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Formulation, evaluation and optimization of ziprasidone hydrochloride capsules

SHASHI BHUSHAN KUMAR[1], MS. RAGINI BUNDELA*[2], DR. SURENDRA SARAF[3], DR. KARUNAKAR SHUKLA[4]

[1]*Research Scholar, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP*

[2]*Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP*

[3]*Professor & Principal, Columbia College of Pharmacy, Raipur CG*

[4]*Professor & Principal, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP*

**Corresponding Author*

Mob.: 8770992900 Email ID: raginibundela34@gmail.com

ABSTRACT

This research focuses on the development, evaluation, and optimization of Ziprasidone Hydrochloride (ZH) capsules, a potent antipsychotic used in managing psychiatric disorders. The process includes formulation design, evaluation of quality attributes, and optimization to improve drug delivery performance. The formulation stage involves selecting appropriate excipients and determining optimal ratios, while the evaluation phase involves rigorous analysis of parameters like weight variation, content uniformity, hardness, disintegration time, and dissolution profiles. The optimization phase uses statistical tools and experimental design methodologies to identify optimal formulation parameters.

Keywords: Ziprasidone Hydrochloride, Formulation, Evaluation, Optimization, Capsules

1. INTRODUCTION

Most novel drug candidates have poor aqueous solubility in water, which is a result of the use of combinational chemistry and high-throughput screening in drug discovery in recent years. In industries, a suitable pharmaceutical technique is typically used to enhance the dissolving of pharmaceuticals that are poorly soluble in water. The method focused on improving the drug's physicochemical characteristics, manufacturing process, and formulation parameters in order to increase the rate of dissolution. A medication that dissolves slowly in gastrointestinal fluid will take longer to dissolve than it does to absorb within the digestive tract **(Horter and Dressman, 1997)**. Understanding the dissolving and absorption characteristics of medications with low water solubility is crucial for their effective formulation into bioavailable pharmaceutical solutions. While increasing the rate of drug dissolution through methods like salt production and particle size reduction are frequently employed, these approaches have practical limits that may prevent the intended augmentation of

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

bioavailability from always being realized. Solid dispersion technique **(Swarbrick, 2013)** is one formulation approach being investigated to improve the bioavailability of poorly water-soluble medicines; it should be set up as an appropriate dose form. It is possible for conventional dosage forms, like pills and capsules, to instantly release their active ingredients into an absorption pool.

An atypical antipsychotic drug called ziprasidone hydrochloride has been licensed by the FDA to treat bipolar disorder-related mixed states, mania, and schizophrenia **(Reynolds, 1982)**. The powder is crystallized white to off-white in color. It dissolves well in methanol and DMSO but is somewhat insoluble in water (21.12 mg/l) **(Deshmukh et al., 2006).** Its plasma protein binding is 99% and its oral bioavailability is 60%. The enzyme aldehyde reductase metabolizes it hepatically, while cytochrome P450 3A4 (CYP3A4) handles minor metabolism **(Reynolds, 1982; Goodman, 1996)**. Ziprasidone is a benzo-thiazolyl-piperazine derivative, used widely for the treatment of schizophrenia and bipolar disorders **(Schatzberg and Nemeroff, 2017)**. Ziprasidone belongs to BCS class II. The oral dose in schizophrenia is 20 mg twice a day with a meal **(Brayfield, 2017)**. Ziprasidone acts as an antagonist of serotonin and dopamine, which selectively binds to 5HT-2, D-2, adrenergic α-1, & α-2, and histamine H-1 receptors. The greater affinity for 5HT-2A in contrast to another anti-schizophrenia drug caused minimum motor adverse effects **(Davis and Markham, 1997).** The half-life of ziprasidone is 6 hours and the therapeutic range is 50 to 130ng/ml **(Urban and Cubala, 2017).** Zipradone Hcl was chosen as a potential medication candidate based on the physicochemical and biologic characteristics mentioned above. Through the use of the solid dispersion technique, efforts were undertaken to increase the medication's solubility and achieve a longer drug release that would require fewer doses, have fewer adverse effects, and increase patient compliance.

2. MATERIAL AND METHOD

2.1 Sample Preparation:

Weigh and transfer about 500 mg of sample into a 25 mL clean, dry beaker and disperse the sample in about 2 mL of dispersion medium with glass rod mildly (disperse the sample until deagglomeration of Particle and looking uniform), then add about 10 mL of dispersion medium, mix with glass rod and sonicate for 60 seconds for uniform dispersion.

2.2 Identification test (by spectroscopy)

a. Infrared absorption spectroscopy:

By potassium bromide disc method: Ziprasidone Hydrochloride was mixed thoroughly with potassium bromide. This physical mixture was compressed and converted in a circular disc. This disc was then placed in the scanning slot of FTIR and scanned to obtain the FTIR of Ziprasidone Hydrochloride. Compare the IR spectrum with similarly recorded spectrum of Ziprasidone Hydrochloride working standard.

b. HPLC method:

The retention time of the major peak in the test preparation should match the standard preparation. To prepare, dissolve 6.8g Potassium phosphate monobasic in water, adjust pH, and filter. Add 22.0 mg of Ziprasidone Hydrochoride, sonicate, and dilute. Prepare a HPLC formulation sample and sonicate for 20 minutes. Filter and inject 200 ppm of Ziprasidone **(Skoog et al., 2013)**.

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

c. Proton NMR Spectroscopy:

The Proton Nuclear Magnetic Resonance (NMR) Spectrum of Ziprasidone Hydrochloride batch Used in formulation is consistent with Proton NMR spectrum of Ziprasidone Hydrochloride reference batch recorded in DMSGd6 on a 300 MHz instrument **(Sharma, 2007)**.

e. By X-Ray Diffraction:

The samples of Ziprasidone Hydrochloride drug substance used in formulation were analyzed by X-ray Powder Diffraction spectroscopy and compare with the reference Ziprasidone Hydrochloride. Formulation also analyzed by X-ray diffraction spectroscopy along with excipient to see the changes in polymorphism **(Skoog et al., 2013)**.

2.3 Powder Characteristics Ziprasidone Hydrochloride:

i) Bulk Density:

Ziprasidone Hydrochloride was accurately weighed and sifted through 20 # and transferred in a 100 ml graduated cylinder. The level was observed without compacting and noted as apparent volume (V0). The bulk density was calculated by the formula **(Lachman et al., 1976)**,

$$BD=M/V_0$$

ii) Tapped Density:

Ziprasidone Hydrochloride was accurately weighed and sifted through 20 # and transferred in 100 mL graduated cylinder. The cylinder was placed on the tapped density tester and was mechanically tapped, allowing it to drop under its own weight that provides a fixed drop from 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and the tapped volume (V1) was measured to the nearest graduated units. The tapping was repeated for additional 750 times and the tapped volume (V2) nearest to graduated units and again tapping was repeated for additional 1250 times and tapped volume was noted. The tapped density was calculated by the formula **(Lachman et al., 1976)**,

$$TD=M/V_2$$

iii) Hausner ratio:

Hausner ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the bulk density **(Lachman et al., 1976)**. Hausner ratio is calculated as:

HR= Tapped density / Bulk density

iv) Compressibility Index (Carr's Index):

The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indicated as compressibility index (CI) and can be calculated as follow **(Lachman et al., 1976)**.

CI= (Tapped density-Bulk density/ Tapped density)*100

v) Flow Properties:

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

Flow properties depend on particle size, shape, porosity and density of bulk powder. The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose **(Lachman et al., 1976)**.

$$\tan \theta = h/r$$

Based on the results obtained from the above mentioned characterizations the formulation was developed. The results for all Ziprasidone Hydrochloride characterizations were discussed in Result and Discussion.

2.4 Loss on drying:

The quantity of moisture present in the Ziprasidone Hydrochloride was determined by using moisture analyzer and can be calculated as follows **(Lachman and Schwartz, 1990)**.

$$\text{LOD} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

2.4.1 FORMULATION METHODS

Batch size -1000 capsules

Batch taken with Roller pressure 4T Roller pressure, Roller speed 6 rpm. Capsules filled with automated capsule filling machine.

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Table no. 1 Development of formula

Sr. No.	Ingredients	Specification	Quantity per unit (mg)	Quantity for batch (g)
Active Pharmaceutical Ingredient				
1	Ziprasidone Hydrochloride	USP	22.64	22.64
Excipients				
2	Lactose Anhydrous (SuperTab 21 AN)	USP-NF	39.235	39.235
3	Pregelatinized Starch (Lycatab PGS)	USP-NF	12.75	12.75
4	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
5	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
Theoretical weight of Lubricated blend			75	75
EHG Capsule				
6	E.H.G Capsule size '5' Blue opaque/White opaque, 'ap' logo & 'ZP 20' on cap & body respectively	IH	1 No.	1000 No.

Required weight achieved and capsules were filled properly by automated capsule filling machine. It is an optimized batch based on this formulation the process and formula optimization to be carried out.

2.4.2 Formula optimization by Roller Compaction method:

2.4.2.1 Factorial designs

Factorial design is an efficient method of indicating the relative significance of a number of variables and their interaction. Factorial design approach shows interaction between factors that a 'one factor at a time' model cannot reveal **(Anderson and Whitcomb, 2017).**

2.4.2.2 Two Level Factorial Designs

A two-level factorial design is an experimental design in which data is collected for all possible combinations of the two factors by considering two levels of each **(Anderson and Whitcomb, 2017)**.

2.4.2.3 Optimization Batches by Roller compaction:

Total 5 optimization batches taken place including one center point

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Table no. 2 Optimization batches formula (in%)

Sr. no.	Ingredients	ZHC6	ZHC7	ZHC8	ZHC9	ZHC10
		In %	In %	In %	In %	In %
	Intra granular					
1	Ziprasidone Hydrochloride	30	30	30	30	30
2	Lactose Anhydrous	52	62	62	42	42
3	Pregelatinized starch	17	7	7	27	27
	Lubrication					
4	Magnesium Stearate	0.5	0.75	0.25	0.75	0.25
	Total	100	100	100	100	100

2.5 CAPSULE EVALUATION:

The Capsules were evaluated for the following parameter.

2.5.1 Weight variation:

Weigh individually 20 units selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the pharmacopeia and none deviates by more than twice that percentage.

2.5.2 Capsule lock length:

20 capsules were selected randomly and lock length was measured using “Mitutoyo” Vernier caliper.

2.5.3 Disintegration Time:

Introduce one capsule into each tube of the disintegration testing apparatus. Here beaker containing water maintained at 37℃ ± 2℃ and operate the apparatus for 30 minutes. Observe the entire capsule, if all the capsules are disintegrated completely within 30 minutes, lift the basket from the fluid and note down the time required .If 1 or 2 tablets fail to disintegrate completely, repeat the test and 12 additional capsules. The requirement is met if not fewer than 16 of the total of l8 capsules tested are disintegrated.

2.5.4 Assay by HPLC:

Dissolve 6.8 g Potassium phosphate monobasic in 1000 mL water and adjust pH to 2.5 ± 0.05 with Orthophosphoric acid. Filter through 0.45µm membrane filter. Weigh accurately about 22.0 mg of Ziprasidone Hydrochoride working standard in 100 ml volumetric flask, add 50mL Diluent and sonicate to dissolve and dilute to volume with diluent (About 200 ppm of Ziprasidone). Weigh 20 capsules and remove the content of the capsule and mix properly.

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

Weigh powder equivalent to 100 mg and transfer in 500 mL volumetric flask. Add about 300 mL of diluent and sonicate for 20 minutes with intermittent shaking (Maintain temperature of sonicator between 20-25^{0}C) and dilute to volume with diluent. Filter through 0.45 µm PVDF Millipore millex filter. Discard first 5 mL of the filtrate and inject (About 200 ppm of Ziprasidone).

2.5.5 Content Uniformity determination: (For 20 mg)

Transfer inner Content of 1 capsule in to 100mL volumetric flask. Add 60 mL of diluent and Sonicate for 20 minutes with intermittent shaking. Dilute up to mark with diluent. Filter through 0.45µm PVDF Millipore Millex filter. Discard first 5 mL of filtrate (About 200 ppm of Ziprasidone.)

2.5.6 In-vitro Drug Release study:

For dissolution of Ziprasidone Hydrochloride capsules media used which is mentioned in office of Generic drug (OGD Media). It is having a dissolution test which will show a difference between one formulation and another. Basically, that you will be able to discriminate between a drug that passes and one that fails. Failure of dissolution can be due to a lot of factors (stability issues, poor formulation, gelatin cross linking). Discrimination media is one part of discriminatory dissolution test. The media should able to meet sink condition. Discrimination of dissolution carried out in media Phosphate buffer pH 7.5 with 2% SLS, Phosphate buffer pH 7.5 with 0.5% SLS, Phosphate buffer pH 7.5 with 0.25% SLS, Phosphate buffer pH 7.5 with 0.1% SLS in dissolution apparatus II (paddle) at 75 rpm. Dissolution carried out of formulation in which quantity of Polysorbate 80 is changes with the reference Ziprasidone capsules **(Costa and Lobo, 2001; Brahmankar and Jaiswal, 1995).**

2.6 ACCELERATED STABILITY STUDY:

The optimized formulation was packed in HDPE bottle and it was then stored at 40^{0}C / 75% RH for 3 month and evaluated their Physical parameter (Description, Weight variation) and Chemical parameter (Assay, Water content, dissolution studies, Related Substances) **(Lachman and Schwartz, 1990)**.

3. RESULTS AND DISCUSSION

3.1 Preformulation Study of Ziprasidone Hydrochloride:

3.1.1. Organoleptic Characteristics:

A sample of API was tested for appearance, taste and odour.

Table 3 Organoleptic Characteristic Ziprasidone Hydrochloride

Property	Result
Description	White to slightly pink powder.
Taste	Bitter
Odour	Odourless Powder

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

Colour	White to light pink
Melting point	319^0C
Water content	4.06%
Assay by HPLC	101.8% w/w

3.1.2. Hygroscopicity:

Table 4: Hygroscopicity.

Ziprasidone Hydrochloride		
Initial Weight	**Weight after 24 hours, at 80%RH +2% RH**	**Percentage increase in mass**
2.00 gm	2.00 gm	0.0 %

3.1.3. Solubility results

Table No. 5: Solubility of Drug Ziprasidone Hydrochloride

Solubility medium	**Solubility of Ziprasidone Hydrochloride**
Water	Practically insoluble
Tetrahydrofuran	Practically insoluble
Isopropyl alcohol	Practically insoluble

3.2. Identification by Spectroscopy:

3.2.1. Infrared absorption spectrophotometry:

The IR Spectrum of the development batch is comparable to the reference Ziprasidone Hydrochloride of Vendor batch. Infrared (IR) absorption spectrum (as KBR pellet) of Ziprasidone Hydrochloride of development batch exhibits absorption bands in the same wave numbers as that of a similar preparation of Ziprasidone Hydrochloride of reference **(Sharma, 2007)**. The assignment of characteristic absorption bands is tabulated below.

Table No. 6 Assignment of characteristic absorption bands

Assignment	**Intensity**	**Frequency (cm-1)**	
		Reference batch	**Batch uses for development**

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

NH stretch	S	3420	3423
Aromatic C-H stretch	W	3075, 3022	3074, 3022
Aliphatic C-H stretch	W	2994, 2936	2994, 2930
C=O stretch	S	1714	1714
Aromatic C=C stretch & C=N stretch	s & m	1631, 1591	1631,1591
CH2 bending	S	1493	1493
C-N stretch	M	1243	1243
Skeletal vibration / bands, out-of-plane, aromatic ring bend	M	774, 744	774, 744
In the Fingerprint region, there are numerous absorption bands, many of which are difficult to assign to specific vibrational modes.			

Where,

s= strong intensity

m= medium intensity

w =weak intensity

The IR spectra of Ziprasidone Hydrochloride reference batch and development batch are provided below.

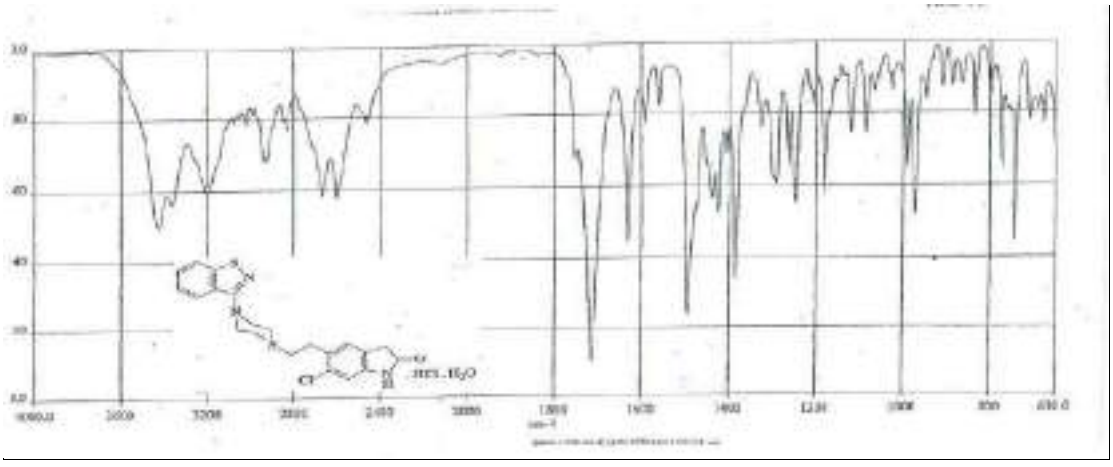

Fig. no.1 IR spectrum of Reference Ziprasidone Hydrochloride

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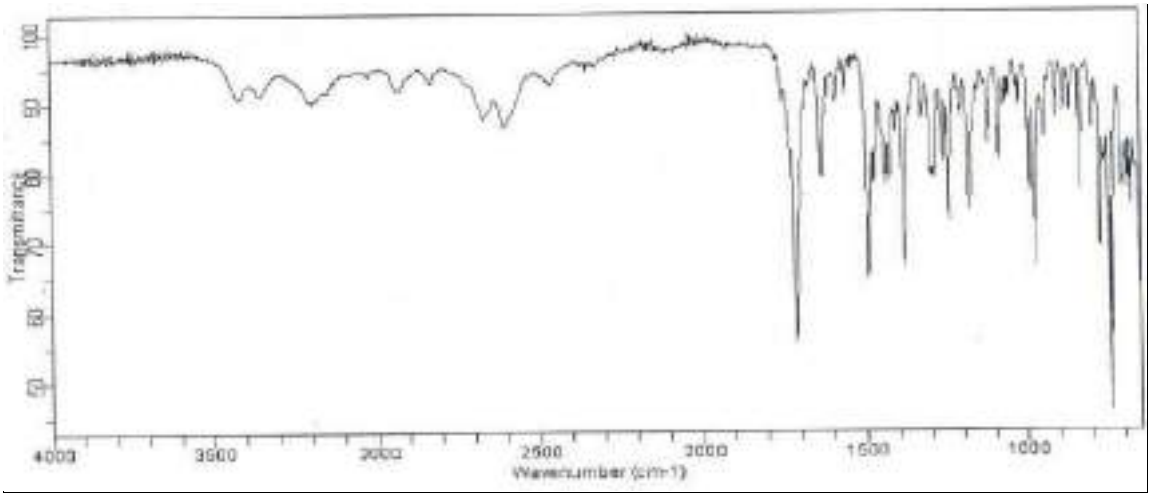

Fig. no.2 IR spectrum of Ziprasidone Hydrochloride used for development batches

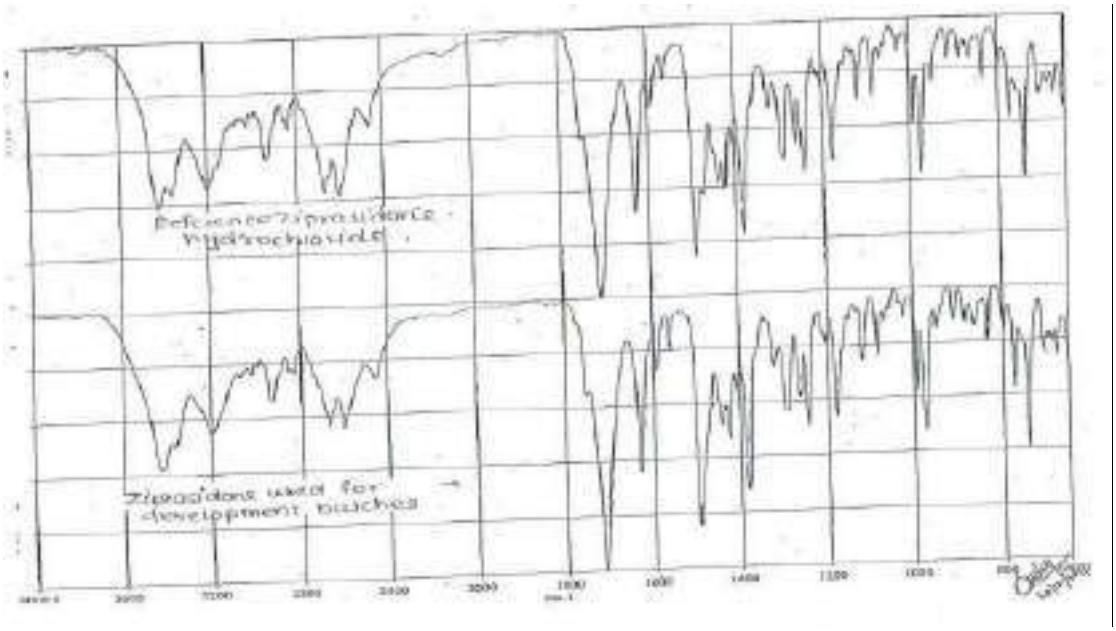

Fig. no.3 Comparison graph of IR spectra of Reference Ziprasidone and Ziprasidone used for batches

3.2.2. Proton NMR Spectroscopy:

The proton nuclear magnetic resonance spectra of Ziprasidone Hydrochloride development batch is consistent with Proton NMR spectrum of Reference Ziprasidone Hydrochloride recorded in DMSG-d6 on a 300 MHz instrument. The assignments of protons and their multiplicity are provided below.

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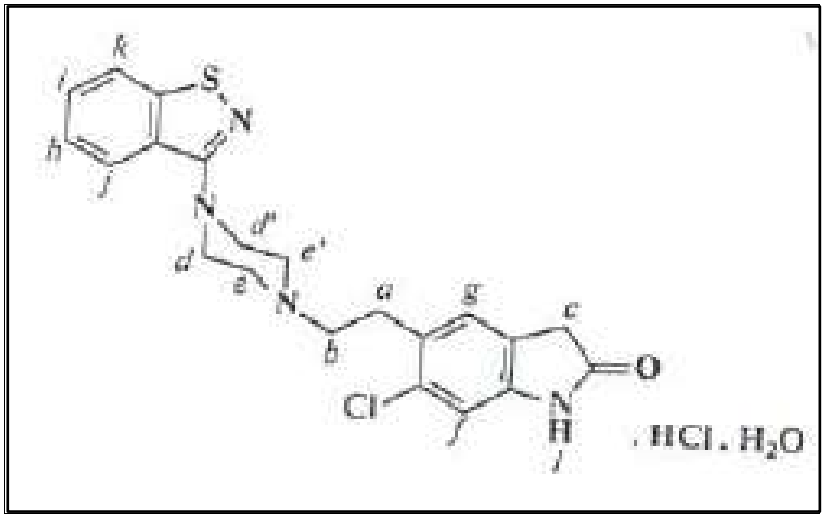

Fig. no.4 Assignment of proton and their multiplicity

The Proton Nuclear Magnetic resonance spectra of Ziprasidone Hydrochloride Reference Ziprasidone Hydrochloride and development batch are provided below.

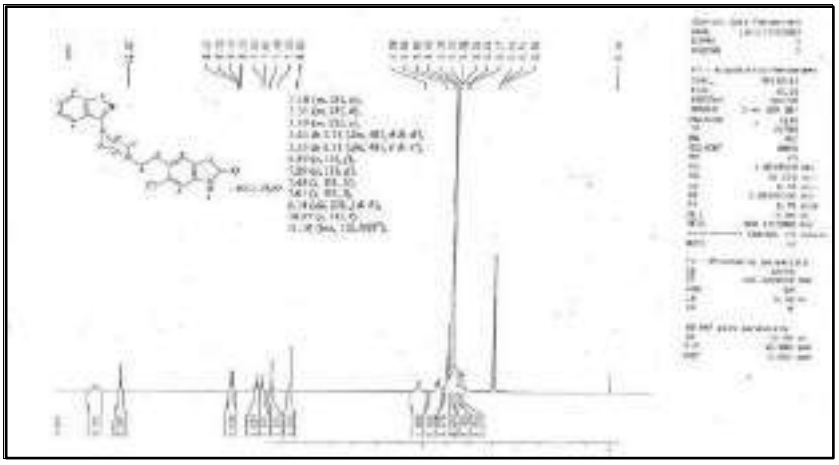

Fig. no.5 NMR spectra of Ziprasidone Hydrochloride used for development batches

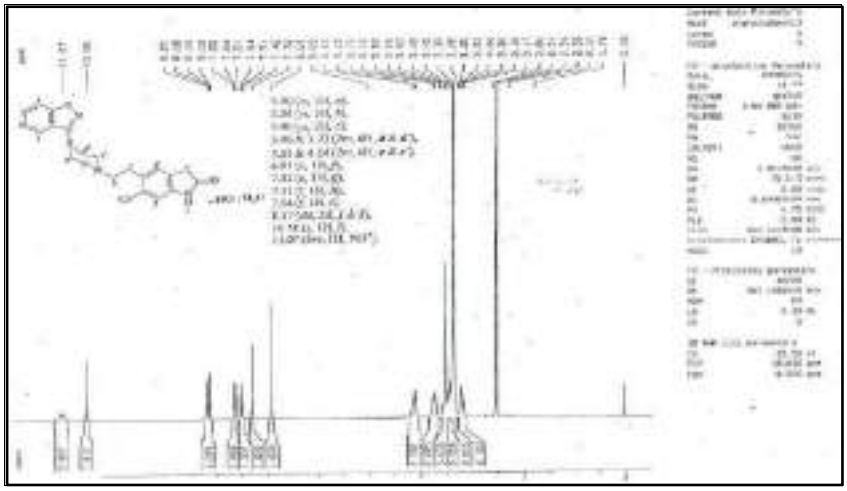

Fig. no.6 NMR of spectra of Reference Ziprasidone Hydrochloride

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

3.2.3. By Mass Spectroscopy:

Mass spectrum of Ziprasidone Hydrochloride development batch shows a protonated molecular ion peak at mlz 413 as that of Reference Spectra of Ziprasidone Hydrochloride. The mass spectra of Ziprasidone Hydrochloride development batch and Reference spectra of Ziprasidone Hydrochloride recorded on AH 2000 (PE SCIEX) LCIMSIMS using a positive ion spray mode exhibits the fragmentation pattern as provided below.

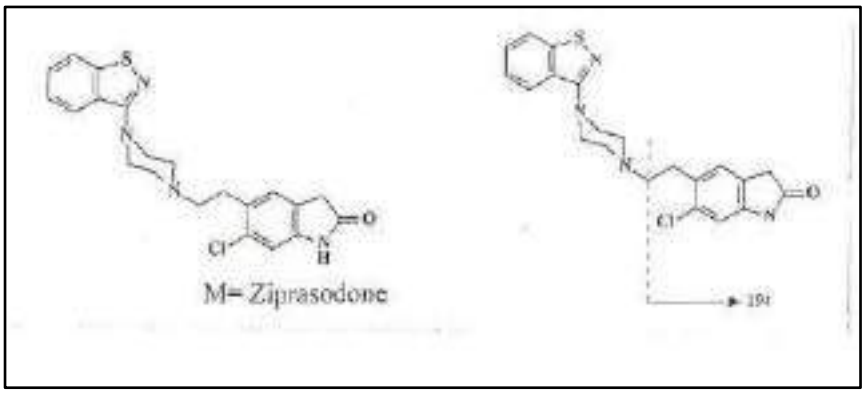

Fig.No.7 Fragmentation pattern of Ziprasidone Hydrochoride

Table No.7 Molecular ion peak

Batch Number	Molecular ion peak[M + H] m/z value
Reference Spectra of Ziprasidone Hydrochloride	413.1
Ziprasidone Hydrochloride development batch	413.2

Table No.8 Fragment ion peak

Batch Number	Fragment ion peak
Reference Spectra of Ziprasidone Hydrochloride	194
Ziprasidone Hydrochloride development batch	194.2

Based on spectral data of development batch and comparison with reference batch, the structure of Ziprasidone Hydrochloride is confirmed.

3.2.4. By X-Ray Diffraction:

MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*

The sample of Ziprasidone Hydrochloride drug substance of were analyzed by X-Ray Powder Diffraction spectroscopy. The X-Ray Powder Diffraction pattern of Ziprasidone Hydrochloride show an identical pattern with reference spectra, and which are concordant to the pattern values/ pattern reported in literature for Ziprasidone Hydrochloride Monohydrate.

The X-ray Diffraction spectra of Formulation of Ziprasidone Hydrochloride capsule also identical with these spectra. This indicates that there is no change in polymorphism after formulation.

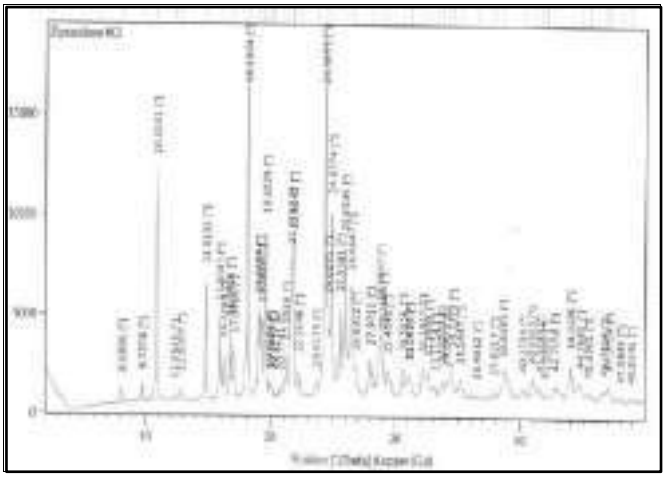

Fig.no. 8 XRD of Ziprasidone Hydrochloride

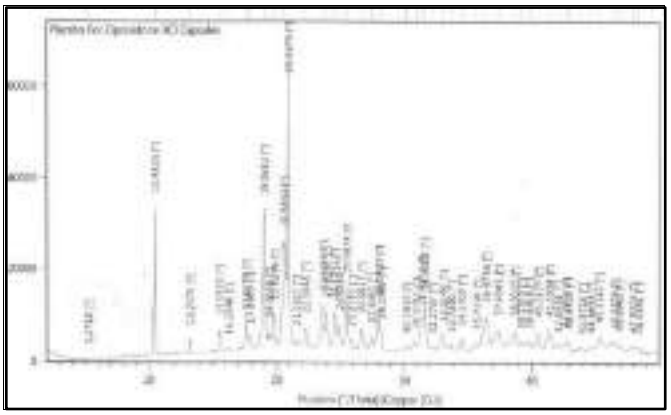

Fig. No. 9 XRD of Placebo for Ziprasidone Hydrochloride Capsules

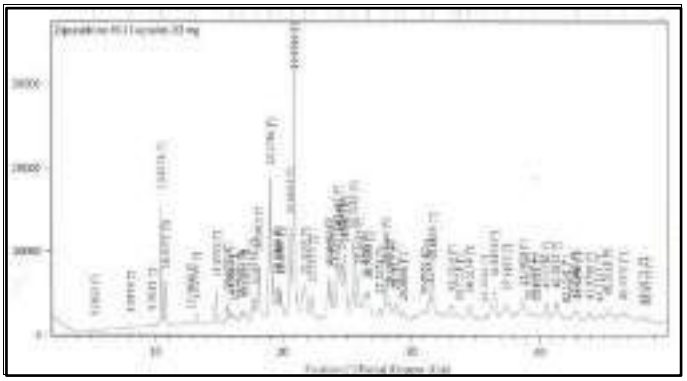

Fig.No. 10 XRD of Ziprasidone Hydrochloride Capsules

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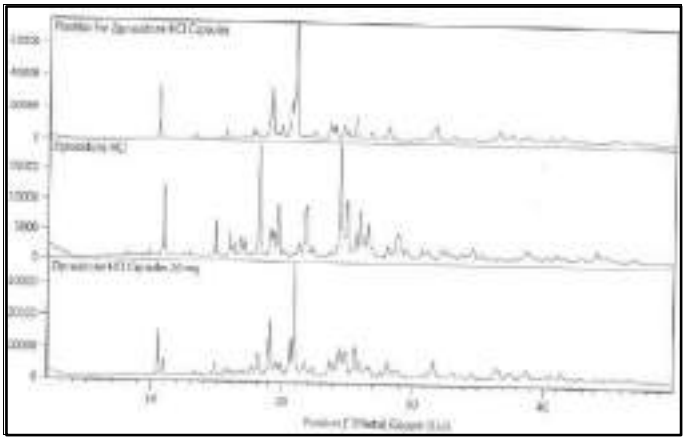

Fig.no. 11 XRD of Ziprasidone Hydrochloride along with excipients

3.3 Powder Characteristics Ziprasidone Hydrochloride

Table No. 9 Powder characteristics of Ziprasidone Hydrochloride

Parameter	Drug	Result
Bulk density	0.241gm/cm^3	-
Tapped density	0.388 gm/cm^3	-
Angle of repose	54°	Poor
Carrs index	37.80 %	Very Poor
Haurners ratio	1.60	Very Poor

3.4 Drug-Excipient Compatibility Study:

3.4.1 Chemical observation and results:

Retated substance study: Impurity Profile of Ziprasidone Hydrchoride USP [Related Substances (By HPLC) (% w/w)]

3.4.1.1. Initial Condition:

a. (Early-eluting method)

Table No. 10 Initial condition (Early-eluting method)

Sr. No	Condition	Ratio	Known impurities in %(limit NMT 0.20% eachunknown max imp(limit NMT0.20%	unknown max imp	total imp (limit NMT	Remark

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	Initial		**ziprasidone related compound A**	**ziprasidone related compound B**	**open ring**	**(limit NMT 0.20%**	**1.0%)**	
	Relative retantion time		0.29	0.7	0.81	NA		
1	Ziprasidone	NA	ND	0	ND	0.031	0.099	Complies
2	Povidone	NA	ND	ND	ND	ND	ND	Complies
3	polysorbate 80	NA	ND	ND	ND	ND	ND	Complies
4	magnesium stearate	NA	ND	ND	ND	ND	ND	Complies
5	pregelatinised starch	NA	ND	ND	ND	ND	ND	Complies
6	lactose monohydrate	NA	ND	ND	ND	ND	ND	Complies
7	silicon dioxide	NA	ND	ND	ND	ND	ND	Complies
8	All excipients	NA	ND	ND	ND	ND	ND	Complies
9	API :lactose monohydrate	1:01	0.022	0	0.019	0.009	0.059	Complies
10	API :lactose monohydrate	1:10	0.025	0	0.022	0.007	0.067	Complies
11	API :lactose monohydrate	1:02	0.019	ND	0.023	0.007	0.049	Complies
12	API :Pregelatinised starch	1:01	0.019	0	0.021	ND	0.055	Complies
13	API :Pregelatinised starch	1:10	0.02	ND	0.023	0.007	0.05	Complies
14	API :Pregelatinised starch	2:01	0.019	0	0.019	0.007	0.055	Complies

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15	API :Povidone	1:01	0.017	0	0.024	ND	0.073	Complies
16	API :Povidone	10:01	0.018	0	0.025	ND	0.071	Complies
17	API :Polysorbate 80	1:01	0.018	0	0.022	ND	0.054	Complies
18	API :Polysorbate 80	10:01	0.019	0	0.022	ND	0.069	Complies
19	API :Magnesium stearate	1:01	0.018	0	0.024	ND	0.071	Complies
20	API :Magnesium stearate	10:01	0.018	0	0.021	ND	0.059	Complies
21	API :All excipients		ND	ND	ND	ND	ND	Complies

b. (Late-eluting method)

Table No. 11 Initial condition (Late-eluting methods)

Sr. No	Condition	Ratio	Known impurities in %(limit NMT 0.20% each		unknown max imp (limit NMT 0.20%	Total imp (limit NMT 0.3%)	Remark
	Initial		ziprasidone related compound C	ziprasidone related compound D			
	Relative retantion time		1.91	2.81	NA		
1	Ziprasidone	NA	ND	0.02	0.031	0.1	Complies
2	Povidone	NA	ND	ND	ND	ND	Complies
3	polysorbate 80	NA	ND	ND	ND	ND	Complies
4	magnesium stearate	NA	ND	ND	ND	ND	Compli

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							es
5	pregelatinised starch	NA	ND	ND	ND	ND	Complies
6	lactose monohydrate	NA	ND	ND	ND	ND	Complies
7	silicon dioxide	NA	ND	ND	ND	ND	Complies
8	All excipients	NA	ND	ND	ND	ND	Complies
9	API :lactose monohydrate	1:01	ND	0.02	0.032	0.1	Complies
10	API :lactose monohydrate	1:10	ND	0.03	0.032	0.1	Complies
11	API :lactose monohydrate	1:02	ND	0.02	0.031	0.1	Complies
12	API :Pregelatinised starch	1:01	ND	0.02	0.031	0.1	Complies
13	API :Pregelatinised starch	1:10	ND	0.03	0.031	0.1	Complies
14	API :Pregelatinised starch	2:01	ND	0.03	0.032	0.1	Complies
15	API :Povidone	1:01	ND	ND	0.03	0	Complies
16	API :Povidone	10:01	ND	ND	0.034	0.1	Complies
17	API :Polysorbate 80	1:01	ND	ND	0.028	0	Complies
18	API :Polysorbate 80	10:01	ND	ND	0.03	0.1	Complies
19	API :Magnesium stearate	1:01	ND	ND	0.033	0.1	Complies
20	API :Magnesium stearate	10:01	ND	ND	0.032	0	Complies

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21	API :All excipients		ND	ND	ND	ND	Complies

3.5 EVALUATION OF DEVELOPMENT BATCHES:

3.5.1 Blend uniformity test of Trail:

Table No. 12 Blend uniformity result of Trial

Sr. No	Sampling Location	Assay (%)
1	LTR	97.8
2	LTF	98.2
3	LMR	98.6
4	LMF	97.5
5	RTR	99.1
6	RTF	98.2
7	RMR	96.3
8	RMF	96.8
9	CMF	98.3
10	CMC	97.5
11	Composite	99.5

3.5.2 Capsules parameter:

Table No. 13 Capsule parameter of Trial

Sr. No	Parameter	Result
1	**Description**	Blue opaque/ white opaque hard gelatin capsule of size ‘5’ with ap logo on cap and ‘ZP 20’ on body in black ink containing white to slightly pink colored powder .
2	**Average weight of filled capsule**	105.02 mg
3	**Capsule lock length**	11.58 mm

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4	**Disintegration Time**	6 min 20 sec
5	**Water content**	3.16% w/w
6	**Assay**	98.6 %
7	**Content Uniformity**	97.5%

- **Weight Variation:**

  In weight variation test, the Pharmacopoeial limit for percent of deviation for capsules weighing less than 300 mg is not more than 10%. The average percent deviation of all capsules was found to be within the limit and hence all formulation passes the weight variation test.

- **Capsule lock length:**
  Capsule lock length of capsules was found to be uniform among all formulations and range d from 11.00 to 11.80 mm**.**
- **Content Uniformity:**

  The drug content was found to be uniform among all formulation and ranged from 85.00% to 115.00%.

- **Assay :**
  Assay of all the formulations was found to be between 95-105% and assay of ZHC5 optimized batch was found to be 98.6%.

3.5.3 Particle size analysis:

Table No. 14 Particle size analysis of Trial

Sieve no.	Empty wt.	Wt. with blend	Wt. of blend	% Retained	Cumulative
30	384	384	0	0	0
40	357.5	358	0.5	1.92	1.92
60	350.5	357.5	7	26.92	28.85
80	343	349.5	6.5	25.00	53.85
100	328	331.5	3.5	13.46	67.31
Pan	549	557.5	8.5	32.69	100.00
			26 g	100 %	

3.6 Dissolution studies of Formula optimization batches:

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Table No. 15 Dissolution data compilation of Formula optimization batch

Time	Reference	ZHC6	ZHC7	ZHC8	ZHC9	ZHC10
0	0	0	0	0	0	0
5	24.1	36.2	19.9	20.9	38.8	35
10	58.4	63.1	52.1	55.2	68.6	64.5
15	71.4	74.6	66.9	69.2	79.3	75.9
20	80.2	80.7	74.5	73.8	84.6	80.9
30	85.9	86.8	83.3	81.5	89.3	86.2
45	91.9	91.1	89.9	87.8	92.7	89.6
60	95.4	93.1	93.5	90.5	94.8	91.5
F1		**6.6**	**8.28**	**2.55**	**5.38**	**5.63**
F2		**55.58**	**55.49**	**80.09**	**68.07**	**63.45**

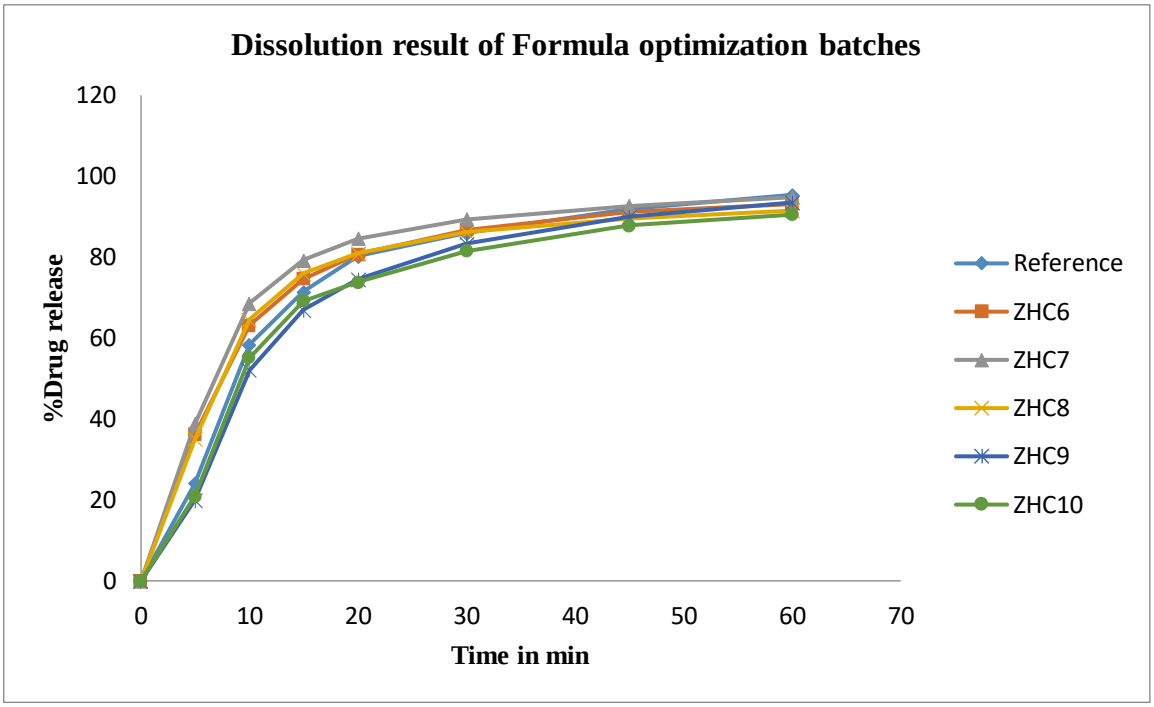

Fig.No. 10 Compilation of Dissolution result of Formula Optimization batches

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3.7 Formula Optimization

Table 16 Factors and their responses for optimization

Sr.no	Factor 1 1A: Pre. Starch	Factor2 B: mg. stearate	Responses 1 Dissolution at 15 min	Responses 2 Dissolution at 60 min
1	17.00	0.50	74.6	93.1
2	7.00	0.25	69.2	90.5
3	27.00	0.75	79.3	94.8
4	27.00	0.25	75.9	91.5
5	7.00	0.75	66.9	93.5

a) Dissolution at 15 minutes.

ANOVA for selected factorial model

Table no 17 Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F value	p-value Prob > F	Model
Model	91.20	1	91.20	21.65	0.0432	significant
A-Pregelatinized starch	91.20	1	91.20	21.65	0.0432	
Curvature	2.52	1	2.52	0.60	0.5201	non-significant
Residual	8.43	2	4.21			
Cor Total	102.15	4				

The curvature effect was not significant for dissolution, the factorial model coefficient was fit using all of the data (including centre point). As shown in following half normal plot and ANOVA results of the unadjusted model, the significant factor affecting capsule dissolution were A (pregelatinized starch), B (Magnesium stearate).

ANOVA for selected factorial model

Table No 18 Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F value	p-value Prob > F	Model
Model	91.20	1	91.20	25.00	0.0154	significant

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A-Pregelatinized starch	91.20	1	91.20	25.00	0.0154	
Residual	10.95	3	3.65			
Cor Total	102.15	4				

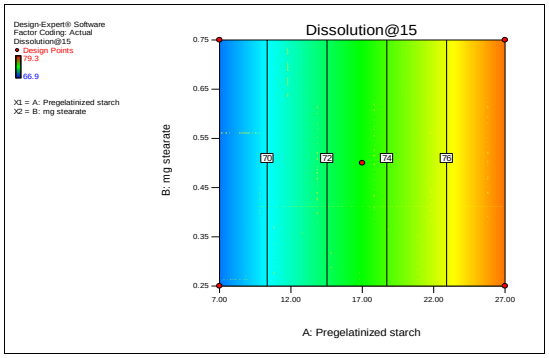

Fig. No. 11 Counter plot for dissolution at 15 minutes

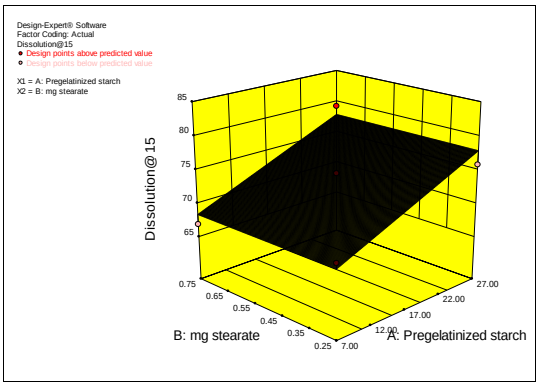

Fig.No. 12 3D graph for dissolution at 15 minutes

Figure No. 11and 12 shows the effect of excipients Pregelatinized starch and Magnesium stearate on dissolution at 15 minutes. Dissolution increased with increasing the concentration of pregelatinized starch. Magnesium stearate dose not shows any significant impact on dissolution at 15 minutes.

b) Dissolution at 60 minutes

ANOVA for selected factorial model

Table No 19 Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F value	p-value Prob > F	Model
Model	11.24	2	5.62	249.89	0.0447	Significant
A-Pregelatinized starch	1.32	1	1.32	58.78	0.0826	
B-mg stearate	9.92	1	9.92	441.00	0.0303	

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Curvature	0.22	1	0.22	9.80	0.1968	not significant
Residual	0.023	1	0.023			
Cor Total	11.49	4				

The following ANOVA is for a model that does not adjust for curvature. This is the default model used for prediction and model plots

ANOVA for selected factorial model

Table No. 20 Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F value	p-value Prob > F	Model
Model	11.25	2	5.62	46.28	0.0212	Significant
A-Pregelatinized starch	1.32	1	1.32	10.88	0.0809	
B-mg stearate	9.92	1	9.92	81.67	0.0120	
Residual	0.24	2	0.12			
Cor Total	11.49	4				

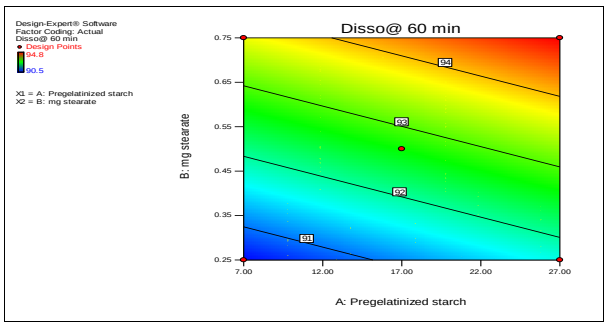

Fig. No. 13 Counter plot for Dissolution at 60 min

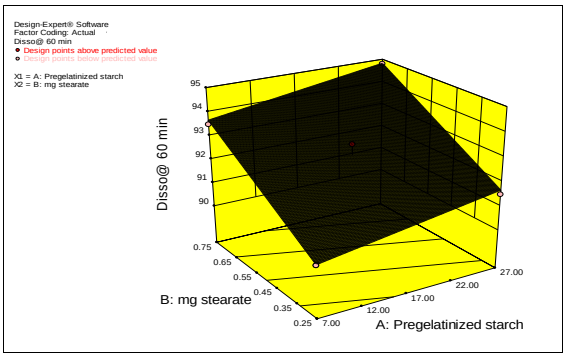

Fig.No. 14 3D graph for dissolution at 60 min

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Figure No. 13 and 14 shows the effect of excipients Pregelatinized starch and Magnesium stearate on dissolution at 60 minutes. Dissolution increased with increasing the concentration of pregelatinized starch and Magnesium stearate. The exhibited acceptable dissolution (> 75% in 60 min). Based on the result of formulation development study, the binding agent pregelatinized starch and extra-granular magnesium stearate were fixed to 07 % to 27% and 0.25 % to 075 %

3.9 Evaluation of Capsules

i. Capsules parameter:

Table No. 21 Physical parameters of capsules

Sr. No	Parameter	Result
1	**Description**	Blue opaque/ white opaque hard gelatin capsule of size '5' with ap logo on cap and 'ZP 20' on body in black ink containing white to slightly pink colored powder .
2	**Average weight of filled capsule**	104.32 mg
3	**Capsule lock length**	11.62 mm
4	**Disintegration Time**	6 min 40 sec
5	**Water content**	2.86% w/w
6	**Assay**	98.3 %
7	**Content Uniformity**	96.5%

3.9.1 Blend uniformity study:

Table No. 22 Blend Uniformity results

Sr. No	Sampling Location	Assay (%)
1	LTR	98.8
2	LTF	96.2
3	LMR	97.6
4	LMF	97.5
5	RTR	98.1

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6	RTF	96.2
7	RMR	97.3
8	RMF	98.8
9	CMF	96.3
10	CMC	97.5
11	Composite	99.5

3.10 STABILITY RESULTS:

3.10.1 Stability of the Capsules:

According to ICH guidelines, selected formulation by Roller compaction method (ZHC5) and by Fluidized bed processer method (ZHCF9) was stored at 40°C temperature and 75 % relative humidity (RH) for a period of 1 months to asset the stability of prepared formulation. Evaluation parameters do not show any major difference and all are in acceptable limits.

3.10.2 By Dry granulation method (Roller compaction):

3.10.2.1 Physical parameter:

Table No.23 Result of stability studies

Parameters	**Time (1 month)**
Weight variation(mg)	105.2
Locking Length	11.53
Disintegration time(sec)	6 min.18 sec

3.10.2.2 Chemical parameter:

Table No 24 Physical parameter of Capsules of stability batch by RC method

Sr. No	**Test**	**Specification**		**ZHC5**	
1	**Dissolution**	**Not less than 75.0% (Q) of the labeled amount of Ziprasidone is**	**Time interval**	**Initial**	**40°C/75 % RH, 6M**
			5	28	6

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		dissolved in 60 minutes.	10	60.2	30.8
			15	73.7	44.8
			20	81	53.1
			30	87.5	63.7
			45	92.3	69.9
			60	95	77.1
			90		
			Infinity	97.5	
			F1	2.18	
			F2	82.98	
2	**Assay**	**95.0 % to 105 5 %**		Not available	94.8
3	**Water content**	**NMT 8 %**		Not available	2.99
4	**Related substances**	**NMT 0.2 %**	Ziprasidone Impurity -C	Not available	BDL
		NMT 0.2 %	Ziprasidone Impurity -D	Not available	0.01
		NMT 0.2 %	Single unknown maximum impurity	Not available	0.023
		NMT 2.0 %	Total impurities	Not available	0.054

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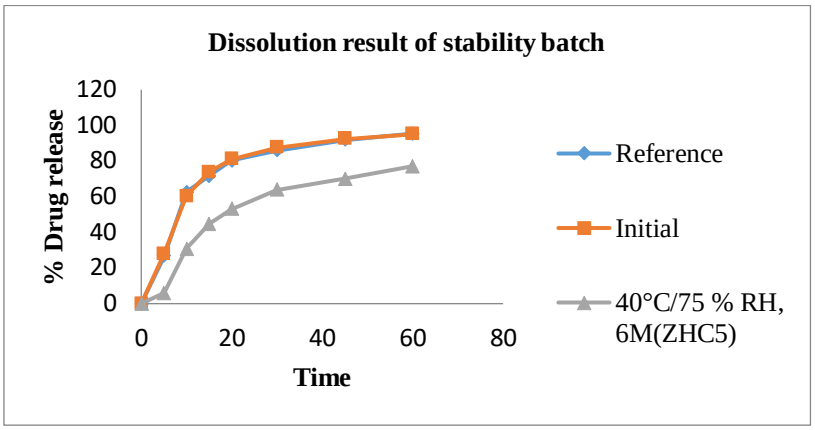

Fig. No. 15 Dissolution result of stability batch (by RC method)

4. DISCUSSION

The Identification test (Spectroscopy, Particle size distribution, XRD) all compared to vendor or reference Ziprasidone Hydrochloride it proved that material used for development is Ziprasidone Hydrochloride. Drug-Excipients studies showed that there is no interaction between drug & excipients. Because in physical observation there is no change in color in chemical observation impurities are within limit. The Formulation of Ziprasidone Hydrochloride Capsules was successfully developed and optimized for immediate drug release profile & assay. The Capsules were prepared by dry compression method (Roller compaction). Formula optimization carried out by 2^2 factorial design. The concentration Binding agent and Lubricating agent were important variables which shows effect on formulation. Process optimization carried out by 2^{3-1} fractional factorial design. Screen used, pre-lubrication and lubrication time are important variables which show effect on formulation. The evaluation results of optimized batch comply with USP criteria. Accelerated stability studies shows that formulation is stable for 1 month.

5. CONCLUSION

In conclusion, the formulation, evaluation, and optimization of Ziprasidone hydrochloride capsules involve a systematic process to ensure the drug's efficacy, safety, and patient compliance. Through rigorous formulation development, comprehensive evaluation techniques, and optimization strategies, a well-balanced and effective dosage form can be achieved. This approach not only enhances the pharmaceutical characteristics of the medication but also contributes to its therapeutic success, promoting better patient outcomes and overall pharmaceutical quality.

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MS. RAGINI BUNDELA*: *Associate Professor, College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP.*