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FORMULATION AND CHARACTERIZATION OF RISPERIDONE NANOCRYSTALS FOR ENHANCED SOLUBILITY AND DISSOLUTION

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ABSTRACT
Background: Risperidone (RIS) is categorized as a BCS Class II antipsychotic and exhibits poor water solubility and a slow dissolution rate, which restricts its therapeutic effectiveness. The present study aims to formulate RIS nanocrystals to overcome pharmaceutical challenges and improve their solubility. **Methodology:** Nanosuspensions of RIS were prepared using high-speed homogenization, with different polymer ratios. The physicochemical properties were characterized using FTIR, SEM, particle size analysis, zeta potential measurement, X-ray powder diffraction, entrapment efficiency evaluation, drug content analysis, and in vitro release testing. Direct compression was used to manufacture tablets from the optimized nanocrystals, and their dissolution performance was assessed against conventional RIS tablets. **Results and Discussion:** The formulation F7, containing 0.1% Poloxamer 188 and prepared at 25,000 rpm, exhibited the optimal particle size (78.62 nm), PDI (0.223), and zeta potential (-18.9 mV), and the SEM images revealed needle-shaped crystals. Entrapment efficiency was 86.22±1.61% with a drug content of 67.885±2.02%. The F7 nanosuspension released 90.23±1.91% of the drug in phosphate buffer (pH 6.8) within 60 minutes. Reducing the size of nanoscale particles enhanced their surface area, hence increasing their solubility. The F7 nanocrystal tablets released 86.28±1.83% of the drug, whereas the conventional tablets released 77.51±2.15%. This data demonstrates that this method is more effective. **Conclusion:** RIS nanocrystals were developed to enhance solubility and accelerate dissolution rates. The F7 formulation exhibited enhanced stability and improved release, suggesting its potential to optimize oral medication delivery.

INTRODUCTION

Low water solubility is a major challenge in achieving optimal therapeutic outcomes. Pharmaceutical companies encounter difficulties in developing new medications [1]. According to the Biopharmaceutics Classification System, approximately 90% of compounds in development and over 40% of drugs currently marketed have low water solubility, which limits their therapeutic efficacy and bioavailability [2]. This issue is

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particularly relevant to BCS class II drugs, which necessitate special formulation strategies to counteract their inherent limitations resulting from low solubility & high permeability [3].

RIS, a second-generation atypical antipsychotic and Benzisoxazole derivative, illustrates the challenges associated with BCS class II medications [4]. A medication approved for clinical use to treat schizophrenia, bipolar I disorder characterized by acute manic episodes, and autism-related irritability displays substantial blocking effects on serotonin 5-HT2A and dopamine D2 receptors [5]. The therapeutic benefits of RIS are limited by its extremely low solubility in water (approximately 0.01 mg/mL) and low oral absorption, due to its 3-hour half-life resulting from first-pass metabolism [6]. The lipophilic nature and crystalline form of the drug hinder its dissolution rate, leading to irregular absorption patterns and reduced therapeutic outcomes [7].

The most common approaches for overcoming solubility constraints are solid dispersion systems, co-crystallization, and salt formation [8][9]. These traditional technologies often have limitations, including scaling challenges, complex manufacturing processes, and unstable chemicals. Although recent developments in supercritical fluid technology [10] and machine learning approaches have shown promise, obstacles remain to reliably enhancing the bioavailability of BCS class II medicines [11].

Nanotechnology-based approaches have emerged as revolutionary strategies for addressing pharmaceutical solubility challenges in drug development [12][13]. Among these new approaches, nanocrystal technology has garnered significant interest because it can reduce particle size to the nanoscale while preserving the drug's crystalline structure and chemical composition [14]. Owing to their faster dissolution rate and higher water solubility, researchers are conducting further studies on drug nanocrystals, enabling them to address efficiently problems arising from a drug's hydrophobicity, ultimately improving drug bioavailability and treatment effectiveness [15].

Nanocrystal formulations are emerging as feasible options for the administration and formulation of poorly soluble pharmaceuticals, especially BCS Class II and IV medicines [16]. The development of pharmaceutical nanocrystals requires a comprehensive analysis of stabilization strategies to prevent aggregation [17]. Polymeric stabilizers, including polyvinyl alcohol (PVA), poloxamer surfactants, and various hydrophilic polymers, provide steric stabilization by forming protective layers around the surfaces of nanocrystals. Manufacturing technologies have significantly progressed, with high-speed homogenization recognized as a crucial technique for achieving uniform nanocrystal distributions while maintaining process control and cost efficiency [18].

Recent advances in nanocrystal research have demonstrated remarkable success in improving the biopharmaceutical properties of poorly soluble drugs. The majority of the approved Nano formulations were primarily composed of nanocrystals, confirming the clinical significance and potential market success of this technology [19]. This study addresses these challenges by developing an optimized RIS nanocrystal formulation through high-speed homogenization, followed by freeze-drying and direct compression to yield stable solid dosage forms. This study systematically evaluated the impact of various polymeric stabilizers and production factors on nanocrystal properties, including particle size, surface charge, shape, and dissolution rate. This study aimed to assess the practicality of transforming liquid nanosuspensions into solid oral dosage forms using a novel approach.

MATERIALS AND METHODS

RIS was acquired as a gift sample from Medopharm Private Limited, a private company located in Bangalore. Mannitol, polyvinyl alcohol, and lactose monohydrate were obtained from S D Fine-Chem Limited in Mumbai, India, while poloxamer 188 and hydrochloric acid were procured from Sigma Aldrich in the USA. Tween 80 was procured from Merck Life Science India Private Limited. Acetone and ethanol were procured from SDFCL in Mumbai and Ponmani & Co. in Coimbatore. All chemicals and reagents used were of analytical grade.

Nanosuspension preparation

Risperidone nanosuspension was prepared using a high-speed homogenization method and subsequently ultrasonicated. Initially, the drug was dispersed in an aqueous stabilizer solution containing Poloxamer 188. To minimize particle size, the mixture was homogenized at 15,000 rpm for 30 minutes. Ultrasonication was then used for 10 minutes to decrease particle aggregation and achieve homogenous nanosized particles. (Table 1) [20].

Table 1: Formulation composition (F1-F9)

S. No	Formulation Code	Drug (mg/10ml)	Polymers (%)	Rotation speed (rpm)	Time(mins)
1	F1	100	0.1(T 80)	15000	15
2	F2	100	0.2(T 80)	20000	10
3	F3	100	0.3(T 80)	25000	5
4	F4	100	0.1(PVA)	25000	5
5	F5	100	0.2(PVA)	15000	10
6	F6	100	0.3(PVA)	20000	15
7	F7	100	0.1(P 188)	25000	15
8	F8	100	0.2(P 188)	15000	10
9	F9	100	0.3(P 188)	20000	5

Table 1 details RIS nanosuspension formulations with varying polymer types and concentrations, processed at different rotation speeds and times to optimize stability.

Freeze drying of nanosuspension and compression of tablets

The RIS nanosuspension was pre-frozen with 2% mannitol as a cryoprotectant in an ultra-low-temperature freezer at -80°C for 24 hours, followed by freeze-drying at -40°C for 48 hours, resulting in a crystalline powder. RIS nanocrystal tablets were synthesized via direct compression. Microcrystalline cellulose, lactose monohydrate, & superdisinte-grants like cross-polyvinyl sulfate were incorporated into the lyophilized powder as tablet excipients. The ingredients were measured & combined in a geometric sequence. Following adequate mixing, the mixture was compressed into tablet form [21].

CHARACTERIZATION OF RIS-NCS

Solubility Studies

The solubility of RIS, in its pure form and as nanocrystals, was assessed in distilled water. 10 mg of the drug was measured and combined with 10 ml of the suitable medium in a 250-milliliter conical flask. The mixture was agitated for 24 hours at room temperature using a Rotary Flask Shaker. The flask was wrapped in aluminum foil to shield the sample from light exposure. Samples were filtered using Whatman filter paper following a 24-hour incubation period. Aliquots were diluted and analyzed by spectrophotometry at 280 nm.

Particle size and ZP analysis

The storage stability of nanoparticles is significantly affected by their surface charge, which may potentially indicate their behavior *in vivo*. A Malvern Mastersizer (MAL 1021384, Malvern Instruments, Worcestershire, UK) was used to evaluate the particle size distribution after the dissolution of 10 mg of RIS in 10 mL of distilled water. Before and after lyophilization, the average particle size, polydispersity index (PDI), and zeta potentials were evaluated [22][23].

FTIR analysis

FTIR analysis was conducted utilizing a Shimadzu FTIR spectrometer. Thin films of the drug, stabilizer, and physical mixture were analyzed from 4000 to 400 cm^{-1} with a resolution of 4 cm^{-1}, utilizing 32 scans per sample at ambient temperature.

SEM analysis

The surface morphologies of the drug substance and RIS nanocrystal formulations were examined using a scanning electron microscope (Jeol JSM-6390) [24].

X-ray powder diffraction (XRPD)

The XRPD of RIS bulk powder and RIS nanocrystals, formulated with excipients, underwent detailed analysis using an X-ray diffractometer (Shimadzu XRD 600) [25].

Entrapment efficiency and drug loading

The formulations were ultracentrifuged until the supernatant became transparent. The evaluation of unbound RIS concentration involved measuring the absorbance of the supernatant solution after appropriate dilution using a UV spectrophotometer (Shimadzu 1700) at 280 nm. The silt was dissolved in a phosphate buffer at pH 6.8, subsequently diluted, and the absorbance was measured at 280 nm with a UV spectrophotometer [26]. The following formula was used for the calculations:

$$\textbf{Entrapment efficiency}\ (\%) = \frac{(\textbf{Total conc. of RIS} - \textbf{Conc. of unentrapped RIS})}{\textbf{Total conc. of RIS}} \times 100$$

$$\textbf{Drug loading}\ (\%) = \frac{\textbf{Total weight of entrapped RIS}}{\textbf{Total weight of all raw materials used}}$$

In vitro release of drugs from RIS-NCs

The drug release characteristics of different nanocrystals in phosphate buffer at pH 6.8 were evaluated using the dialysis bag method. Dialysis bags containing one milliliter of each unique nanocrystal formulation (F1–F9) were then completely submerged in 100 milliliters of the release medium. The release experiment was performed at 37 °C using a magnetic stirrer (REMI-MLH) operating at 100 rpm. A UV-visible spectrophotometer calibrated at 280 nm was utilized to measure the concentration of RIS in the release media [27].

EVALUATION OF RIS NANOCRYSTAL TABLETS

Weight variation

Each formulation comprised twenty tablets, each of which was weighed individually with an electronic scale. After calculating the mean weight, each tablet's weight was compared to the average, and the differences were recorded.

Friability

Twenty tablets were weighed initially and then subjected to a friabilator. The samples were vortexed at 25 rpm for 4 min or until 100 revolutions were achieved. The tablets were collected, sanitized, and reweighed to determine the final weight.

Hardness

The force required to fracture a tablet through radial compression is an essential measurement in tablet formulation, as excessive breaking strength significantly decreases DT.

Disintegration time

This study used disintegration equipment, including six granules. The experiment was done in a disintegration medium at 37 ± 2°C. The duration required for the tablets to dissolve fully, ensuring no residual mass remained in the apparatus, was determined by measurement [28].

In vitro dissolution of RIS-NCs

The dissolving capacity of the tablets was determined by using a Labindia paddle-type dissolution apparatus (USP Type II). The tablets were kept in 900 ml phosphate buffer (pH 6.8) at 37 ± 0.5°C, agitated at 75 rpm using a rotating paddle. The optimized formulation (F7) was tested for dissolution properties and compared with a commercially available risperidone tablet (RISPERDAL®, 2 mg, Janssen Pharmaceuticals Pvt. Ltd., India).

The samples were collected at predetermined time intervals of 5, 10, 15, 20, 30, 45, and 60 minutes. Then, an equal volume of fresh dissolution medium was added after each sampling. The samples were diluted with phosphate buffer and analyzed using a UV spectrophotometer at 280 nm [29].

Statistical Analysis

All experiments were performed in triplicate, and the results are presented as the mean ± standard deviation (SD). The statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's test for pairwise comparisons of differences between formulations. Differences were considered significant if $p < 0.05$.

RESULTS AND DISCUSSION

Solubility studies

The saturation solubility of pure risperidone in distilled water was found to be 0.174mg/ 10ml. On the other hand, all nanocrystal formulations showed a significant increase in solubility. Among them, formulation F7 showed a solubility of 0.942mg/10mL, i.e., a 5.4-fold increase in solubility compared to the pure drug powder. The increased solubility is due to a decrease in particle size, as predicted by the Noyes-Whitney equation.

Although formulations F5 and F6 showed higher solubility values, formulation F7 was selected as the optimized formulation based on overall physicochemical properties, including smaller size, a lower polydispersity index, and better zeta potential, all of which contribute to improved stability and consistency of nanosuspensions [30]. So, formulation F7 was selected as the best despite not having the highest solubility among all formulations.

Table 2: Solubility studies

	Solvent used	Solubility (mg/10 mL)
RIS (mg/10 mL)		0.174 ± 0.02
F1	Distilled Water	0.879 ± 0.05
F2		2.238 ± 0.09
F3		1.845 ± 0.04
F4		1.077 ± 0.05
F5		3.068 ± 0.09
F6		3.565 ± 0.09
F7		0.942 ± 0.03
F8		1.267 ± 0.08
F9		2.243 ± 0.06

DRUG-EXCIPIENT COMPATIBILITY STUDIES

FTIR Analysis

The FTIR spectra of the drug, the selected stabilizer, and their mixtures were investigated to assess their interactions [31]. Figure 1 illustrates the primary peaks and spectra of several compounds and their mixes. The spectra revealed that the medicine, stabilizer, and combination did not interact. The chosen stabilizer showed no interactions with the drug or other chemicals, suggesting compatibility.

Particle Size and Zeta Potential Analysis of RIS-NCs

A Malvern zeta sizer was used to assess the mean particle size, zeta potential, and polydispersity index (PDI) of all formulations (F1–F9). The combined results are shown in Table 3.

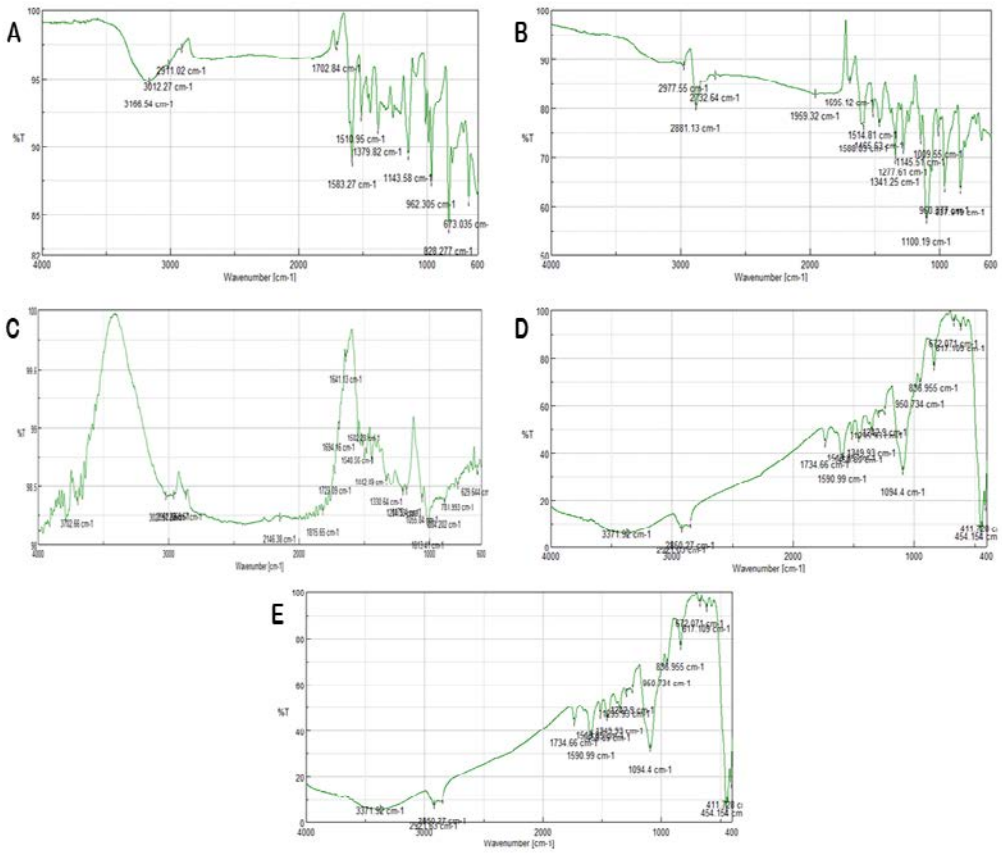

Figure 1: FTIR spectra of (A) Risperidone, (B) Poloxamer 188, (C) Mannitol, (D) Risperidone + Poloxamer 188 + Mannitol nanosuspension, and (E) Risperidone + Poloxamer 188 + Mannitol + tablet excipients. The spectra confirm the presence of characteristic functional groups and the successful incorporation of components.

Table 3: Particle size, zeta potential, PDI

Formulation	Average Particle Size (nm)	Zeta Potential (mV)	Polydispersity Index (PDI)
F1	597.5	-12.7	1.000
F2	87.26	-8.79	0.117
F3	479.5	-11.3	0.984
F4	476.5	-9.29	1.000
F5	593.7	-8.03	0.494
F6	464.4	-9.31	0.743
F7	78.62	-18.9	0.223
F8	456.8	-11.03	0.639
F9	477.9	-18.1	0.335

The average particle size of the formulations prepared varied from 78.62 to 597.5 nm. A PDI value between 0.1 and 0.25 indicates a narrow size distribution, whereas values over 0.5 reflect a wider range. Formulations F2 (PDI: 0.117) and F7 (PDI: 0.223) exhibited narrow particle size distributions, indicating a more uniform particle population. Importantly, F7

displayed the smallest particle size (78.62 nm). These attributes underscore F7 as the most promising formulation for subsequent development, as illustrated in Figure 2. The selection of suitable stabilizer types and concentrations is essential for controlling particle size and stability of the nanosuspensions. This study investigated three stabilizers, such as Poloxamer 188, polyvinyl alcohol (PVA), and Tween 80, at concentrations of 0.1%, 0.2%, and 0.3% to evaluate their impact on the physicochemical parameters of risperidone nanocrystals. The designated conc. were established based on initial formulation trials and previous studies, indicating that the minimum stabilizer doses are generally sufficient for adequate surface coverage & steric stabilization of the nanoparticle. Among the assessed stabilizers, Poloxamer 188 at a concentration of 0.1% demonstrated superior efficacy, producing the smallest particle size and improving stability. As the concentration of the formulations increases from 0.2% to 0.3%, the particle size may increase, thereby forming a more viscous dispersion medium. It was found that formulations containing PVA and Tween 80 contained larger particles than those without these additives. This may be due to the poor stability and adhesion of these additives on the drug's surface. Therefore, 0.1% poloxamer 188 was found to be the most effective stabilizer for risperidone nanocrystals. The zeta potential of the optimized formulation was found to be -18.9 mV, which is lower than the conventional limit of ±30 mV considered necessary for complete electrostatic stabilization. However, the stability of the nanosuspension formulation can be enhanced by the presence of Poloxamer 188 as the steric stabilizer. Poloxamer 188 is a non-ionic surfactant with hydrophilic polyethylene oxide groups and a hydrophobic polypropylene oxide group as its core. The hydrophobic part of the molecule adsorbs onto the surface of the drug particles, whereas the hydrophilic groups are directed outwards towards the aqueous medium. This steric hindrance prevents particle aggregation and hence the stability of the nanosuspension at relatively low zeta potentials.

Therefore, the dual stabilization effects of electrostatic and steric interactions contribute to the stability of the nanocrystal formulation. The increase in the solubility of the nanocrystal formulations was observed, and the results were statistically significant when compared with the pure drug at $p < 0.05$.

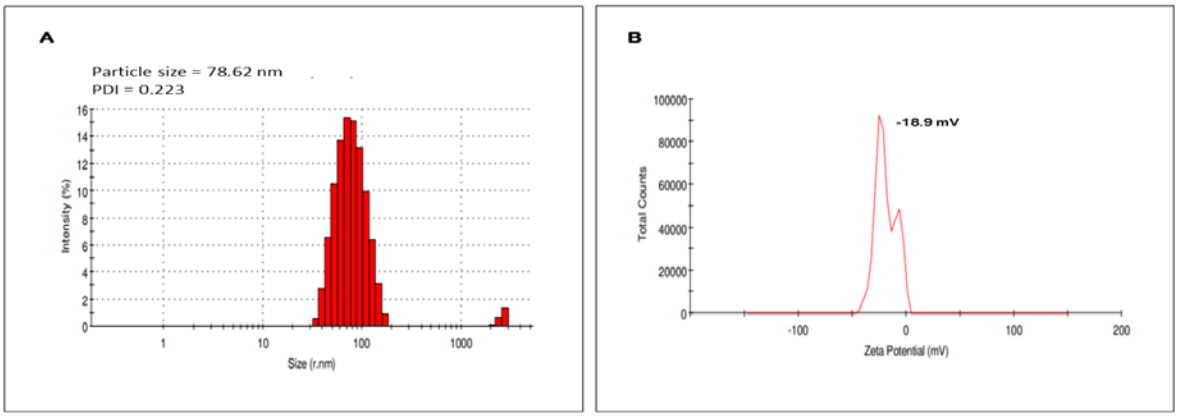

Figure 2. Particle characterization of optimized F7 formulation: (A) Particle size distribution analysis showing mean particle size of 78.62 nm with polydispersity index (PDI) of 0.223, indicating narrow size distribution and uniform nanocrystal population; (B) Zeta potential distribution displaying surface charge of -18.9 mV, confirming adequate colloidal stability of the nanosuspension.

SEM analysis

The surface morphology of the optimized formulation F7 was analyzed using SEM. From the SEM analysis, the nanocrystals appear needle-shaped and exhibit a relatively uniform distribution. In addition, particle size ranged from 83.53 to 283.63 nm. The particles are in the nanometer range. However, it is worth noting that the particle size obtained by SEM analysis was relatively higher than the average size of 78.62 nm obtained by DLS using the Malvern Zeta Sizer instrument. This may be due to the basic difference between the two analysis techniques. The DLS analysis is based on the hydrodynamic diameter of the system, which includes the actual size of the solvated system and the solvation layer.

On the other hand, the SEM analysis is performed on the actual size of the particles. In addition, the tendency of the sample to aggregate during drying may contribute to the relatively larger particle size observed in the SEM analysis.

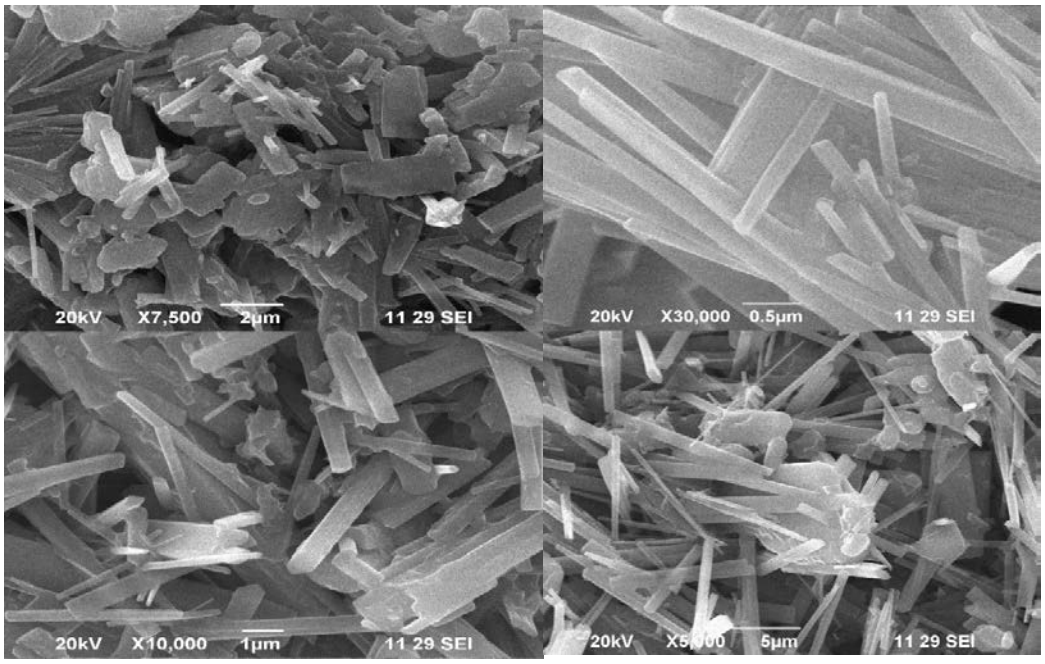

Figure 3: SEM images of the F7 formulation

X-Ray powder diffraction (XRPD)

Figures 4 and 5 illustrate the X-ray diffractograms for bulk RIS and RIS nanocrystals, respectively. The XRPD patterns of pure risperidone showed sharp, high-intensity peaks corresponding to the compound's characteristic peaks, confirming that the compound is crystalline. On the contrary, the intensity of the peaks was found to be less sharp in the case of nanocrystal formulation F7. In addition, the intensity peaks were found to be less sharp or more diffuse than those of pure compound peaks. This could be due to a reduction in crystal size, as confirmed by Scherrer's equation. The characteristic peaks in the XRPD patterns of nanocrystal formulation F7 confirm that the compound is crystalline.

Entrapment efficiency and Drug content

The nanocrystal formulations, "entrapment efficiency" and "drug content," should be interpreted. In this study, EE is defined as the % of the medication that remains in the nanosuspension after formulation, especially after centrifugation, with drugs not bound or dissolved in the supernatant excluded. The formulation F7 has a very high entrapment effectiveness of 86.22%, indicating that very little drug is wasted during formulation.

Drug content, on the other hand, is defined as the actual drug content in the formulation as opposed to the theoretical content. The drug content is 67.885%, but this may be influenced by factors such as losses during formulation, inability to recover all the drug after formulation, or the presence of a stabilizer. The difference between entrapment efficiency and drug content is quite significant for nanocrystal formulations, because these formulations are mostly drug, with only a small percentage of other agents.

***In vitro* drug release studies**

The in vitro release of RIS nanosuspensions was assessed using the dialysis bag diffusion method in a phosphate buffer at pH 6.8. Table 5 shows that formulation F7 exhibits the highest cumulative drug release, at 90.23% ± 1.91%. The enhanced release profile was achieved by reducing particle size, thereby increasing surface area and improving drug dissolution rate. The findings indicate that nanosizing significantly improves the solubility characteristics of medications such as RIS, which are intrinsically poorly soluble. The improvement in drug release from the optimized nanocrystal formulation, i.e., F7, was statistically significant compared with the pure drug and the market tablet at $p < 0.05$. The dialysis bag method was used to carry out the in vitro drug release study. The nanosized drug particles were effectively separated from the dissolution medium using this method, with only the drug that is in solution being able to diffuse through the membrane. The dialysis bag method is commonly used with nanosuspension drug delivery systems because it avoids interference caused by drug particles in the release medium. Although it is acknowledged that using a dialysis bag interferes with drug release, this interference has been minimized by using an appropriate molecular weight cut-off.

Sink conditions were also maintained during the dissolution study by using a sufficient volume of dissolution medium with respect to the drug concentration. This ensured that the drug concentration in the release medium remained below its solubility limit, thereby facilitating drug diffusion through the membrane. The drug release profile obtained using this method is therefore a true reflection of the dissolution behavior of this drug formulation [32].

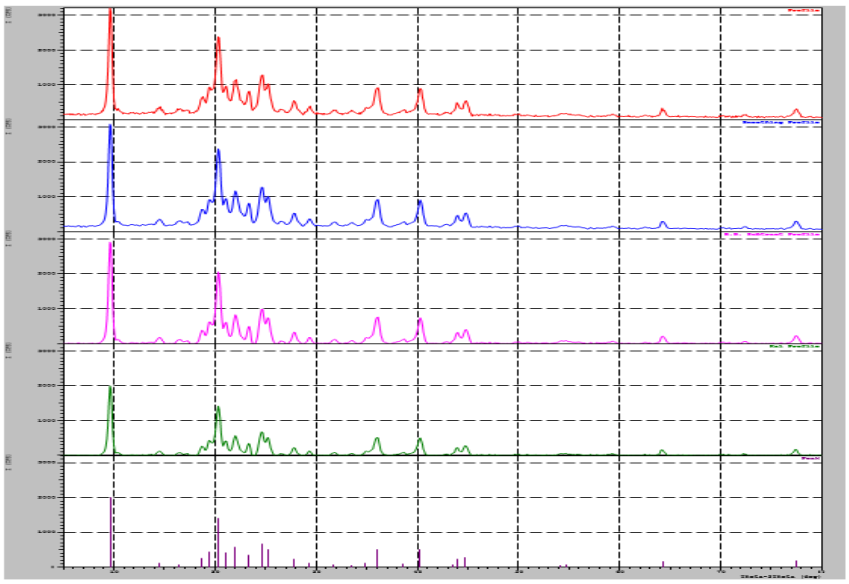

Figure 4: X-ray diffractogram of bulk RIS powder

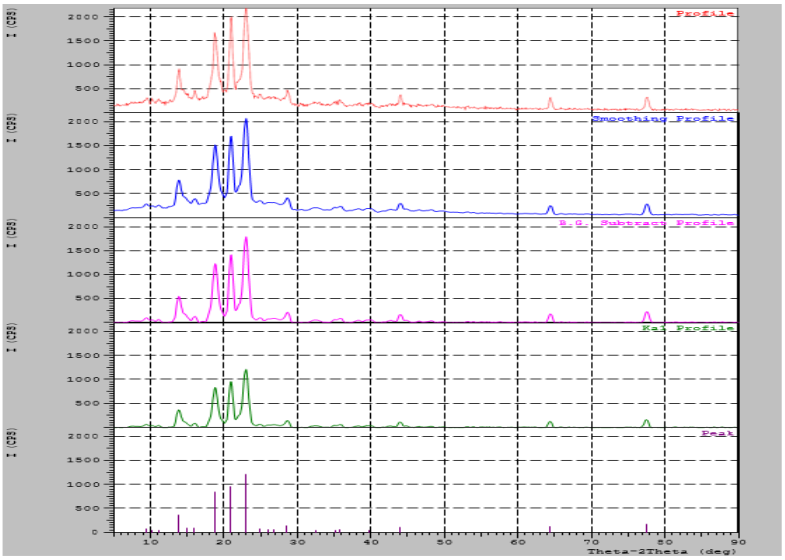

Figure 5: X-ray diffractogram of RIS nanocrystals

Table 4: Entrapment efficiency & drug content

Sl. No.	Formulation code	EE ± Std. deviation (%)	DC (%)
1	F1	57.585±2.29	45.965±0.50
2	F2	60.14±1.28	47.465±0.78
3	F3	51.58±1.04	42.575±3.47
4	F4	73.365±1.63	57.875±2.62
5	F5	62.445±2.17	51.015±1.30
6	F6	79.475±1.12	66.27±0.76
7	F7	86.22±1.61	67.885±2.02
8	F8	71.6±1.06	60.035±0.50
9	F9	65.6±0.61	51.015±1.34

Evaluation of RIS nanocrystal tablets

The physical properties of risperidone nanocrystal tablets (F7) were found to be uniform and sufficient for mechanical strength. The tablets were measured at 5 ± 0.37 kg/cm², indicating sufficient mechanical strength. The average weight of each tablet was 102 ± 2.41 mg, indicating that all tablets were uniform in weight. The friability value was found to be 0.352%, which is within acceptable limits. The disintegration time was found to be 14 ± 0.58 seconds, indicating that the tablet disintegrates quickly, which is desirable (Table 6).

Table 5: Cumulative Percentage Drug Release of Formulations (F1–F9) in Phosphate Buffer pH 6.8

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	8.23	8.58	8.85	9.51	10.5	12.42	15.58	10.31	9.14
10	13.26	15.56	13.54	14.52±8.16	16.42±1.53	26.10±2.84	24.36±0.63	15.52±1.56	17.52±1.33
15	32.55±1.54	31.53±2.15	32.46±2.17	32.14±3.25	35.57±1.87	44.24±2.74	44.15±0.48	35.25±1.67	36.42±1.48
20	39.58±1.65	40.25±1.36	41.35±3.24	48.57±3.46	48.14±1.89	55.35±1.09	55.52±0.78	47.40±1.11	47.51±3.58
30	51.13±1.58	54.09±1.54	49.28±1.48	57.14±2.65	57.35±5.14	69.37±1.02	68.54±0.59	57.54±3.86	57.14±2.98
45	57.51±1.74	63.11±1.95	56.52±1.58	61.14±6.47	62.57±8.25	74.06±0.74	74.53±0.47	63.38±3.58	63.52±2.58
60	66.06±1.36	70.17±0.32	62.38±0.21	72.21±0.47	70.15±1.25	87.27±1.78	90.23±1.91	73.43±2.14	72.28±3.52

Table 6: Tablet evaluation parameters

Formulation Code	Hardness (kg/cm²)	Average Tablet Weight (mg)	Friability (%)	Disintegration Time (sec)
F7	5 ± 0.37	102 ± 2.41	0.352	14 ± 0.58

In vitro dissolution

The dissolution test for tablets was performed utilizing a paddle-type dissolution tester. Tablets were immersed in 900 mL of phosphate buffer (pH 6.8) at 37 °C and agitated with a rotating paddle at 50 rpm. The findings are presented in Table 7 and Figure 6.

Table 7: Dissolution comparison (F7 vs marketed)

Time (mins)	RIS Nanocrystal Tablet	Tablets Marketed RIS
5	9.49 ± 1.91	6.70 ± 0.59
10	23.53 ± 0.56	17.85 ± 0.14
15	41.59 ± 1.89	33.23 ± 1.54
20	63.06 ± 0.32	53.15 ± 3.54
30	74.65 ± 0.44	64.28 ± 2.69
45	86.28 ± 2.18	77.51 ± 0.65

The in-vitro drug release profile of RIS nanocrystal tablets (F7) exhibits a dissolution rate of 86.2, which is higher than that of RIS tablets (77.51%). The increase in DR resulted from a reduction in particulate size.

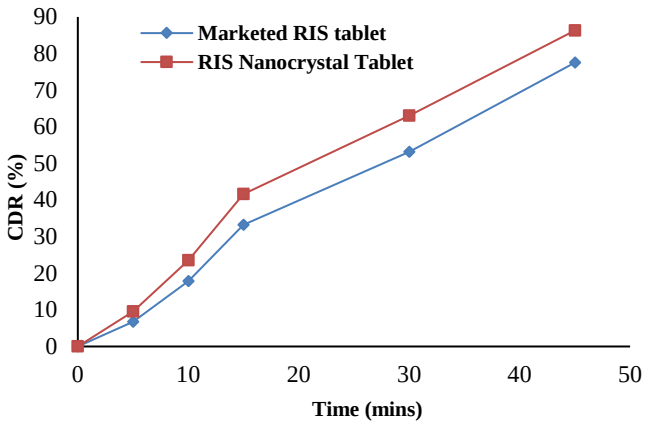

Figure 6: Percentage cumulative drug release of RIS nanocrystal tablets (F7) and marketed tablets

Drug release kinetics

This study assesses the patterns and mechanisms of drug release from RIS-loaded nanocrystals utilizing zero-order, first-order, Higuchi, and Korsmeyer-Peppas mathematical models as illustrated in Figure 7. Table 16 presents the regression coefficient (R^2) along with the corresponding n values. The zero-order release kinetics of the F7 formulation in phosphate buffer at pH 6.8 demonstrated a significant correlation coefficient (R^2 = 0.995).

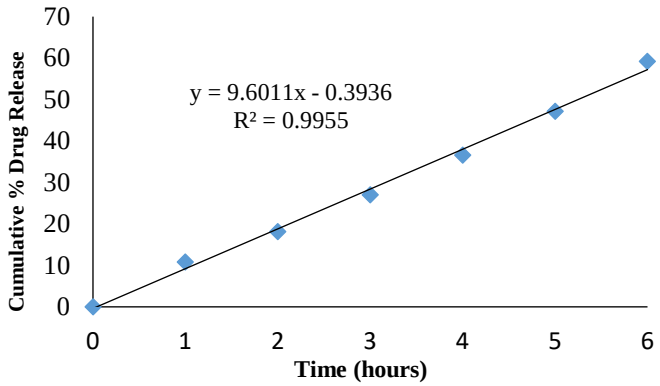

Figure 7: Zero-order release of the F7 formulation

CONCLUSION

The risperidone nanocrystals prepared in this study showed significant improvements in solubility, particle size, and dissolution behavior compared with the pure drug and commercial tablet formulations. The optimized formulation, F7, exhibited nanosized particles (78.62 nm), a narrow size distribution (PDI 0.223), and rapid drug release (86.28% at 45 min). However, it is noteworthy that this study is limited to in vitro studies, and there were no studies on in vivo bioavailability and pharmacokinetics. The enhancement in drug activity cannot be conclusively established. Further studies are required to prove

the enhancement in bioavailability and therapeutic activity of the prepared formulation. The study demonstrated that nanocrystal formulations could be a potential tool for addressing solubility problems associated with BCS Class II drugs such as risperidone, with significant potential for future clinical investigations.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
M. Subramani conceptualized the study, supervised the experimental work, analyzed the data, and wrote the original draft with subsequent review and editing. R. Arulkumar conducted the validation studies, performed investigations, and contributed to data curation. P. Manikandan participated in methodology development, conducted investigations, performed data curation and validation, and contributed to manuscript review and editing. P. K. Varshini assisted in manuscript review and editing. S. Mounisha contributed to data curation, manuscript review, and editing. All authors have read and approved the final manuscript.

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