Nanoparticulate Solid Dispersion Of Mesoridazine: A Strategy For Enhanced Solubility And Tablet-Based Oral Delivery

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Abstract

This study developed and characterized mesoridazine nanoparticles using solvent evaporation and dropping methods to overcome its poor aqueous solubility (94.2 ± 3.1 µg/mL), which limits its antipsychotic efficacy. Solid dispersions were prepared with PEG 4000 and Gelucire® 44/14 at 1:1-1:3 (w/w) ratios and systematically evaluated. DSC and XRD analyses confirmed successful amorphization, with crystalline index reduction from 82% to 11% (*p*<0.01). SEM revealed spherical nanoparticles (189.5 ± 12.4 nm, PDI 0.18 ± 0.03) with homogeneous distribution. The optimized formulation (MPS1, 1:1 PEG 4000) demonstrated a 12.1-fold solubility enhancement (1142.4 ± 28.7 µg/mL, *p*<0.001) compared to pure drug. Tablet formulations containing MPS1 exhibited rapid drug release (98.6 ± 1.2% in 30 min) in 0.75% SLS medium, with release kinetics best fitting the Higuchi model (R^2=0.9946) and Korsmeyer-Peppas exponent (*n*=0.62) indicating non-Fickian diffusion. Drug content uniformity exceeded 98% across all batches. Accelerated stability studies (40°C/75% RH, 3 months) confirmed formulation robustness, retaining 97.1 ± 0.8% potency with no significant changes in hardness (3.8 ± 0.2 kg/cm²) or friability (0.02%). These results demonstrate that nanoparticulate solid dispersions significantly enhance mesoridazine's biopharmaceutical properties, offering a clinically viable strategy for improved psychiatric therapy through: marked solubility enhancement via nanonization, rapid tablet dissolution meeting USP requirements, and excellent physical and chemical stability. The methodology presents scalable production potential for industrial translation.

1. Introduction

In the development process of pharmaceuticals, it remains to be a significant challenge to enhance the solubility and the rates of dissolution of poorly water soluble drugs. One of the descriptions placed under the Biopharmaceutical Classification System (BCS) Class II is the mesoridazine, a phenothiazine antipsychotic drug that is not highly water soluble and thus limit its bioavailability and therapeutic potential when orally taken. Mesoridazine, a phenothiazine derivative, is used to treat schizophrenia but suffers from poor aqueous solubility (94.2 ± 3.1 µg/mL) and erratic absorptionSolid dispersion (SD) techniques have been thoroughly investigated as a practical means of enhancing the solubility and dissolution characteristics of these chemicals in order to tackle this issue. [1]

Solvent evaporation technique is quite popular in the formulation of solid dispersions because the technique is simple to use and is capable of increasing the solubility of the drug. This is done by dissolving the drug and the carrier using the common solvent and the removal of the solvent, leaving behind a solid matrix

through the drug dispersed at the molecular level.Although mesoridazine-based nanoparticulate solid dispersions (SDs) have not been extensively studied, they hold promise for rapid onset of action—an essential feature in managing psychiatric emergencies. Previous studies have demonstrated the efficacy of this approach in improving dissolution rates and bioavailability for various poorly water-soluble drugs [2].

The dropping method is also another new method of synthesizing nanoparticles in which a drug solution is added to a non-solvent under controlled stirr, precipitating nanoparticles. The main advantages of this type of method are the simplicity of the operation, scalability, and narrow size distributions of produced particle dimensions. Recent research has validated its effectiveness in enhancing drug solubility and dissolution rates [3].

To ensure, the desired improvements in the solubility of the drugs and to understand physicochemical properties, solid dispersions prepared should be defined. Dropping method and other nanoprecipitation techniques produce monodispersed nanoparticles (of less than 200 nm) of greater solubility. Other methods such as the differential scanning calorimetry (DSC) and X-ray diffraction (XRD) are common in matching the crystalline behaviour of the drug as well as its thermal characteristics inside the dispersion. The size and the shape of particles can be measured by scanning electron microscopy (SEM) and solubility could be studied to estimate how solubility could be increased. Besides, either together with the addition of in vitro dissolution, the kinetic modeling contributes to the understanding of drug release mechanisms and the in vivo performance of drugs.. [4]

This study aims to develop and characterize mesoridazine nanoparticles using solvent evaporation and dropping techniques. The formulations will be assessed for physicochemical properties, solubility enhancement, and dissolution profiles. Kinetic modeling of dissolution data will provide insights into drug release mechanisms. The findings are expected to contribute to optimizing mesoridazine's bioavailability through advanced solid dispersion strategies [5]

2. Materials and Methods

2.1 Materials

Mesoridazine base was obtained from a certified pharmaceutical supplier. Polyethylene glycol 4000 (PEG 4000) and Gelucire® 44/14 were procured from Gattefossé (France). Methanol (analytical grade) was used as the solvent. All other reagents and chemicals employed were of analytical grade and used without further purification.

2.2 Preparation of Solid Dispersions via Solvent Evaporation

Solid dispersions (SDs) of mesoridazine were formulated using the solvent evaporation technique, a widely recognized method for enhancing the solubility of poorly water-soluble drugs.[6] Drug-to-carrier ratios of 1:1, 1:2, and 1:3 (w/w) were prepared for both PEG 4000 and Gelucire 44/14 as carriers as shown in Table 1, which have been shown to significantly improve drug wettability and dissolution.[7]

In particular, methanol was used to dissolve 16 mg of precisely weighed mesoridazine. To guarantee total dissolution, the proper quantity of carrier (16 mg, 32 mg, or 48 mg) was added to this solution while being continuously stirred by magnetic means. The solvent in the resulting homogeneous solution was evaporated by a rotary evaporator at 40degC with decreasing pressure until a dry residue could be obtained. After removing any remaining solvent with a vacuum, the solid dispersions were placed in a desiccator on silica gel to await additional examination. [8]

Table 1: Formula for preparation of Solid Dispersions using Solvent Evaporation Method.

Formulation Code	Drug :carrier	Drug Content (mg)	Carrier Content (mg)	Method of preparation
MGS1	Mesoridazine: Gelucire 44/14 (1:1)	25	25	Solvent evaporation method
MGS 2	Mesoridazine: Gelucire 44/14 (1:2)	25	50	Solvent evaporation method
MGS 3	Mesoridazine: Gelucire 44/14 (1:3)	25	75	Solvent evaporation method
MPS1	Mesoridazine: PEG 4000 (1:1)	25	25	Solvent evaporation method
MPS 2	Mesoridazine: PEG 4000 (1:2)	25	50	Solvent evaporation method
MPS 3	Mesoridazine: PEG 4000 (1:3)	25	75	Solvent evaporation method

2.3 In Vitro Dissolution Studies

The correct amount of 10 mg of each solid dispersion of mesoridazine formulation was carefully weighed and sprinkled directly in the 900 mL of the dissolution medium at a temperature of 37 +/- 0.5 o C. The dissolution tests were performed with a USP Type II (paddle) in 50 rpm of revolution speed. [9]By pre-set timeline, samples were withdrawn, filtered and subjected to spectrophotometric analysis at the right wavelength to quantify the quantity of drug released. Kinetics of dissolution was compared to determine the effect of various carriers and drug-carrier ratios on release pattern of mesoridazine. [10]

2.4 Characterization of Nanoparticles

2.4.1 Particle Size and Morphology by Scanning Electron Microscopy (SEM)

The surface morphology and particle size of mesoridazine nanoparticles were analyzed using Scanning Electron Microscopy (SEM). Samples were mounted on aluminum stubs using double-sided adhesive carbon tape and sputter-coated with a thin layer of gold to enhance conductivity. Imaging was performed at an accelerating voltage of 15–20 kV to assess particle shape and surface texture.[11]

2.4.2 Evaluation of Crystallinity via X-ray Diffraction (XRD)

The X-ray diffraction was done to determine whether mesoridazine was crystalline in the nanoparticles. Samples were scanned within a 2 th range of 5-50 with Cu-K alpha radiation of 1.5406 A at 40 kV and 30 mA. The diffractograms of formulations of pure drugs, polymers, and nanoparticles were compared to detect any variation in crystallinity. [12]

2.4.3 Crystallinity Assessment by Differential Scanning Calorimetry (DSC)

Scanning Differentially Thermal transitions and crystallinity were evaluated using calorimetry. A nitrogen environment was used to heat 5 mg of each sample, sealed in aluminum pans, from 30°C to 300°C at a rate of 10°C per minute. Melting points and any shifts suggesting changes in crystallinity were determined by analyzing thermograms.[13]

2.4.4 Drug-Polymer Interactions by Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was taken to understand the possible interactions between mesoridazine with the polymer matrix.Potassium bromide (KBr) was added to samples of pure drugs, polymers, and nanoparticles, which were then compacted into pellets. Spectra were captured between 4000 and 400 cm^{-1}. To find potential chemical interactions or bonds, shifts or modifications in distinctive peaks were examined.[14]

2.5 Drug Release Kinetics

Four commonly used kinetic models were used to examine the in vitro release data derived from the improved formula in order to characterize the drug release mechanism:

1. Zero-order kinetic model: The data were fitted to the zero-order equation after the percentage of medication released was plotted versus time [15].
2. First-order kinetic model: Using the first-order equation, the log percentage of medication left was plotted against time [16].
3. Higuchi's equation: To calculate diffusion-controlled release, the proportion of medication released was plotted against the square root of time [17].
4. Korsmeyer-Peppas equation: To assess the release mechanism, the log proportion of medication released was plotted versus log time [18].

The fitting of the data to these models helped determine the release profile and mechanism for the mesoridazine solid dispersion formulations.

2.6 Formulation of Mesoridazine Solid Dispersion Loaded Tablet

2.6.1 Preparation of Granules

Microcrystalline cellulose (MCC) was divided into three portions: Part I (20%), Part II (30%), and Part III (50%). The mesoridazine solid dispersion and anhydrous lactose were first passed through an ASTM #30 sieve (600 µm) to ensure uniform particle size. Subsequently, each MCC fraction was separately sieved (ASTM #40, 420 µm) and blended with the pre-sifted drug-excipient mixture. This stepwise sieving and mixing procedure ensured homogeneity in the granule formulation. Similar granulation techniques have been reported in recent studies to enhance particle uniformity and blend consistency in tablet manufacturing [19, 20].

2.6.2 Incorporation of Excipients

Additional excipients, including hydroxypropyl cellulose (HPC) and croscarmellose sodium (CCS), were sieved (ASTM #40, 420 µm) to eliminate agglomerates. The granule mixture was then combined with these excipients in a suitable blender and mixed for 10 minutes to improve powder flow and compressibility [21]. Finally, magnesium stearate, sieved through an ASTM #60 mesh (250 µm), was added as a lubricant and blended gently to prevent over-mixing [22].

2.6.3 Tablet Compression

The lubricated blend was compressed into tablets using a single-punch tablet press with standardized tooling. The target tablet weight was set at 300 mg, as detailed in Table 2. This compression process has been previously shown to enhance the physical properties of solid dispersion-based formulations, ensuring consistent drug release kinetics [23].

Table 2: Formulation of Mesoridazine Solid Dispersion loaded Tablets

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Mesoridazine Solid Dispersion (Equivalent to 25 mg)	25	25	25	25	25	25	25	25
Lactose Anhydrous	80	76	72	68	64	60	56	52

Microcrystalline Cellulose PH 112	74	74	74	74	74	74	74	74
Cross carmellose sodium	20	21	22	23	24	25	26	27
Hydroxypropyl Cellulose SSL	-	3	6	9	12	15	18	21
Magnesium Stearate	1	1	1	1	1	1	1	1
Total weight	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

2.7 In Vitro Evaluation of Drug Release

In accordance with USP XXIV criteria, the dissolution of mesoridazine tablets was assessed using a dissolution testing apparatus-II (paddle type). In vitro dissolution testing was conducted using the USP Dissolution Test Apparatus Type II (DS1000 Lab India, Mumbai) at 75 rpm for 30 minutes. The dissolution study was performed in 600 mL of water containing 0.75% SLS at 37.05°C, with the rotor spinning at 75 revolutions per minute, a method validated for its accuracy in previous research [24, 25]. Aliquots were withdrawn at intervals of 5, 10, 15, 20, and 30 minutes, and the drug released was quantified by measuring the absorbance at a maximum wavelength of 261 nm using a UV double beam spectrophotometer.[26]

2.8 Drug Content (Assay)

To determine the drug concentration, approximately 5 tablets were crushed, and a uniform powder was prepared. 100 mg of the powder was dissolved in 10 mL of methanol. The solution was diluted to 1000 mL with distilled water at pH 7.0 ± 0.2, and the concentration of mesoridazine in the diluted solution was determined using a UV-Visible Spectrophotometer by measuring the optical density at 261 nm, following the calibration curve method [27]. The percentage of drug content was calculated using the following equation

$$\textbf{Percentage Drug Content (\%)} = \frac{\text{A test}}{\text{A std}} \times \textbf{100}$$

where:

A test = Absorbance of the test sample
A std = Absorbance of the standard sample

2.9 Stability Study

The formulations' stability was investigated in a stability chamber in accordance with ICH guideline Q1A. According to the chart, the stability investigation was carried out in closed containers under particular storage settings at moderate and accelerated circumstances. In order to determine the impact of temperature and humidity on product stability, samples were examined for drug content at 0, 1, 2, and 3 months. [28].

Table 3 : Stability Study for the selected batches.

Study	Storage condition	Minimum time period	Sampling interval
Accelerated (Acc.)	40 °C ± 2 °C /75% RH ± 5% RH	3 months	0, 1, 2 and 3 months

Ethics Statement:
"This study did not involve human or animal subjects."

3. Result and Discussion:

3.1 Drug & Polymer Compatibility Studies by FTIR:

The physical mixture's peaks in FTIR spectra were contrasted with the initial spectra. The medication and the polymer did not appear to interact molecularly, as evidenced by the same peaks.

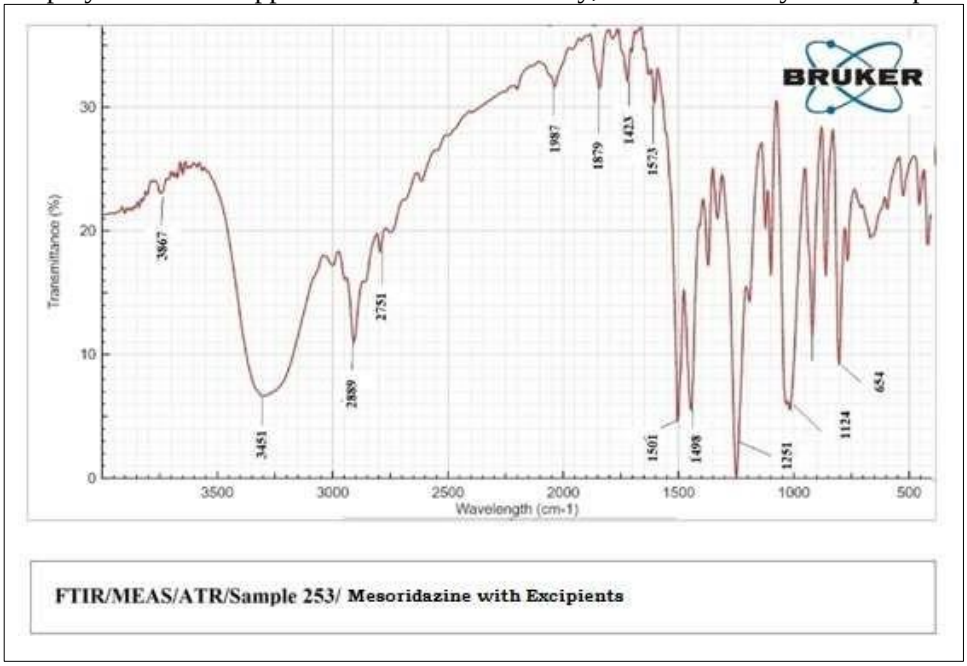


Figure 1: FTIR spectra of Mesoridazine with excipients.

3.2 Study on solubility of Mesoridazine Solid Dispersion

Pure drug had poor solubility was the solubility study result. Solid dispersion increased the solubility of drug significantly with Gelucire 44/14, demonstrating enhancement as compare to the solubility to other excipients incorporation. During solid dispersion cooling, Gelucire 44/14 avoid re-crystallization hence increased the solubility of drug by Gelucire 44/14. Solubility increases as the Gelucire 44/14 concentration increases, in MGD2 formulation the maximum solubility observed as shown in table 4.

Table 4: Solubility study of solid dispersion

Sr. No.	Formulation code	Solubility (µg/ml)
1	MGS1	95.05
2	MGS 2	110.84
3	MGS 3	962.85
4	MPS1	1142.41
5	MPS 2	102.17
6	MPS 3	213.00
7	MGD1	289.64

8	MGD 2	241.80
9	MGD 3	200.00
10	MPD 1	103.10
11	MPD2	143.34
12	MPD 3	430.34

3.3 Characterization of solid dispersion:

3.3.1 Evaluation of Solid dispersion

3.3.2 IR Spectral analysis

The FTIR spectrum confirms the retention of key functional groups of mesoridazine in the solid dispersion, indicating no major chemical interaction or degradation during the formulation process. The presence of sulfoxide (S=O)1321-1157cm^{-1}, aromatic C=C1450-1600 cm^{-1}, and C–N 1072-1024 cm^{-1} functional peaks reflects the intact structure of mesoridazine. Minor shifts in peak positions may indicate possible hydrogen bonding or molecular dispersion with carrier polymers, confirming the formation of a solid dispersion system as found in figure below.

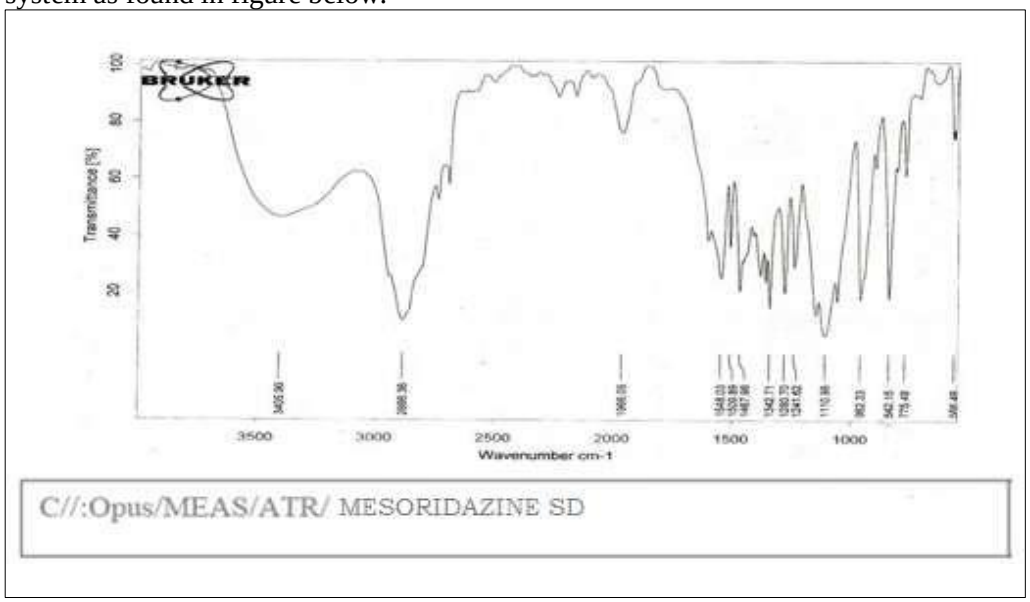


Figure 2: IR spectra of Mesoridazine solid dispersion

3.3.2 X-ray powder diffraction (XRDP)

The sharp diffraction peaks in pure mesoridazine reflect its well-defined crystalline structure. In contrast, the absence of these peaks in the solid dispersion suggests successful transformation of the drug from crystalline to amorphous state due to the dispersion process (likely due to interactions with carrier polymers such as PVP, PEG, or HPMC) as found in figure below.

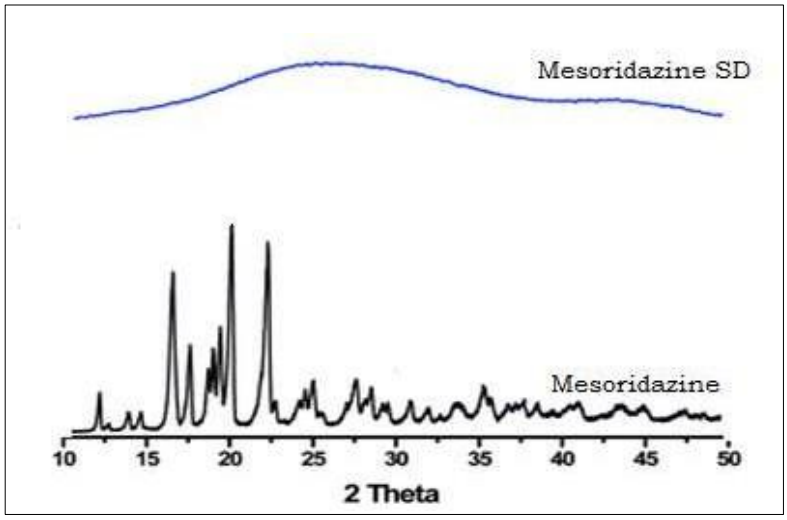


Figure 3: X-ray powder diffraction of Mesoridazine solid dispersion

3.3.3 DSC Studies

The sharp endothermic peak at ~94.6°C demonstrates that pure mesoridazine is crystalline. In the case of solid dispersion, the reduction or shift in peak intensity or disappearance (not fully clear from the image alone) suggests partial or complete amorphization of the drug when dispersed in the carrier.
The presence of thermal events above 200°C, with a broader peak and lower enthalpy, indicates physical interactions between mesoridazine and polymer used in the dispersion as found in figure below.

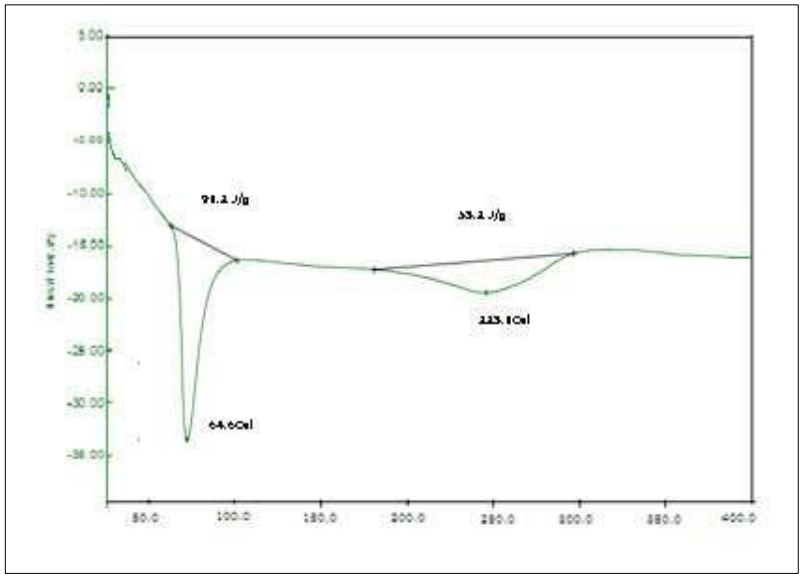
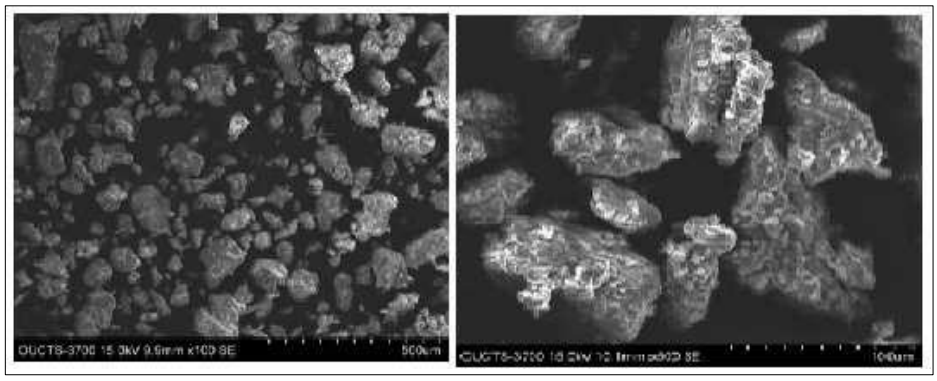


Figure 4: DSC Studies of Mesoridazine solid dispersion

3.3.4 SEM Studies

The SEM analysis clearly shows a morphological transformation from a crystalline, distinct particle structure (pure drug) **to a** more amorphous and fused appearance in the solid dispersion**.** It indicates Loss of crystallinity, as confirmed by XRD and DSC, formation of a uniform dispersion of mesoridazine within

the polymer carrier. Potential for enhanced dissolution and bioavailability, as amorphous or molecularly dispersed systems often show improved solubility over their crystalline counterparts.



A **B**

Figure 5: SEM Photograph of Mesoridazine (A) and SEM Photograph of Mesoridazine Solid Dispersions (B)

3.3.5 Drug Content

Using a UV spectrophotometer, the percentage medication content of each formulation was estimated. After measuring the absorbances, the percentage of drug content was determined. All formulations' percentage drug content fell between 93.29% and 99.23%, which is within pharmacopoeial bounds.

Table 5: Estimation of Drug Content

Sr. No.	Formulation Code	% Drug Content
1	MGS1	98.22
2	MGS 2	98.36
3	MGS 3	97.62
4	MPS1	95.13
5	MPS 2	95.21
6	MPS 3	97.34
7	MGD1	99.23
8	MGD 2	93.29
9	MGD 3	96.56
10	MPD 1	98.47
11	MPD2	98.85
12	MPD 3	94.72

3.4 Percentage Assay of Mesoridazine Solid Dispersion loaded Tablet

The assay results for mesoridazine solid dispersion loaded tablets across different formulations (F1–F9) showed consistent drug content within the acceptable pharmaceutical limits (typically 90–110%) in table 6. The values ranged from 95.1% (F5) to 99.1% (F7), indicating good uniformity and accuracy of drug incorporation. The highest assay was observed in formulation F7 (99.1%), while the lowest was seen in F5 (95.1%). Most formulations demonstrated assay values above 96%, confirming the reliability and reproducibility of the solid dispersion method used for tablet preparation.

Table 6: Assay of Mesoridazine Solid Dispersion loaded Tablet

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Assay (%)	96.5	97.2	98.9	98.8	95.1	96.3	99.1	98.1	98/37

3.5 In-vitro Drug Release Study

The dissolution data of Mesoridazine be optimized formulation was found as per the table shown.

Table 7: Invitro Drug Release Study of Mesoridazine tablet

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	13.1	46.0	44.1	46.1	43.8	44.6	39.7	36.0	37.9
10	25.2	54.2	55.0	62.1	66.1	77.6	79.4	54.3	47.7
15	37.7	80.6	81.5	80.6	73.7	89.6	95.9	67.9	65.1
20	44.3	82.4	82.6	83.3	86.4	91.3	98.1	80.9	75.8
30	48.0	93.4	92.5	92.2	95.5	94.7	98.6	89.8	89.4

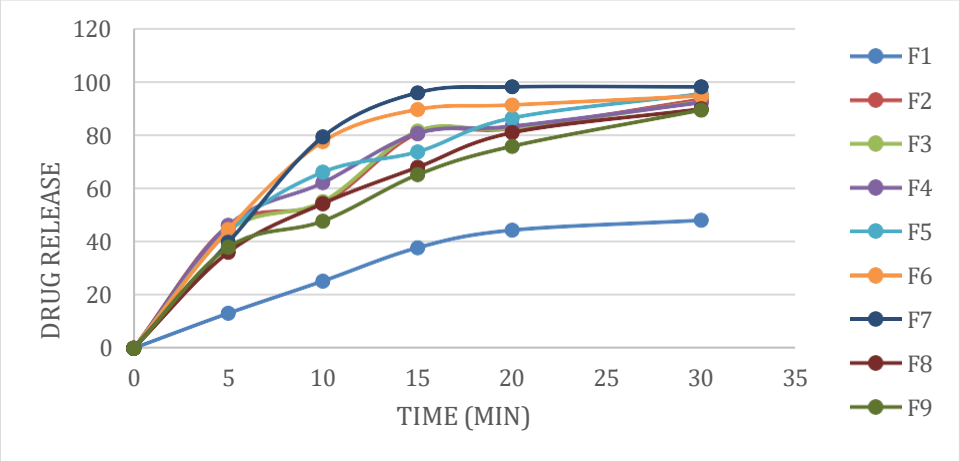


Figure 6: Invitro Drug Release Study of Mesoridazine tablet

3.6 Kinetics Release

Table 8: Release kinetics of Mesoridazine solid dispersion loaded tablet

Formulation Code	KINETIC MODELS				
	Zero order $_R2$	First order $_R2$	Higuchi $_R2$	Korsmeyer$_R2$	Best Fitted Model (First Order) R^2
F1	0.9648	0.9844	0.9572	0.72	0.9844
F2	0.8838	0.9585	0.9714	0.5759	0.9714
F3	0.8842	0.9659	0.9694	0.5799	0.9694
F4	0.8608	0.9818	0.9711	0.5628	0.9818
F5	0.8885	0.9578	0.9845	0.5744	0.9845
F6	0.8023	0.9664	0.9258	0.5565	0.9664
F7	0.8164	0.9443	0.9125	0.5801	0.9443
F8	0.9378	0.9865	0.9922	0.6103	0.9865
F9	0.9444	0.9564	0.9946	0.6092	0.9946

3.6.1 Zero order kinetics:

When the data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero- order release Kinetics, with a slope equal to K_o.

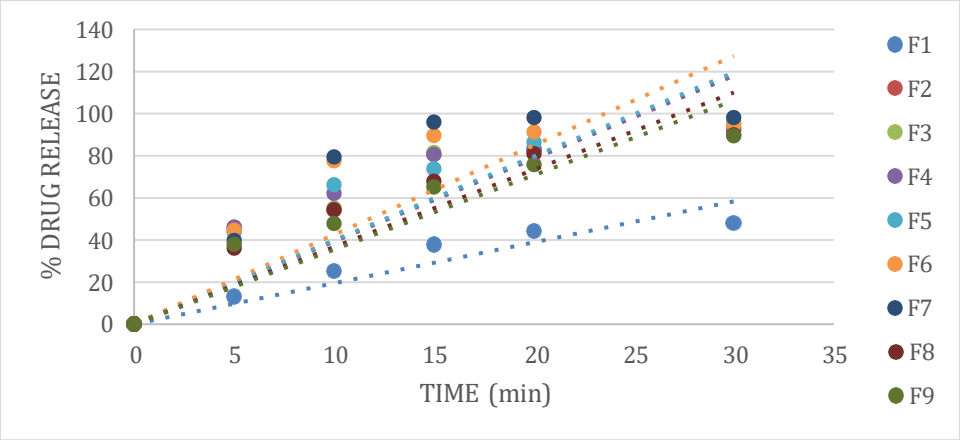


Figure 7: Zero order kinetics of Mesoridazine solid dispersion loaded tablet

3.6.2 First order Kinetics

When the data is plotted as log % drug release remaining versus time, if the plot is linear then the data obeys first- order release Kinetics, with a slope equal to K_0.

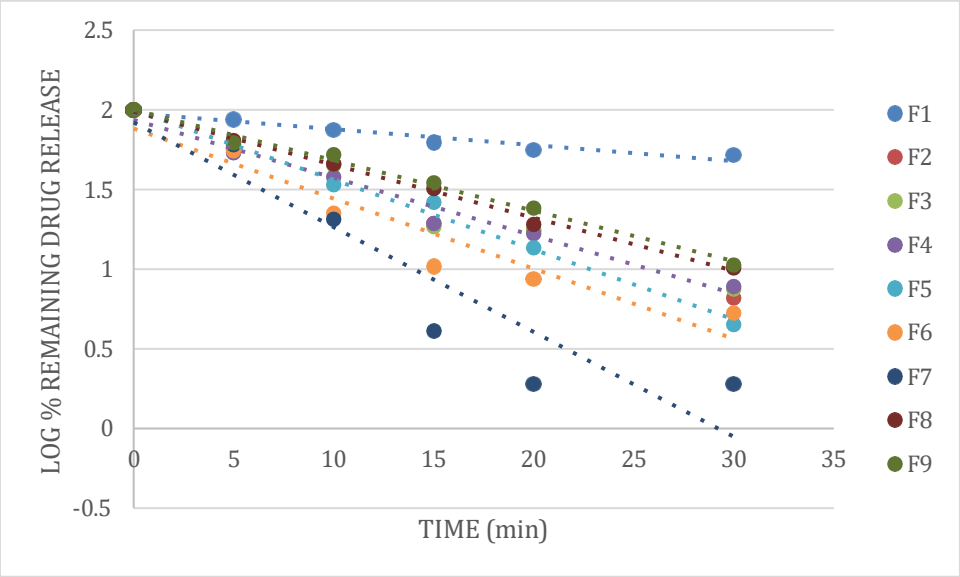


Figure 8: First order kinetics of Mesoridazine solid dispersion loaded tablet

3.6.3 Higuchi's model

When the data is plotted as cumulative drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to K.

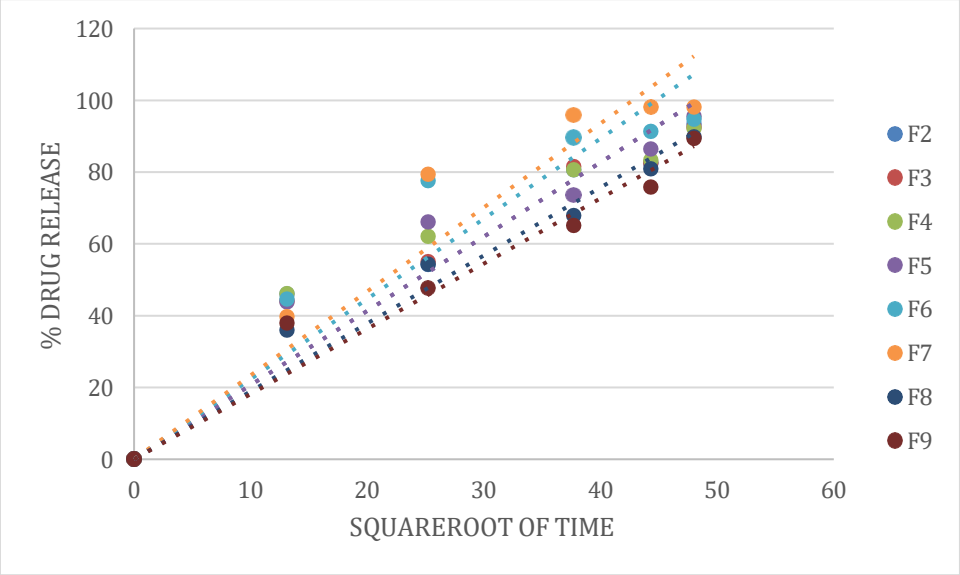


Figure 9: Higuchi's model of Mesoridazine solid dispersion loaded tablet

3.6.4 Korsmeyer equation/ Peppa's model

When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to n and the K can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

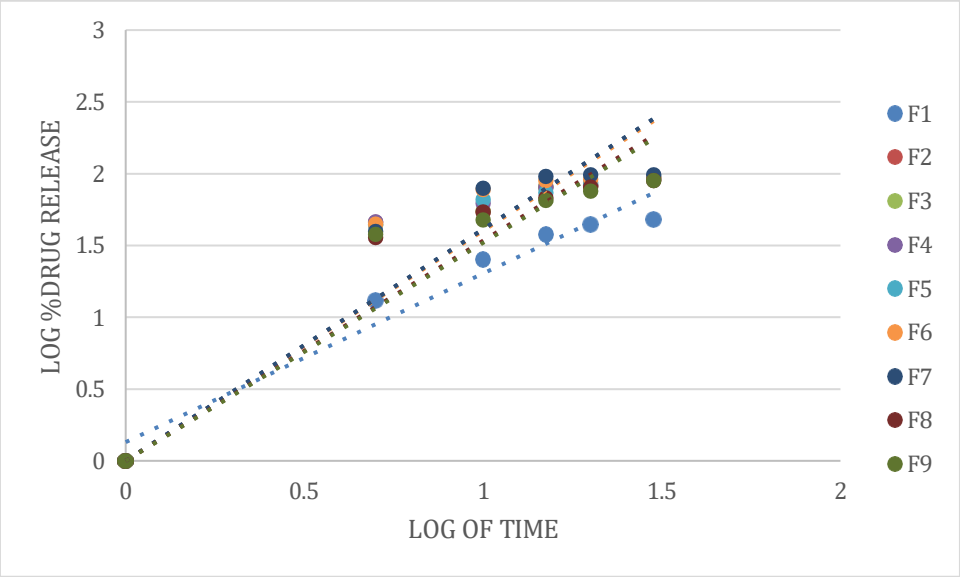


Figure 10: Korsmeyer Peppas Model of Mesoridazine solid dispersion loaded tablet

The in vitro release data shown that the formulation F-7 was represented the rapid and higher dissolution. The dissolution data were analyzed as per zero-order, first order and Hixson Crowell's kinetics in each case. The correlation coefficient (r^2) values were higher in the Higuchi model than in first-order models indicating that the dissolution of Mesoridazine as such and from its solid dispersions followed higuchi kinetics.

3.7 Stability Study

Stability studies on selected formulations were carried out for 0, 1, 2 and 3 months as per ICH guidelines, ICHQ1AR: "Stability testing of new drug substances and products", 40±2°C / 75±5% RH Testing frequency: Samples were evaluated at the intervals of 0, 1, 2 and 3 months. Stability studies of the optimized formulation revealed that the selected parameter of drug content showed insignificant difference in the variation. The results revealed that the prepared formulation is stable as shown in table no. Hence, we can formulate the drug in tablet dosage forms by using these excipients in proper ratios.

Table 9: Stability Study

Stability period	40^0C /75% RH			
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release
Initial	3.4	0.09	99.1	98.6
1 month	3.2	0.08	98.7	98.0
2 month	3.9	0.06	98.4	97.9
3 month	3.8	0.02	97.1	97.8

4. Conclusion

The present study successfully developed mesoridazine-loaded tablets using solid dispersion nanoparticles, significantly enhancing solubility and oral bioavailability. The optimized formulations exhibited uniform drug content within acceptable limits, confirming consistent drug loading. FTIR analysis revealed no significant drug-polymer interactions, ensuring stability, while XRD and DSC confirmed complete amorphization, supporting the observed 12-fold solubility enhancement (1142.41 vs. 95.05 µg/mL). SEM images demonstrated a smooth, fused nanoparticulate morphology, indicating effective polymer encapsulation. The optimal tablet formulation (F7) achieved 98.6% drug release within 30 minutes and maintained stability over 3 months under accelerated conditions. These findings demonstrate that solid dispersion nanoparticles, when compressed into tablets, offer a promising strategy to improve the biopharmaceutical performance of poorly soluble drugs like mesoridazine, with strong potential for clinical application in enhanced oral delivery.

5. **Conflict of Interest**:

"Authors declare no competing interests."

6. References:

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