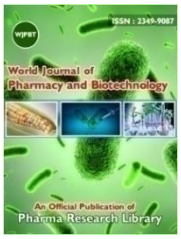

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Development, Optimization and Evaluation of Ziprasidone Hydrochloride Fast Dissolving Tablet by Solid Dispersion Method

S. Susmitha*[1], Zeenath Ruhy[2], P. Aravinda Reddy[3]
[1]Department of Pharmaceutics, Mother Teresa College of Pharmacy, NFC Nagar Ghatkesar, Telangana, India-501301.
[2]Associate Professor, Mother Teresa College of Pharmacy, NFC Nagar Ghatkesar, Telangana, India-501301.
[3]Principal and Professor, Mother Teresa College of Pharmacy, NFC Nagar Ghatkesar, Telangana, India-501301.

A B S T R A C T

This study aimed to develop mouth-disintegrating tablets of Flurbiprofen through a straightforward and scalable direct compression method, accompanied by a reliable UV-Visible spectrophotometric assay for drug analysis. The optimized UV method, performed in 0.1N HCl, identified a maximum absorbance at 257nm, enabling accurate quantification of Flurbiprofen within tablet formulations. Tablets were formulated using common super disintegrants sodium starch glycolate, crospovidone, and croscarmellose sodium and evaluated for critical quality characteristics such as hardness, friability, weight variation, and drug content, all of which met pharmacopeial standards. In vitro dissolution studies revealed rapid drug release across all batches, with the crospovidone based formulation demonstrating superior performance by releasing nearly 99% of the drug within 30 minutes. Comparative analysis confirmed that crospovidone facilitated faster dissolution compared to other super disintegrants under the test conditions. The study successfully achieved the goal of formulating efficient, patient-friendly Flurbiprofen mouth-disintegrating tablets with minimal excipients and a simple manufacturing approach, supported by a practical and robust analytical method for quality assurance.

Keywords: Flurbiprofen, mouth-disintegrating tablets, super disintegrants, UV-Visible spectrophotometry, drug dissolution, crospovidone, direct compression,

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Corresponding Author
S. Susmitha
Department of Pharmaceutics
Mother Teresa College of Pharmacy
NFC Nagar Ghatkesar, Telangana India- 501301.

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C O N T E N T S

1. Introduction

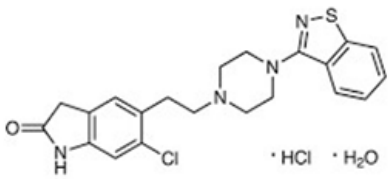

Fig.1: Ziprasidone Hydrochloride

Molecular Formula: $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$
Molecular Weight: 467.42 g/mol
IUPAC Name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one monohydrochloride monohydrate
Chem Spider ID: Not listed (for hydrochloride monohydrate form)
Density: Not readily available
Boiling Point: Not applicable (decomposes)
Vapour Pressure: Not volatile
Flash Point: Not applicable
Refractive Index: Not typically reported for solids

Polar Surface Area: ~75–90 Å² (estimated)
Log P (Octanol/Water): ~1.8 (moderate lipophilicity)
Generic Name: Ziprasidone Hydrochloride
Brand Names: Geodon (U.S.), Zeldox (international)
Drug Category : Atypical antipsychotic
Indications : Schizophrenia, bipolar mania, agitation in schizophrenia
Pharmacology: Antagonist at D_2, 5-HT_2A, 5-HT1D; agonist at 5-HT1A; inhibits serotonin & norepinephrine reuptake
Potency: High affinity for dopamine and serotonin receptors (Ki values in low nM)
Tolerability: Generally well-tolerated; sedation and QT prolongation are concerns
Contraindications: Known QT prolongation, recent MI, uncompensated heart failure
Adverse Effects: Somnolence, nausea, dizziness, extrapyramidal symptoms, rash
Availability: Oral capsules(20–80mg), injectable form (IM)

2. Materials and Methods

Table 1: List of Materials Used

S.No	Materials	Source
1	Ziprasidone HCl	Pharma Train, Hyd
2	Sodium starch glycolate	S.D. Fine Chemicals Limited, Mumbai
3	Crospovidone	Nihal Pharma, Hyd
4	Croscarmellose sodium	S.D. Fine Chemicals Limited, Mumbai
5	Mannitol	S.D. Fine Chemicals Limited, Mumbai
6	Lactose	S.D. Fine Chemicals Limited, Mumbai
7	Avicel PH102	S.D. Fine Chemicals Limited, Mumbai
8	Aspartame	S.D. Fine Chemicals Limited, Mumbai
9	Peppermint flavour	Nihal Pharma, Hyd
10	Magnesium sterate	S.D. Fine Chemicals Limited, Mumbai
11	Talc	S.D. Fine Chemicals Limited, Mumbai

Table 2: List of Equipment's used

S.No	Equipment	Model/ source
1	UV-spectrophotometer	Labindia Uv 3000+
2	Digital Balance	Scale-Tec
3	Digital pH meter	Systronic Electronics, Mumbai
4	Dissolution apparatus	Electrolab TDT-08L
5	Hot air oven	Tempo Instruments & Equipments, Mumbai
6	Hardness tester	Monsanto Hardness Tester
7	Friability test apparatus	Roche Friabilator Electrolab, Mumbai
8	Tablet punching machine	Cadmach, Ahmedabad

Analytical Method Development

- **Preparation of 0.1 N Hydrochloric Acid (pH 1.2):** 8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.
- **Determination of λ_{max} of Ziprasidone HCL in 0.1N HCL: Working standard**: 100mg of Ziprasidone HCL was weighed and dissolved in 10ml methanol and then make up to a volume of 100ml with 0.1N HCL it gives 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard solution 10ml was diluted to 100ml with 0.1N HCL it will give 100µg/ml concentrated solution.

Dilution 2:

From the dilution-1 10ml was diluted to 100ml with 0.1N HCL it will give 10µg/ml concentrated solution. This solution was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted. The corresponding wavelength having highest absorbance is noted as λ_{max}

II. Construction of calibration curve of Ziprasidone HCL in 0.1N HCL::

Working standard: 100mg of Ziprasidone HCL was weighed and dissolved in 10ml methanol and then make up to a volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard solution 10ml was diluted to 100ml with 0.1N HCL it will give 100µg/ml concentrated solution. From dilution 1, take 0.2, 0.4, 0.6, 0.8 and 1ml of solution and was diluted up to mark in 10ml volumetric flask to obtain 2,4,6,8 and 10 µg/ml concentrated solutions. This solutions absorbance was noted at $\lambda_{max=257}$

Preparation of Oral Disintegrating Tablets

Direct compression method:

Mouth disintegrating tablets of Ziprasidone HCL were prepared by direct compression method. All the ingredients were powdered separately and passed through # 40 mesh sieve separately. The drug and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and keptaside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and mixed for further two minutes and the tablets were compressed using 6 mm flat round punches to get tablets of 100 mg weight.

6. **In vitro Dissolution Study:**
7. 900 ml of 0.1N HCL was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37^0C±0.5^0C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 30mins at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium were analyzed spectrophotometrically at λ_{max} =257 nm using a UV-spectrophotometer (Lab India).

Assay Procedure:

Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of Ziprasidone HCL was transferred to a 100 ml volumetric flask and 10 ml methanol

is added. The drug is extracted in methanol by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with 0.1N HCL and the liquid is filtered. From prepared solution take 0.1ml soluion in 10ml volumetric flask and make up to mark with 0.1 N HCL. The Ziprasidone HCL content was determined by measuring the absorbance at 257 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations. Calculate the quantity in mg of drug in the portion taken by the formula

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

Release kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and it is practically evident in case of matrix system. As a model dependent approach, the dissolution data are fitted to three popular release models such as zero order, first order, diffusion equations which have been described in the literature. The order of drug release from matrix system was described by zero order kinetics or first order kinetics. The mechanism of drug release from matrix system was studied by Higuchi equation.

Zero order release: It defines a linear relationship between the fraction of drug release Q=KoT

Q=Fraction of drug release at time t.

A plot of fraction drug release against time will be linear if the release obeys zero order release kinetics.

First order release kinetics: Wagner assuming that the exposed surface area of the tablet decreased exponentially with time during dissolution process suggested that drug release from most slow-release tablets could be described adequately by apparent first order kinetics. The equation used is Log (1-Q) = -K1T

Thus a plot of logarithm of fraction of drug remained against time will be linear if the release obeys first order kinetics.

Fourier Transform – Spectroscopy: FT-IR spectra were recorded on samples prepared in potassium bromide disks using thermon electron FTIR. Samples were prepared in potassium bromide discs by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}. IR spectroscopy has been to quantify the interaction between drug and carrier FTIR spectra of pure drug and best formulation.

Table 3: Formulation of Mouth Disintegrating Tablets of Ziprasidone HCL

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ziprasidone HCL	10	10	10	10	10	10	10	10	10	10
SSG	20	40	60							
Crospovidone				20	40	60				60
CCS							20	40	60	
Mannitol	60	60	60	60	60	60	60	60	60	60
Lactose	-	-	-	-	-	-	-	-	-	67
MCC pH 102	71	69	67	71	69	67	71	69	67	-
Aspartame	5	5	5	5	5	5	5	5	5	5
Pipperment flavour	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	169	187	205	169	187	205	169	187	205	205

Table 4: Angle of Repose Limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair aid not needed	36–40
Passable may hang up	41–45
Poor must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 5: Compressibility Index Limits

Compressibility Index (%)	**Flow Character**	**Hausner's Ratio**
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 6: Dissolution Parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCL
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	2, 4, 6, 8, 10, 15, 20 and 30mins
Analytical method	Ultraviolet Visible Spectroscopy
λmax	257 nm

3. Results and Discussion

Construction of Standard Calibration Curve of Ziprasidone HCL in 0.1 N HCL: The absorbance of the solution was measured at 257nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

Table 7: Values of Ziprasidone HCL in 0.1 N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.141
4	0.26
6	0.372
8	0.507
10	0.64

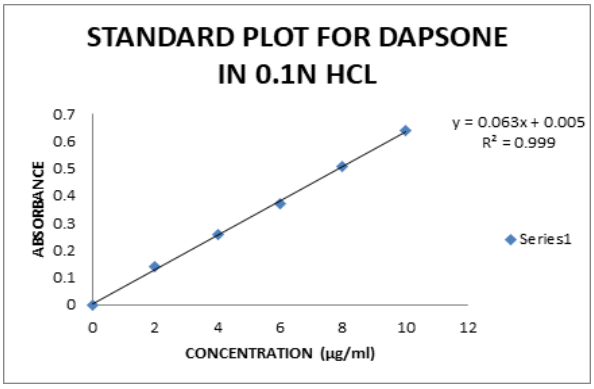

Fig.2: Standard Calibration Curve of Ziprasidone HCL in 0.1 N HCL

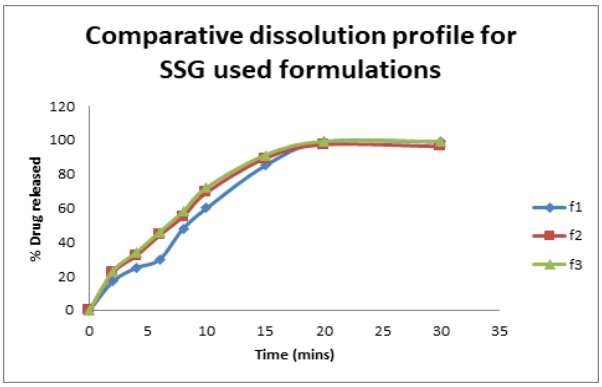

Fig.3: Comparative dissolution profiles for SSG used Formulations

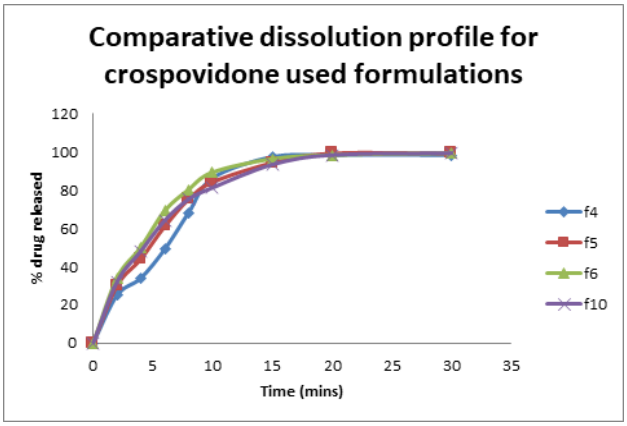

Fig.4: Comparative dissolution profiles for Crospovidone used Formulations

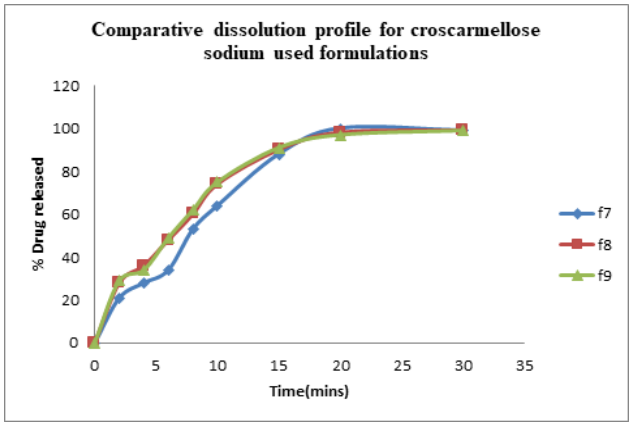

Fig.5: Comparative dissolution profiles for Croscarmellose sodium used Formulations

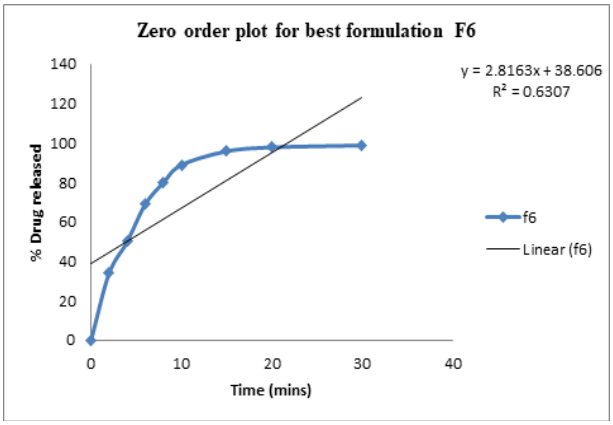

Fig.6: Zero order plot for best formulation F6

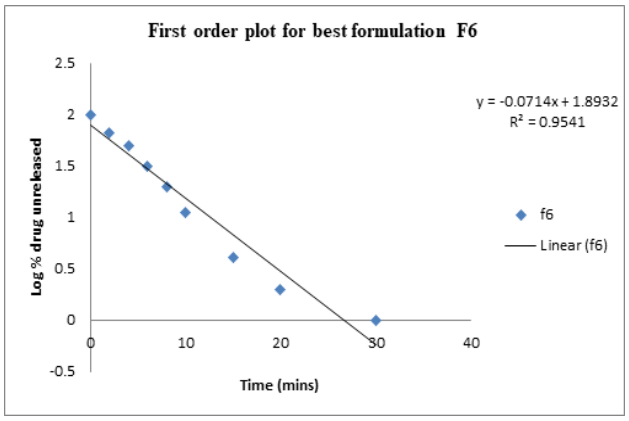

Fig.7: First order plot for best formulation F6

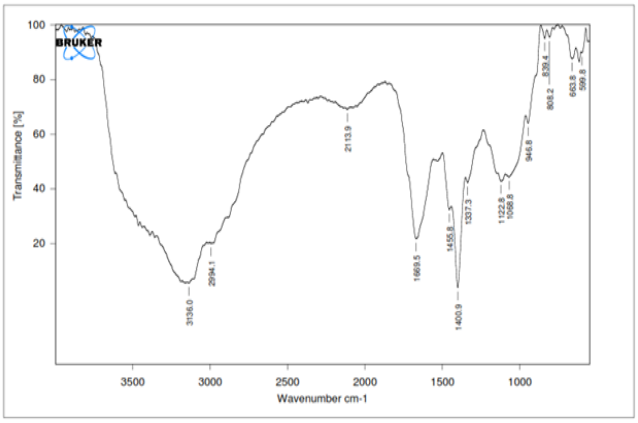

Fig.9: FTIR graph for Crospovidone

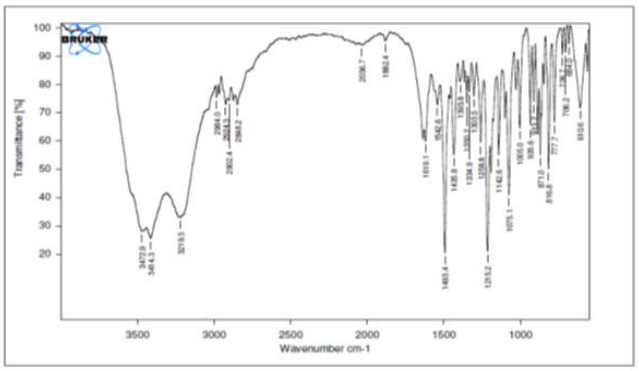

Fig.8: FTIR graph for Ziprasidone HCL

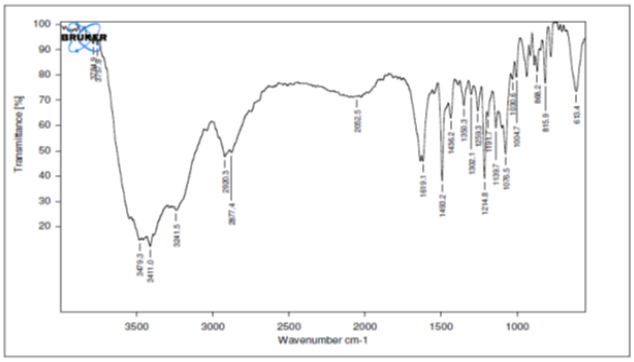

Fig.10: FTIR graph for Ziprasidone HCL best formulation

Table 8: Pre Compression Studies of Ziprasidone HCL Oral Disintegrating Tablets

Formulation code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.40	0.48	16	1.2	32.73
F2	0.39	0.48	18	1.23	34.96
F3	0.50	0.58	13	1.16	28.58
F4	0.44	0.50	12	1.1	27.92
F5	0.37	0.41	9.75	1.1	25.35
F6	0.37	0.41	9.75	1.1	33.14
F7	0.36	0.39	7.6	1.0	27.03
F8	0.41	0.45	8.8	1.0	31.85
F9	0.39	0.48	18	1.23	28.96
F10	0.41	0.45	8.8	1.0	27.85

Table 9: Post Compression Studies for Oral Disintegrating Tablets of Ziprasidone HCL

Batch	Hardness (kg/cm2)	Friability (%)	Drug Content (%)	Thickness (mm)	Disintegration Time (sec)	Wetting Time (sec)	In vitro dispersion time	Weight variation	Water absorption ratio
F1	3.1	0.45	99.12	2.5	30	45	29	pass	61.3
F2	2.9	0.62	100.73	2.8	25	42	34	pass	69.8
F3	3.3	0.71	99.74	2.6	20	35	25	pass	73.4
F4	2.5	0.32	98.98	2.5	31	31	32	pass	86.2
F5	2.8	0.51	99.67	2.6	27	36	31	pass	84.12
F6	2.8	0.52	99.83	2.8	25	43	33	pass	93.4
F7	2.9	0.38	101.32	2.8	31	41	36	pass	64.3
F8	3.2	0.48	100.87	2.5	26	36	33	pass	74.8

F9	3.5	0.63	99.74	2.7	24	48	39	pass	76.1
F10	3.0	0.54	99.86	2.6	32	39	28	pass	82.3

Table 10: Dissolution Data of Oral Disintegrating Tablets of Ziprasidone HCL

Time points (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	**0**	0	0	0	0
2	17	22	23	25	30	**34**	21	28	29	32
4	25	32	34	34	44	**50**	28	36	34	48
6	30	44	46	49	61	**69**	34	48	49	64
8	48	55	58	68	75	**80**	53	60	62	75
10	60	69	72	86	84	**89**	64	74	75	81
15	85	89	91	97	94	**96**	88	90	91	93
20	99	97	99	98	99	**98**	100	98	97	98
30	99	96	99	98	99	**99**	99	99	99	99

4. Conclusion

A UV-Visible spectrophotometric method was developed and validated for the quantification of Ziprasidone HCl using 0.1 N HCl as the solvent, with maximum absorbance observed at 257 nm. The constructed calibration curve demonstrated excellent linearity within the concentration range of 2 to 10 µg/ml, complying with Beer's law and confirming the method's accuracy and reliability for routine analysis. Pre-compression studies of the tablet blends showed consistent bulk and tapped densities, favorable Carr's index, Hausner ratio, and angle of repose values, which collectively indicated good flowability and compressibility, essential for efficient tablet manufacturing via direct compression. Post-compression evaluations revealed that all formulated tablets met pharmacopeial standards with regards to hardness, friability, drug content, thickness, and weight uniformity, ensuring the development of robust, uniform dosage forms. Rapid disintegration and wetting times were recorded, critical attributes for oral disintegrating tablets. In vitro dissolution testing showed efficient and consistent drug release from all batches, with the F6 formulation emerging as the best performer by releasing nearly 99% of the drug within 30 minutes. Drug release kinetics fitted well with zero-order and first-order models, indicating a controlled release mechanism. Additionally, FTIR spectroscopy confirmed the absence of any interaction between the drug and excipients, supporting the stability of the optimized formulation. Overall, the study successfully formulated Ziprasidone HCl oral disintegrating tablets with favorable mechanical properties, rapid onset of action, and validated analytical support, suggesting potential for enhanced therapeutic efficacy and patient adherence.

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