solubility (mg/ml)	Carr's Index	Hausner's ratio
SA 1	98.78 ± 0.78	91.32 ± 0.12	26.76 ± 0.68	0.1557 ± 0.0009	0.1836 ± 0.0013	23.45 ± 0.98	15.22	1.179
SA 2	98.84 ± 0.53	90.73 ± 0.08	23.81 ± 0.31	0.1551 ± 0.0009	0.1844 ± 0.0013	23.98 ± 1.06	15.86	1.188
SA 3	99.33 ± 0.63	91.46 ± 0.18	24.51 ± 0.28	0.1551 ± 0.0009	0.1836 ± 0.0013	23.47 ± 1.29	15.51	1.183
SA 4	99.31 ± 0.40	91.37 ± 0.98	25.86 ± 0.23	0.1562 ± 0.0009	0.1829 ± 0.0013	24.69 ± 1.04	14.58	1.170
SA 5	99.56 ± 0.11	91.49 ± 0.18	22.33 ± 0.28	0.1560 ± 0.0009	0.1822 ± 0.0013	25.08 ± 0.85	14.57	1.184

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SA 6	99.06 ± 0.48	90.56 ± 0.17	24.16 ± 0.30	0.1557 ± 0.0009	0.1844 ± 0.0013	24.62 ± 1.14	15.57	1.184
SA 7	98.88 ± 0.64	90.85 ± 1.07	26.85 ± 0.35	0.1551 ± 0.0009	0.1844 ± 0.0013	24.60 ± 1.01	15.86	1.188
SA 8	98.14 ± 0.24	91.42 ± 0.21	23.35 ± 0.25	0.1557 ± 0.0009	0.1836 ± 0.0013	24.31 ± 1.03	15.22	1.179
SA 9	98.85 ± 0.49	90.85 ± 1.11	25.95 ± 0.33	0.1557 ± 0.0009	0.1844 ± 0.0013	23.57 ± 1.34	15.56	1.184

1.5.1 Drug content and Percentage Yield

Drug content of spherical agglomerates batches are shown in Table 3 which found in between 98.14 ± 0.24 to 99.56 ± 0.11 % that complies with test criteria 98-101%. As shown in Figure 3 when the concentration of carrier was increases the interaction between drug particle increases in spherical agglomerates and increased the drug content. While percentage yields of spherical agglomerates of prepared batches are shown in Table 3 where percentage yield of design batches were found in between 90.56 ± 0.17 to 91.49 ± 0.18 %.

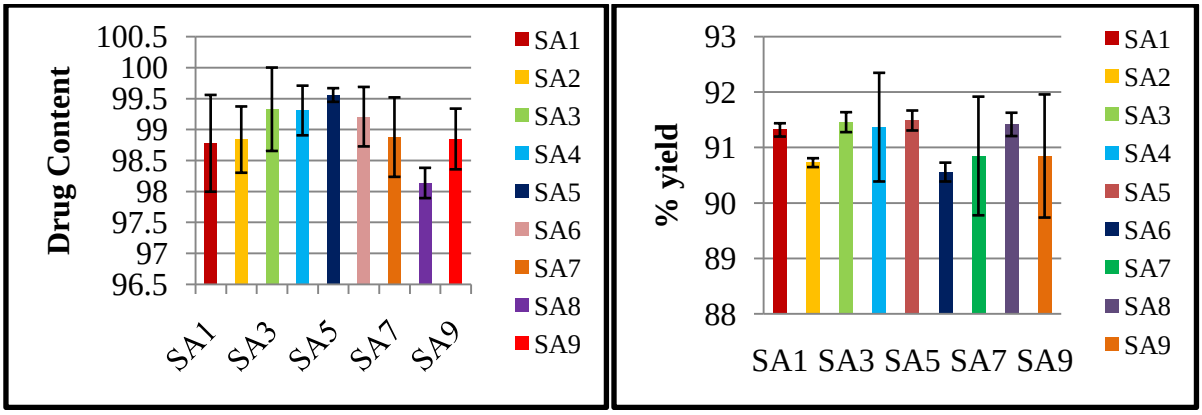

Figure 3: Drug content and Percentage yield

1.5.2 Flow characteristics:

Angle of repose of spherical agglomerates batches are shown in Table 3. The Angle of repose of batches were found in between 22.33° ± 0.23 to 26.85° ± 0.35 which showed angle of repose <30° and indicates that design batches had good flow properties. The Bulk density and Tapped density of design batches were found in between 0.1551 ± 0.0009 to 0.1562 ± 0.0009 (gm/ ml) and 0.1822 ± 0.0013 to 0.1844 ± 0.0013 (gm/ ml) respectively. Carr's indexes of spherical agglomerates batches are shown in Table 3. The carr's index of design batches were found in between 14.57 to 15.86 which indicates that design batches had good flow and compressibility properties. Hausner's ratios of spherical agglomerates batches are shown in Table 3 where design batches were found to be <1.25 which indicates that all the batches has good flow property.

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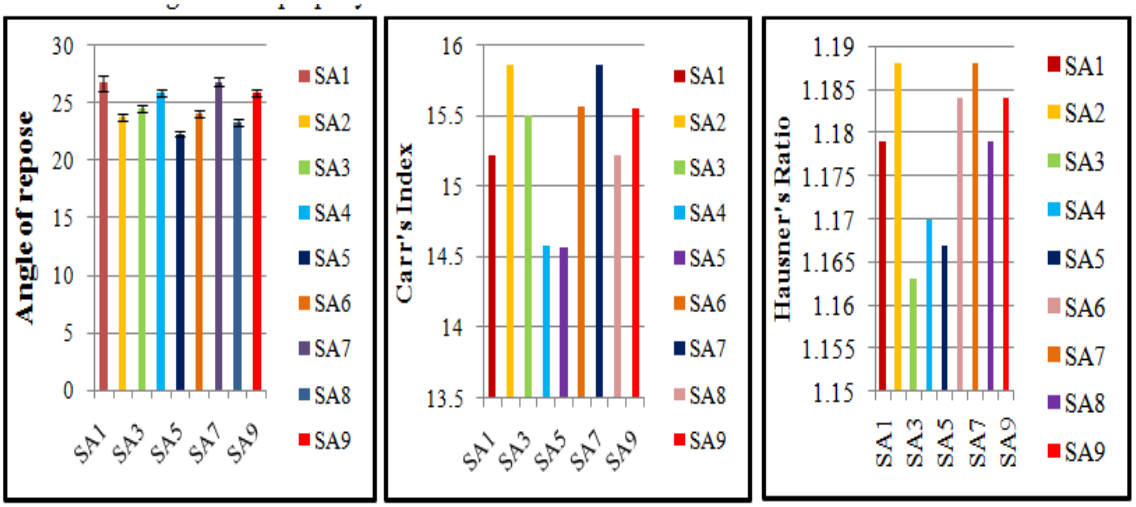

Figure 4: Flow characteristics of Aripiprazole SA

1.5.3 Solubility Study

Solubility of spherical agglomerates batches are shown in Table 3. The Solubility of design batches were found in between 23.45 ± 0.98 to 25.08 ± 1.04 mg/ml, which was shows that the aqueous solubility of Aripiprazole spherical agglomerates improves compare to pure Aripiprazole.

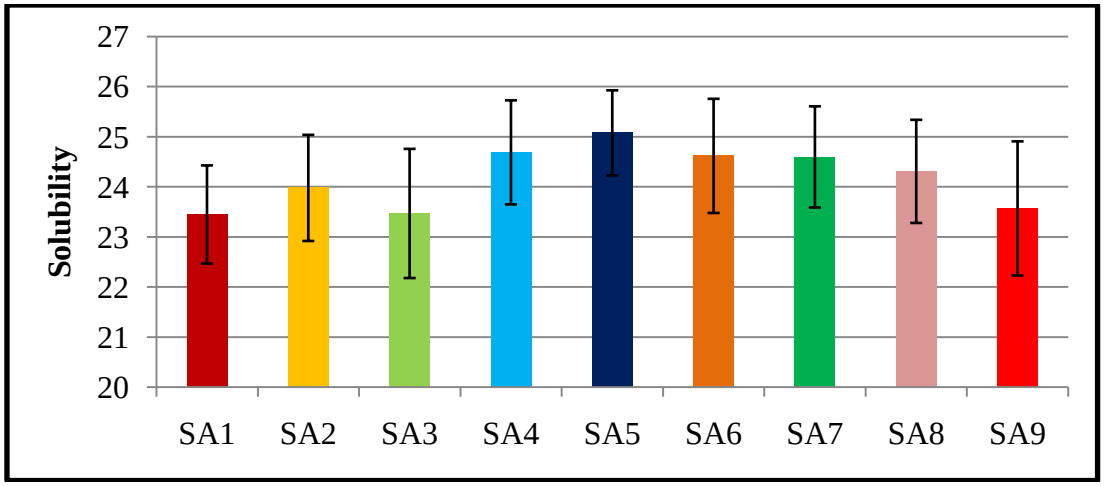

Figure 5: Solubility of Aripiprazole SA

1.5.4 Cumulative % drug release

In-vitro drug release study of Spherical agglomerates was carried out in 0.1N HCl using USP apparatus type II at 37° ± 0.5°C temperature. As shown in Table 3, the SA3, SA7 and SA9 batches of spherical agglomerates shows 85.68 %, 82.79% and 84.88 % drug release respectively which was lower drug release compare to SA4, SA5 and SA6 batches that was 94.61%, 96.77 % and 93.38% respectively at 30 min. From the above results it was found that as concentration of Carrier decreased, the cumulative % drug release was decreased and as concentration of Carrier increased, the cumulative % drug release was increased.

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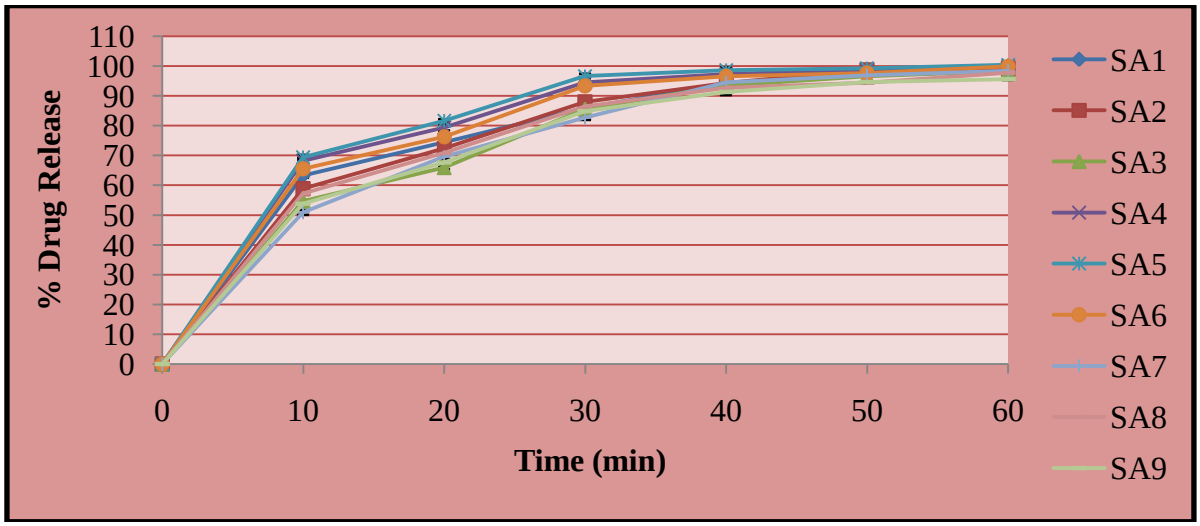

Figure 6: In vitro Drug release of Aripiprazole SA

1.6 Scanning Electrone Microscopy

The scanning electron microscopy of pure APZ and spherical agglomerates of APZ are shown in Figure 7. Pure drug powder appeared to fine crystalline, irregular shaped. However, the spherical agglomerates of APZ appeared as spherical in shape, improved size indicating that the APZ spherical agglomerates formed.

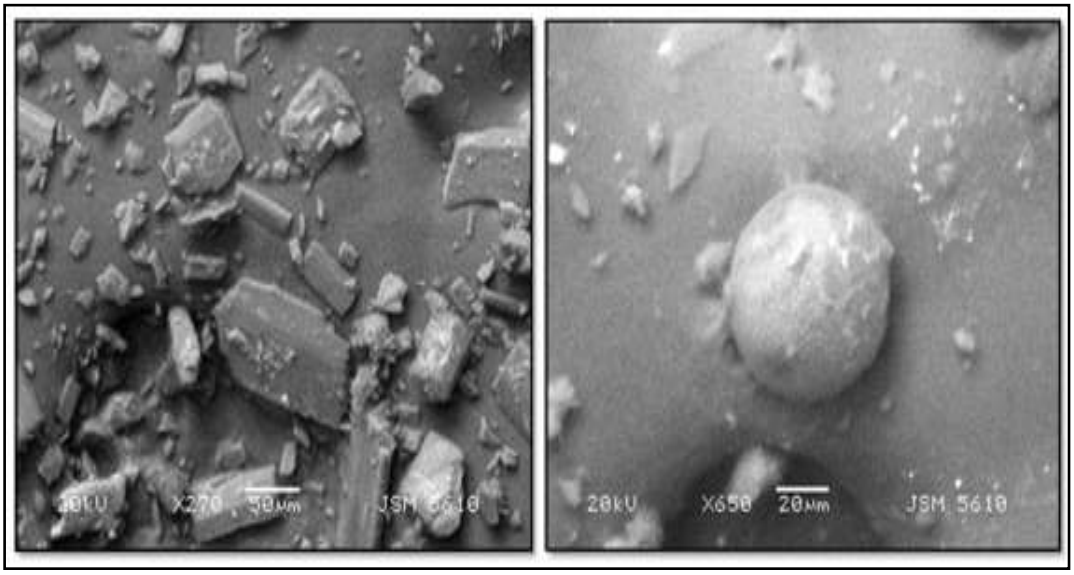

Figure 7.SEM image of A) pure APZ and B) APZ Spherical agglomerates

1.7 Preparation of solid dosage form

1.7.1 Formulation of Tablet by optimized batch

Table 4: Formula of Aripiprazole tablet

Ingredient	Quantity(mg)
Aripiprazole spherical agglomerates	20 mg
Micro-crystalline cellulose	40 mg
CCS	6 mg
Talc	2 mg
Magnesium stearate	2 mg
Total weight	70 mg

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1.7.2 Evaluation parameters for Tablets of Aripiprazole spherical agglomerate:

Table 4 shows evaluation parameter for tablet of Aripiprazole spherical agglomerates. A result of hardness, thickness, diameter, weight variation, drug content, disintegration time and friability (< 1 %) of tablet were found within a limit.

Table 5: Post-compression evaluation parameter

Test Parameter	Result
Weight variation (mg)	70.08
Hardness (kg/cm^2)	3.34 ± 0.28
Thickness (mm)	2.13 ± 0.11
Diameter (mm)	6.0 ± 0.0
Disintegration time (sec)	33.67 ± 2.08
Friability (%)	0.57 ± 0.11
Drug content (%)	99.34 ± 0.38

All values are ± SD which are mean of 3 determinations

1.7.3 Comparison of % drug release at 30 min of optimized batch tablet with marketed product and pure drug (Aripiprazole)

As shown in Figure 8 the tablet of optimized batch of spherical agglomerates showed > 90% drug release in 30 min which was greater than the % drug release prepared conventional tablet of Aripiprazole while marketed tablet of Aripiprazole showed up to 70.49% drug release in 30 min.

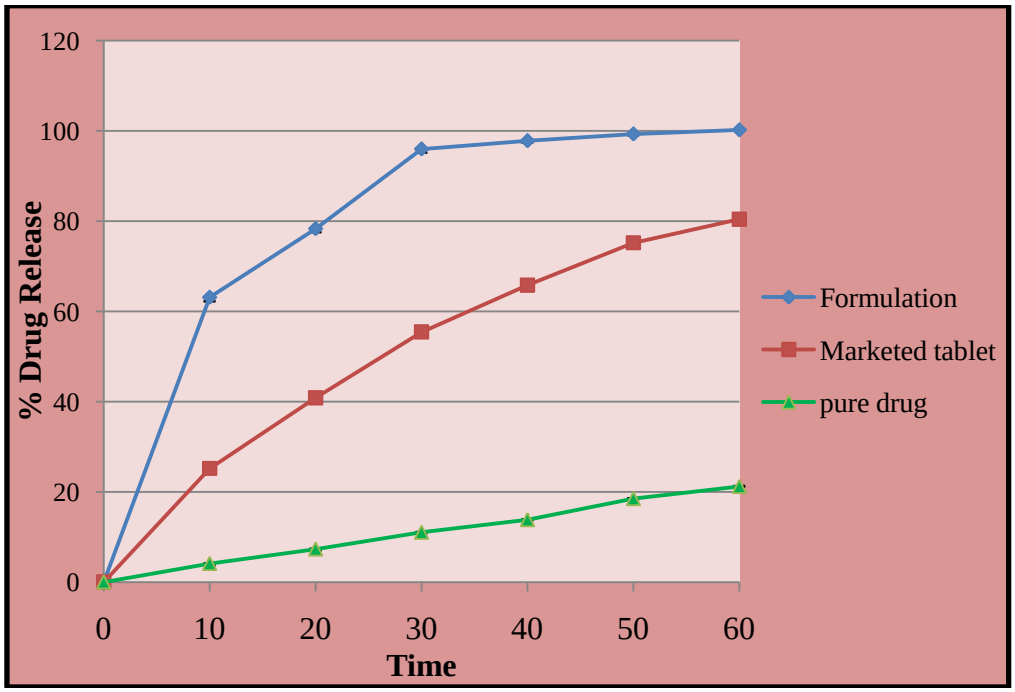

Figure 8: Comparison of % drug release of Aripiprazole different tablet dosage form

1.8 Accelerated stability studies

1.8.1 Physiochemical Evaluations

Accelerated stability study data of optimized batch shown in Table 6 and 7 revealed that there were no significant change in physical parameters when stored at temperature and humidity condition of 40 ± 2 ºC / 75 ± 5 % RH respectively and at room temperature for 30 days.

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Table 6: Stability data of optimized batch of Spherical agglomerates

Condition	Angle of repose	Carr's Index	Hausner's ratio
Initial	22.74 ± 0.22	14.90 ± 0.28	1.175 ± 0.003
After 15 days			
40 ± 2°C/ 75 ± 5% RH	22.90 ± 0.12	15.07 ± 0.04	1.177 ± 0.006
After 30 days			
40 ± 2°C/ 75 ± 5% RH	23.04 ± 0.22	15.19 ± 0.05	1.178 ± 0.006

All values are ± SD which are mean of 3 determinations

Table 7: Stability data of Tablet of optimized batch of Spherical agglomerates

Condition	% Drug content	Cumulative % drug release at 30 min	
Initial	99.20 ± 0.58	**Time (min)**	**% CDR**
		0	0
		10	65.12 ± 0.87
		20	81.33 ± 0.75
		30	96.89 ± 0.70
After 15 days			
40 ± 2°C/ 75 ± 5% RH	98.84 ± 0.23	0	0
		10	63.05 ± 0.81
		20	78.18 ± 0.70
		30	95.71 ± 0.67
After 30 days			
40 ± 2°C/ 75 ± 5% RH	98.44 ± 0.08	0	0
		10	62.95 ± 0.62
		20	78.04 ± 0.55
		30	94.63 ± 0.59

All values are ± SD which are mean of 3 determinations

IV. CONCLUSION

In the present study, Spherical agglomeration of drug is advantageous technique to improve the dissolution rate and Solubility. Aripiprazole is a BCS class IV drug having a poor aqueous solubility (0.0032 mg/ml) as well as poor flow property and compressibility. Hence it can be concluded that present spherical agglomerates formulation would be helpful to preparing tablet by direct compression rather than granulation and can provide better drug release rate over marketed formulation. So, it improved manufacturing process as well as may be maximize the therapeutic benefit. SEM study reviled the substantial change in shape and surface morphology of APZ after formulated into spherical agglomerates. These results indicate the effective application of the Spherical agglomeration technique in the preparation of agglomerates.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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