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Formulation and Characterization of Spherical Agglomerates of Zotepine for Dissolution Enhancement and Improvement of Micromeritics Property

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KEYWORDS

Zotepine, Spherical agglomerates, Quasi Emulsion Solvent Diffusion method, Central composite design.

ABSTRACT:

The objective of the present work was to formulate spherical agglomerates of Zotepine, a BCS class II antipsychotic drug with a half-life of 21 h and bioavailability below 10%, to improve its physicochemical and dissolution properties. Spherical agglomerates were prepared using acetone (good solvent), dichloromethane (bridging liquid), and water (poor solvent). Preformulation studies, λmax determination (259 nm in methanol, 260 nm in 0.1 N HCl), and FTIR confirmed drug–excipient compatibility. Optimization studies revealed that solvent concentrations had minimal effect, while polymer concentration (PVP K30) increased yield and particle size but reduced drug release; higher stirring speeds enhanced drug release and reduced particle size without affecting yield. A central composite design was employed to evaluate the effects of stirring speed (X1) and PVP K30 concentration (X2) on % yield (Y1), drug release at 20 min (Y2), and particle size (Y3). The optimized formulation showed 65.54% yield, 78.15% release at 20 min, and a particle size of 322.24 µm, with SEM confirming spherical morphology. Spherical agglomerates of poorly soluble drug Zotepine could be prepared successfully.

Introduction

The oral route remains the most widely used and preferred method of drug administration due to its convenience, patient compliance, and cost-effectiveness. However, nearly 40% of marketed drugs and more than 70% of new chemical entities (NCEs) suffer from poor water solubility, leading to challenges in bioavailability and therapeutic efficacy. Various strategies such as salt formation, co-crystallization, particle size reduction, solid dispersions, and nanotechnology have been employed to enhance solubility and dissolution.

Spherical agglomeration is one such promising technique that transforms drug crystals into spherical forms, thereby improving micromeritic properties, compressibility, and dissolution rate. Several methods—including solvent change, ammonia diffusion, quasi-emulsion diffusion, and neutralization—have been developed to optimize agglomeration. By addressing solubility limitations, spherical agglomeration holds significant potential in the formulation of poorly water-soluble drugs and in the development of advanced oral drug delivery systems. I was used Zotepine drug ($C_{18}H_{18}ClNOS$, MW: 331 g/mol). Zotepine acts as a dopamine (D1, D2) and serotonin (5-HT7a, 5-HT7c) receptor antagonist, with additional inhibition of noradrenaline reuptake. These actions contribute to improvement in both negative and cognitive symptoms of schizophrenia.

MATERIALS AND METHODS

The active pharmaceutical ingredient (API) used in this study was Zotepine, procured from Symed Labs Limited, Hyderabad. Among the excipients, polyvinylpyrrolidone K30 (PVP-K30) was obtained from Balaji Drugs. The organic solvents employed included acetone (RFCL Limited, Ankleshwar) and dichloromethane (Chemdyes Corporation, Rajkot). In addition, distilled water was used as a solvent throughout experimental work.

The study was carried out using various laboratory instruments and analytical equipment. A digital electronic weighing balance (Model CA123, Reptech, Mumbai) was employed for accurate weighing of materials. Drug analysis was performed using a UV–Visible Spectrophotometer (Model 1800, Shimadzu, Japan). Sample preparation and mixing were facilitated with a mechanical shaker (AdirDutt Operations Pvt., India), centrifuge (Model RM-12C, Remi), and magnetic stirrers (Remi), including a model with a hot plate

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attachment. For dissolution testing, a USP dissolution apparatus type II (Model TDT-06, Electrolab, Mumbai) was utilized, while the digital melting point apparatus (Model DMPA-312) was used for thermal analysis

Experimental Work

The pure drug Zotepine was evaluated for preformulation studies, determination of λmax, preparation of calibration curve, FT-IR and drug excipients compatibility studies, preliminary trial batches, and screening of factors, preparation and optimization of Spherical Agglomerates.

1 Preformulation studies

1.1 Physical Appearance: Drug was evaluated for colour, odour and shape.

1.2Melting Point Determination: Melting point of zotepine was determined by using melting point apparatus. Observed data value was compared with the theoretical value.

1.3 Flow Properties: The flow properties of the drug was estimated by determining the angle of repose, carr's index, Hauser's ratio, tapped density, Bulk density.

1.4 Angle of Repose: The angle of repose, defined as the maximum angle between the surface of a powder pile and the horizontal plane, was determined by the funnel method. Powder was allowed to flow from a funnel fixed 2 cm above a flat surface until a pile was formed. The radius (r) and height (h) of the pile were measured, and the angle of repose (θ) was calculated using the formula: $\theta = \tan^{-1}(h/r)$

1.5 Carr's Index: One of the important measures that can be obtain from bulk and tapped density determination was the percentage compressibility or the carr's index. The Carr's

index was calculated by following equation, Carr's index = (Bulk density – Tapped density)/Tapped density * 100

1.6 Hausner's ratio: Hausner's ratio is defined as a ratio of a tapped density to bulk density. It was measure of relative importance of inter particulate interaction. A Hausner's ratio greater than 1.25 is consider to be an indication of poor flowability. Tapped density and bulk density was measured and the Hausner's ratio was calculated by the following equation, Hausner's ratio = Tapped density/Bulk density

2. Determination of λmax by UV – visible spectroscopy in methanol and 0.1 N HCl

The λmax of Zotepine, 50 mg of Zotepine was weighed accurately and transfer to a 50 ml of volumetric flask. The volume was adjusted to 50 ml with methanol to get a 1000 µg/ml stock solution. The further stock solution was diluted appropriately in order to get a concentrations 100 µg/ml, which was analyzed by using UV-VIS Spectrophotometer against methanol as blank solution. Similar process of dilution was followed for 0.1 N HCl and maximum absorbance was observed.

3. Calibration Curve of Zotepine

3.1 In Methanol: A stock solution of Zotepine (1000 µg/mL) was prepared in methanol. Working solutions (2–10 µg/mL) were obtained by serial dilution. Absorbance was measured at 259 nm using a UV–Visible spectrophotometer with methanol as blank. Calibration was performed in triplicate, and the linear regression equation was generated from mean absorbance values.

3.2 In 0.1 N HCl: A stock solution of Zotepine (1000 µg/mL) was prepared in 0.1 N HCl. Working solutions (2–12 µg/mL) were prepared by dilution. Absorbance was measured at 260 nm against 0.1 N HCl as blank. Experiments were carried out in triplicate, and a calibration curve was constructed.

4. FT-IR Studies of Zotepine : FT-IR spectroscopy was performed to confirm drug identity. Drug and KBr (1:5) were triturated, compressed into a pellet, and scanned in the range of 4000–450 cm^{-1} after baseline correction with KBr.

4.1 Drug–Excipient Interaction Study FT-IR spectroscopy was performed to assess compatibility of Zotepine with excipients. Drug and excipients (1:1) were stored at 40 °C/75% RH for one month. Each mixture was blended with KBr (1:5), compressed into pellets, and scanned in the range 4000–450 cm^{-1} using KBr for baseline correction. The combinations studied were:

1. Zotepine + PVP K30
2. Zotepine + Magnesium stearate
3. Zotepine + Talc
4. Zotepine + Lactose

5.Preparation of spherical Agglomerates of Zotepine

5.1 Selection of solvent system Various solvents i.e. Iso propyl alcohol, Chloroform, Acetone, methanol, Ethyl acetate, Dichloromethane, ethanol, Water were screened with different polarity for selection of good solvent and bridging liquid. An excess amount of Zotepine as added to each selected solvent (2 ml) in Eppendorf tube and all saturate solution was kept for 24 hrs at constant room temperature on Mechanical shaker with constant stirring speed at 120 rpm. Then solution were filtered, diluted with methanol and concentration of drug in each solvent was determined by UV- visible spectrophotometer at 259 nm against methanol as blank. The experiments were

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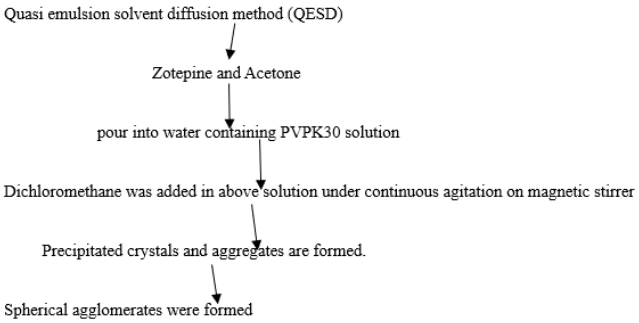
performed in triplicate and solubility value was calculated using methanol Calibration curve. Based upon solubility data good solvent, bridging liquid and poor solvent were selected.

5.2 Method for Preparation of Spherical Agglomerates



Filtration using Whatman filter paper and dried at room temperature and Evaluated for various in vitro evaluation parameters.

5.3 Selection of concentration of good solvent, Bridging liquid: To optimize the preparation of spherical agglomerates, preliminary trials were carried out by varying critical formulation and process parameters, including the concentration of good solvent, bridging liquid, polymer, and stirring speed. Acetone was used as a good solvent, dichloromethane (DCM) as a bridging liquid, water as a poor solvent, and PVP K30 as the primary polymer. In the selection of the concentration of good solvent, three batches (G1–G3) were prepared by varying acetone volume (4, 3, and 2 ml, respectively) while keeping other parameters constant (Table 5.1). Similarly, the influence of bridging liquid concentration was studied by preparing batches (B1–B3) with different volumes of DCM (6, 5, and 4 ml, respectively) (Table 5.2). For polymer selection and concentration studies, PVP K30 was tested at 0.4%, 0.6%, and 0.8%, along with comparative evaluation of other polymers such as Soluplus, β–cyclodextrin, HPMC K15, and HPMC K5 at 0.6% (Table 5.3). Finally, the effect of stirring speed was investigated in batches (S1–S5) by varying the speed from 500 to 1500 rpm (Table 5.4). The agglomerates obtained from these trials were further evaluated to identify the optimum conditions for formulation development.

Trial	Acetone (ml)	DCM (ml)	PVPK30 (%)	WATER (ml)	Stirring speed (rpm)
G1	**4**	5	0.6	60	750
G2	**3**	5	0.6	60	750
G3	**2**	5	0.6	60	750

(Table 5.1)

Trial	Acetone (ml)	DCM (ml)	PVPK30 (%)	WATER (ml)	Stirring speed (rpm)
B1	2	**6**	0.6	60	750
B2	2	**5**	0.6	60	750
B3	2	**4**	0.6	60	750

(Table 5.2)

Trial	Concentration (%)	Acetone (ml)	DCM (ml)	WATER (ml)	Stirring speed (rpm)
PVP K30	**0.4**	2	5	60	750
	0.6	2	5	60	750

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	0.8	2	5	60	750
Soluplus	**0.6**	2	5	60	750
β–cyclodextrin	**0.6**	2	5	60	750
HPMC K15	**0.6**	2	5	60	750
HPMC K5	**0.6**	2	5	60	750

(Table 5.3)

Trial	Acetone (ml)	DCM (ml)	PVPK30 (%)	WATER (ml)	Stirring speed (rpm)
S1	2	5	0.6	60	**500**
S2	2	5	0.6	60	**750**
S3	2	5	0.6	60	**1000**
S4	2	5	0.6	60	**1250**
S5	2	5	0.6	60	**1500**

(Table 5.4)

6. Optimization of Spherical Agglomerates by Central Composite Design (CCD) Traditional trial-and-error methods for formulation development are often time-consuming and less efficient. To overcome this, a central composite design (CCD) was employed for systematic optimization of Zotepine spherical agglomerates. CCD enables evaluation of the main, interaction, and quadratic effects of independent variables with minimal experimental runs, thus providing maximum information. In this study, a two-factor, three-level CCD was applied, where independent and dependent variables were selected based on preliminary trials (Table 5.11). Experimental design software (version 10) generated 11 experimental runs, and the polynomial model obtained was used to assess the influence of formulation variables and optimize the batch.

6.1 Characterization of optimized batch of spherical agglomerates

7. Morphological study: The morphology of optimized batch of spherical agglomerates was done by using scanning electron microscopy (SEM).

7.1 Scanning electron microscopy (SEM): Surface morphology and shape of drug and spherical agglomerates was determined using scanning electron microscopy. the samples were staged on an aluminium stub coated with Au in a vacuum sputter coater and analysed under a microscope with an ET detector running at a 10 kV accelerating voltage at 10000–80000 X magnification.

7.2 Residual solvent test: Residual solvents may be a critical impurity in excipients, drug substances and ultimately drug products, because they may cause toxicity and safety issues, and affect physicochemical properties of drug substances and drug products. Generally, the solvents are not completely removed by practical manufacturing techniques. As a result, the solvent can be a crucial parameter in the process at times.. The general procedure of European Pharmacopoeia for residual solvent determination in pharmaceutical products included analysis of many solvents by residual solvent test.

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RESULTS AND DISCUSSION

preformulation study: The physical properties of pure drug were found to be as shown in Table.1.1

Sr. No.	Physical Properties	Standard	Result
1.	Color	White	White
2.	Nature	Crystalline powder	Crystalline powder

Table.1.1

1.2 Melting Point Determination: The melting point of Zotepine was found to be as shown in Table 1.2

Melting Point	88.24 °C

Table 1.2

1.3 Flow properties of the drug: The flow properties of pure drug Zotepine Obtained are shown in Table 1.3

Sr. No.	Flow Properties	Result	Discussion
1.	Angle of Repose	46.25	Poor
2.	Bulk Density	0.55	-
3.	Tapped Density	0.71	-
4.	Carr's Index	27.53	Poor
5.	Hauser's Ratio	1.35	Poor

Table 1.3

2. Determination of λmax: The drug was scanned by UV visible spectroscopy in methanol and 0.1 N HCL which is shown in figure 2.1 & 2.2 respectively. The result showed that the drug has λmax at 259 nm and λmax 260 nm respectively.

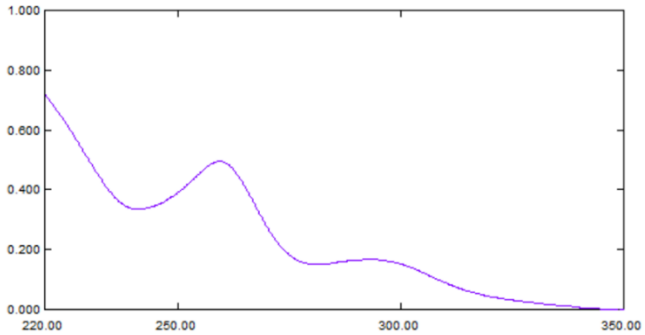

Fig 2.1 Determination of λmax in Methanol

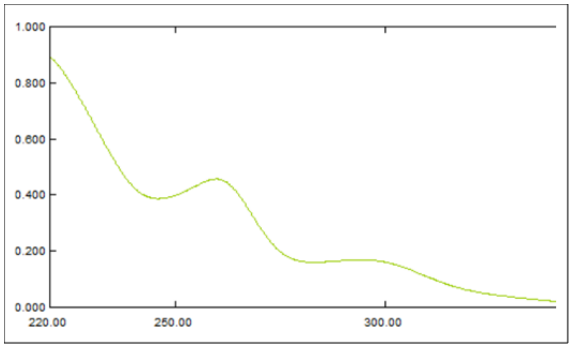

Fig 2.2 :-Determination of λmax in 0.1 N HCL

3.1 Calibration Curve of Zotepine in Methanol: Zotepine exhibited maximum absorbance at 259 nm. The calibration curve showed linearity in a concentration range of 2-12 µg/ml and the correlation coefficient was found to be 0.9983 in methanol. Overlay spectra, calibration curve data and calibration curve are shown in figure.3.1

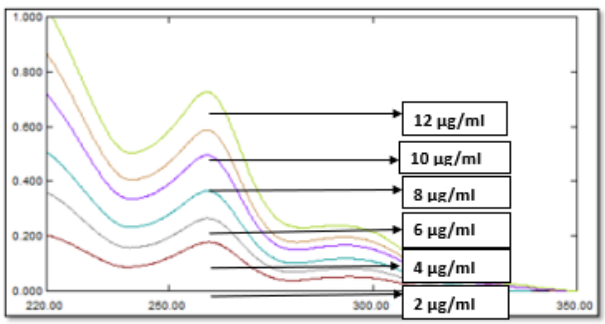

fig.3.1 **Overlay spectra of calibration curve of Zotepine in Methanol**

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Table 3.1:- Calibration curve of of Zotepine in methanol

Sr. No	Concentration µg/ml	Absorbance Mean ± SD
1	0	0
2	2	0.177 ± 0.0020
3	4	0.274 ± 0.0020
4	6	0.396 ± 0.0037
5	8	0.493 ± 0.0020
6	10	0.596 ± 0.001
7	12	0.725 ± 0.0015

Table 3.1

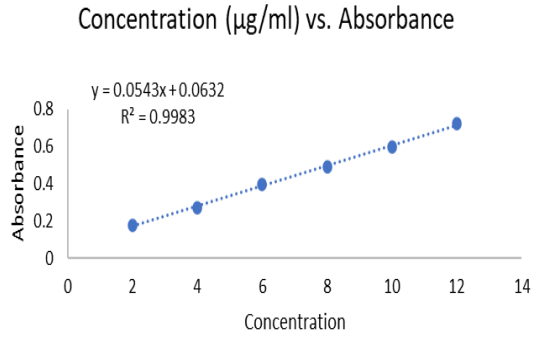

fig.3.2

3.2 Calibration Curve of Zotepine in 0.1 N HCL with Overlay spectra: Zotepine exhibited maximum absorbance at 260 nm. The calibration curve showed linearity in a concentration range of 2-14 µg/ml and the correlation coefficient was found to be 0.9996 in 0.1 N HCL. Overlay spectra, calibration curve data and calibration curve are shown in figure 3.3

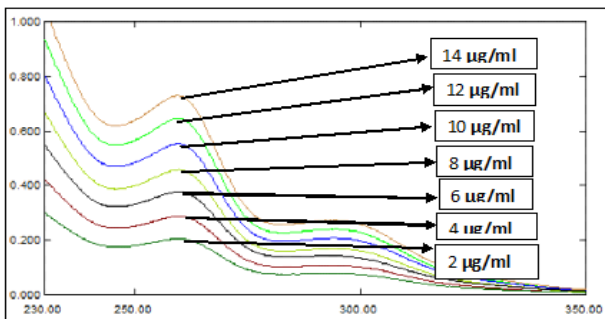

fig 3.3

Sr.no	Concentration µg/ml	Absorbance Mean ± SD
1	0	0
2	2	0.204 ± 0.0015
3	4	0.287 ± 0.001
4	6	0.375 ± 0.0015
5	8	0.457 ± 0.0015
6	10	0.552 ± 0.002
7	12	0.644 ± 0.0015
8	14	0.727 ± 0.0020

Tab. 3.2

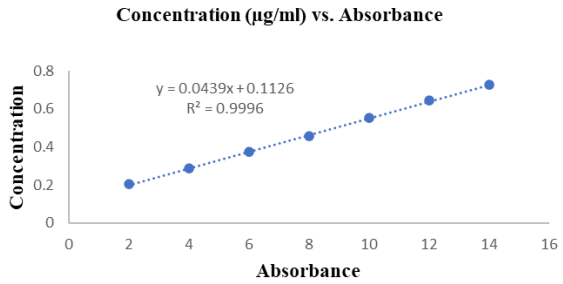

fig 3.4

4. FT-IR Study of Zotepine: An FT-IR spectrum of the drug was shown in below figure 4.1. All characteristic peaks of pure zotepine -C-C, -C=C stretching, --C-O and -C-H (bending)were present in FT-IR spectra which confirmed the drug as zotepine. Characteristic peaks of zotepine are shown in below table 4.1

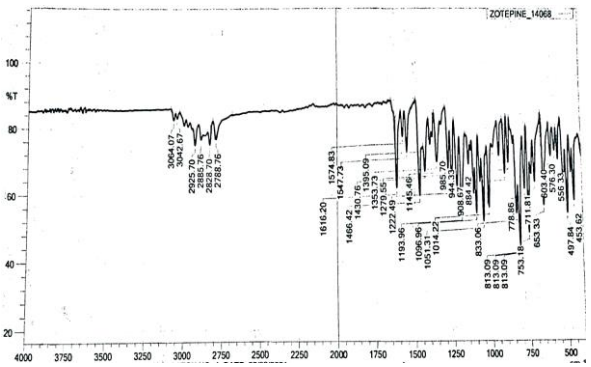

fig .4.1 **FT-IR Spectra of pure Zotepine drug**

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Sr. No.	Functional Group	Standard value (cm^{-1})	Observed value (cm-1)
1.	-C-C	3100 – 2900	2925.70
2.	-C=C stretching	1600	1547.73
3.	-C-H stretching (aliphatic)	3150 – 2850	2885.76
4.	-C-O	1100-100	1145.46

Table 4.1 Peak of functional group in FT-IR spectra of dru

4.1 Drug-Excipients compatibility studies

Figures shows that peak of the functional group of zotepine with excipient showed no significant change. Hence drug – Excipient compatibility study was found to be compatible.

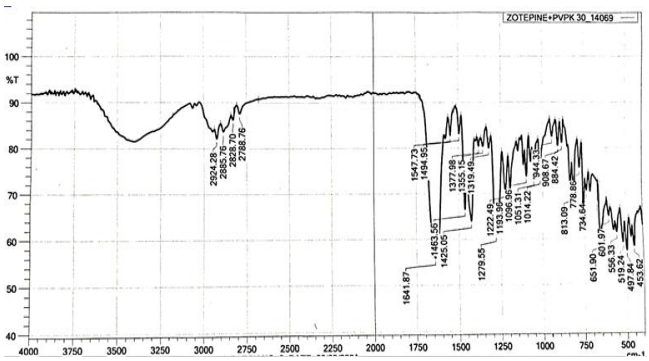

Fig 4.1.1 FT-IR study of Zotepine and PVP K30

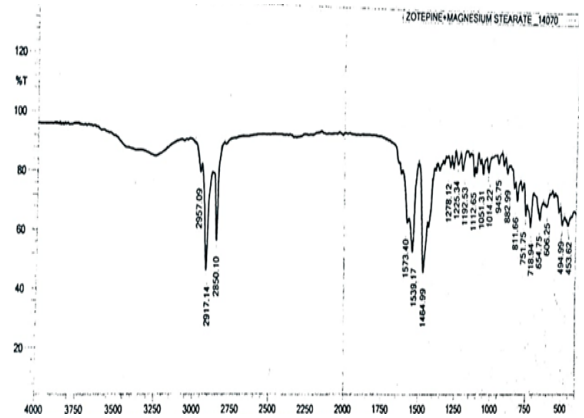

Fig. 4.1.2 FT-IR study of Zotepine and Magnesium Stearate

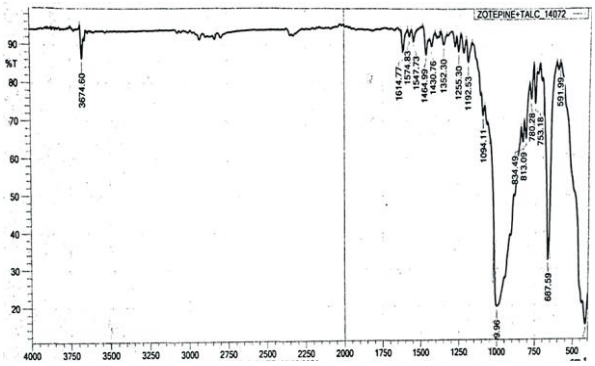

Fig4.1.3 FT-IR study of Zotepine and Talc

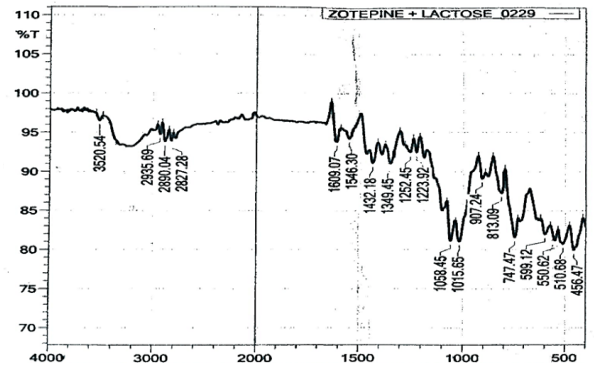

Fig 4.1.4 FT-IR study of Zotepine and Lactose

5. **Preparation of spherical agglomerates of Zotepine**: 8 solubility study of Zotepine in various solvents.

Sr. No.	Solvents	Solubility (mg/ml) Mean± SD
1	Chloroform	24.39 ± 0.12
2	Acetone	17.62 ± 0.14
3	Ethanol	16.28 ± 0.17
4	Dichloromethane	8.32 ± 0.10
5	Ethyl acetate	4.28 ± 0.12
6	Iso-propyl-alcohol	2.66 ± 0.25
7	Methanol	4.27 ± 0.15
8	Water	0.002 ± 0.08

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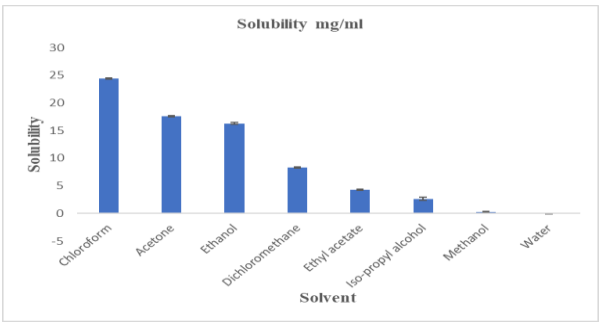

Fig 5.1

Zotepine showed the lowest solubility in water (0.002 mg/ml), hence water was selected as a poor solvent. From solubility studies, acetone and chloroform showed the highest solubility, but spherical agglomerates were not obtained with chloroform. Therefore, acetone was chosen as the good solvent and DCM as the bridging liquid.

5.1 Good solvent: As shown in Table 5.2, varying acetone concentration (2–4 ml) produced no significant effect on % yield, drug release, or particle size. Batch G3 (2 ml acetone) showed the highest yield (68.66%), drug release (80.33%), and particle size (325.31 µm). Thus, 2 ml acetone was selected for further studies.

Trial	Acetone (ml)	DCM (ml)	PVPK30 (%)	WATER (ml)	Stirring speed (rpm)	% yield	%drug Release	Particle Size (µm)
G1	**4**	5	0.6	60	750	60.56	71.43±0.19	295.54
G2	**3**	5	0.6	60	750	65.24	78.62±0.21	297.61
G3	**2**	5	0.6	60	750	68.66	80.33±0.19	325.31

Table 5.2

5.2 Bridging liquid: From Table 5.3, changing DCM concentration (4–6 ml) had minimal influence on yield, drug release, and particle size. Batch B2 showed higher drug release and larger agglomerate size; therefore, 5 ml DCM was fixed as the bridging liquid concentration for further studies.

Trial	Acetone (ml)	DCM (ml)	PVPK 30 (%)	WATER (ml)	Stirring speed (rpm)	% yield	% Drug Release	Particle Size (µm)
B1	2	**6**	0.6	60	750	65.32	72.33±0.22	335.36
B2	2	**5**	0.6	60	750	68.85	79.76±0.10	315.24
B3	2	**4**	0.6	60	750	63.73	74.46±0.22	307.16

Table 5.3

6. Central composite design

Central composite Experimental design was selected as experimental design. And by using Design expert 10.3. Total 9 batches were prepared and evaluated for different evaluation parameter independent variable speed (X1), concentration of polymer (X2). Out of which % yield (Y1) ,% drug release at 20 min (Y2) and particle size (Y3) as dependent variable based on the evaluation data given in table 6.11 and 6.12.

6.1 Evaluation parameters of spherical agglomerates of central composite designed batches

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The % yield of spherical agglomerates ranged from 61.23–68.87%, with SA8 showing the highest yield (68.87%). Drug content was 95.93–99.32%, with SA2 exhibiting the maximum (99.32%). Drug release at 20 min ranged from 70.21–81.39%, with SA2 showing the highest release (81.39%). Overall, increasing polymer concentration led to higher yield and particle size but reduced drug release, whereas increasing stirring speed (750–1250 rpm) enhanced drug release and reduced particle size, with no major effect on yield.

Batches	**% yield**	**Drug Content (%)**	**% Drug Release at 20 min**	**Particle Size (µm)**
SA1	61.23	98.51	76.67±0.13	354.47
SA2	64.45	99.32	81.39±0.13	293.65
SA3	68.21	95.93	71.53±0.13	378.81
SA4	67.45	97.76	73.94±0.19	305.62
SA5	63.72	98.04	74.94±0.13	387.54
SA6	65.87	97.36	79.35±0.05	288.86
SA7	61.57	98.25	80.17±0.11	320.54
SA8	68.87	99.14	70.21±0.17	329.12
SA9	64.42	99.07	74.17±0.14	325.26

Table 6.1

6.2 Evaluation parameters of spherical agglomerates flow properties of central composite designed batches: The angle of repose of all the batches was found to be in range of 25.68 ± 0.11– 31.06±0.07 , carr's index 20.14 – 24.65 and husner's ratio 1.19 – 132.

From the above table it was found that SA 2 having lowest angle of repose (25.68 ± 0.11), carr's index (20.14) and hausner's ratio (1.19). So it was having a good flow property.

Batches	Angle of repose	Bulk Density	Tapped density	Carr's Index	Hausner's Ratio
SA1	28.06±0.12	0.25±0.04	0.36±0.02	21.25	1.32
SA2	25.68±0.11	0.22±0.02	0.30±0.04	20.14	1.19
SA3	26.26±0.13	0.24±0.02	0.35±0.01	24.35	1.20
SA4	27.86±0.08	0.28±0.01	0.32±0.04	23.54	1.21
SA5	26.40±0.14	0.29±0.01	0.33±0.02	20.31	1.13
SA6	28.81±0.09	0.28±0.03	0.37±0.030	21.52	1.32

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SA7	26.55±0.05	0.25±0.02	0.31±0.03	22.21	1.24
SA8	31.06±0.07	0.29±0.03	0.38±0.02	22.36	1.22
SA9	29.24±0.12	0.24±0.02	0.30±0.03	24.65	1.25

Table 6.2

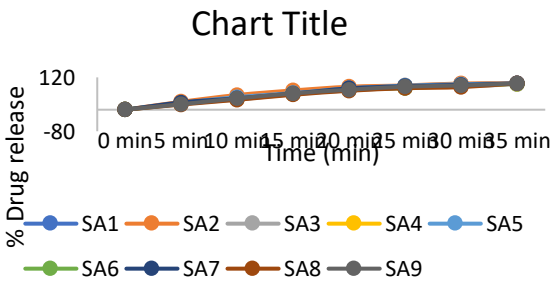
6.3 In vitro drug release of spherical agglomerates of central composite designed batches: * All value are Mean ± SD which are mean of 3 determination

The % drug release of all the batches was found to be in range of(70.21 – 81.32)% at 20min.

From the above table batch SA2 showed higher % drug release at 20 min Which is 81.32 %. Batch SA8 showed lower % drug release at 20 min Which is 70.21 %. As the concentration of polymer increases leads to decrease in % drug release.

Batches	% Drug release at time (20 min)							
	0 min	5 min	10 min	15 min	20 min	25 min	30 min	35 min
SA1	0	24.71±0.14	43.62±0.15	62.62±0.11	76.84±0.13	86.73±0.20	94.81±0.22	97.31±0.18
SA2	0	27.38±0.15	45.57±0.25	63.53±0.29	82.32±0.13	90.13±0.20	97.31±0.14	98.10±0.15
SA3	0	21.81±0.10	37.66±0.41	57.54±0.25	71.54±0.13	81.00±0.11	86.52±0.08	94.50±0.20
SA4	0	22.97±0.22	39.78±0.10	59.12±0.11	73.96±0.19	82.50±0.20	89.65±0.09	96.55±0.14
SA5	0	24.71±0.18	46.82±0.21	61.47±0.28	79.34±0.13	88.99±0.20	94.54±0.22	97.01±0.25
SA6	0	21.87±0.17	40.48±0.09	58.40±0.28	74.48±0.05	80.12±0.22	88.91±01.14	96.20±0.19
SA7	0	27.07±0.29	42.46±0.15	60.06±0.18	79.17±0.11	87.33±0220	92.29±0.10	97.11±0.22
SA8	0	19.13±0.21	36.73±0.18	55.39±0.13	70.21±0.17	79.56±0.11	83.88±0.021	97.04±0.24
SA9	0	20.23±0.17	41.75±0.19	60.35±0.20	74.17±0.14	85.46±0.10	89.81±0.09	96.02±0.17

Table 6.3



6.4 Formula for the optimized batch of Spherical agglomerate of Zotepine.

Ingredients	Quantity
Drug	100 mg
Acetone	2 ml
Dichloromethane	5 ml
PVPK30	0.49
Stirring speed	1005.18

Table 6.4 Formula for optimized batch

6.5 Evaluation parameters of optimized batch

Parameters	Result
% Yield	65.54±0.05
Drug release at 20 min (%)	78.15±0.07
Particle size (µm)	322.24±0.04
Drug content (%)	99.54±0.02

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Angle of repose	31.25±0.04
Bulk density	0.31±0.03
Tapped density	0.35±0.02
Carrs index	9.64±0.01
Hausners ratio	1.09±0.03

Table 6.5

7. **Morphology study:** Morphological study of optimized batch of spherical agglomerates was done by using SEM.

7.1 **Scanning electron microscopy (SEM):** Spherical shape was found to be agglomerates was done by SEM.

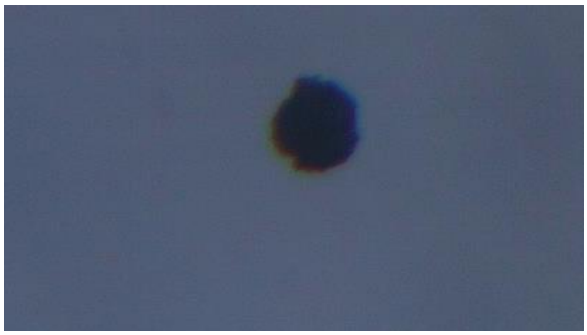

Fig 7.1

7.2 Residual solvent analysis by GC-HS (Figures 7.2 and 7.3) showed acetone and DCM peaks at retention times of 4.207 and 4.408 min, respectively, in standards. No corresponding peaks were observed in spherical agglomerates, indicating complete solvent evaporation. As per ICH limits (acetone 5000 ppm, class 3; DCM 600 ppm, class 2), the agglomerates were free from residual solvents and thus safe from potential toxicity.

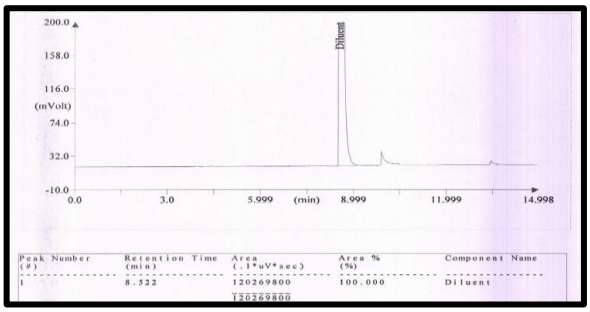

Fig 7.2 Gas chromatogram for determination of Acetone and DCM in spherical agglomerates in Zotepine.

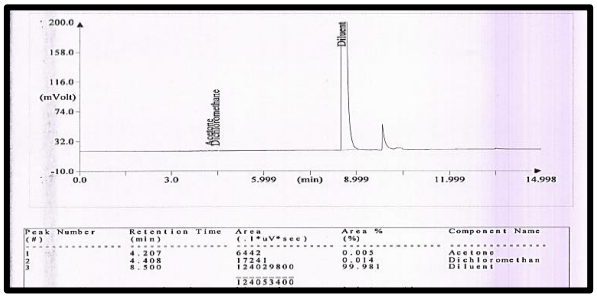

Fig 7.2 Gas Chromatogram for determination of Acetone and DCM as standard solvents

CONCLUSION

Zotepine, a BCS class II antipsychotic used in schizophrenia, shows low aqueous solubility, block-shaped crystals, and only 10% bioavailability (t½ 21 h). Spherical agglomeration was employed to improve its flowability, compressibility, packability, and dissolution. Preformulation studies confirmed λmax at 259 nm (methanol) and 260 nm (0.1 N HCl), with linear calibration curves (r^2 = 0.9983 and 0.9996). FTIR confirmed drug–excipient compatibility.

Solubility screening identified acetone (17.62±0.14 mg/ml) as the good solvent, dichloromethane (8.32±0.10 mg/ml) as the bridging liquid, and water (0.02±0.08 mg/ml) as the poor solvent. A central composite design evaluated the effects of stirring speed (X1) and PVP K30 concentration (X2) on % yield (Y1), % drug release at 20 min (Y2), and particle size (Y3). The optimized batch showed 65.54% yield, 78.15% release, and 322.24 µm particle size, with spherical morphology confirmed by SEM.

Residual solvent analysis by GC-HS detected acetone (0.005 ppm) and DCM (0.014 ppm), both within ICH limits. XRD confirmed partial amorphous conversion, while SEM demonstrated uniform spherical agglomerates.

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