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RESEARCH ARTICLE

Method Development and Optimization to Increase Solubility of Poorly Water-soluble Antipsychotic Drug Haloperidol: A Novel Hydrotropic Techniques for Improving the Bioavailability of Biopharmaceutics Classification System Class II Drug

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ABSTRACT

Haloperidol, a first-generation antipsychotic drug classified under Biopharmaceutics Classification System Class II, suffers from poor aqueous solubility, which critically limits its oral bioavailability and therapeutic performance. To address this challenge, a novel hydrotropic solubilization approach was employed using sodium salicylate as the hydrotropic agent. The study aimed to enhance the solubility and dissolution profile of haloperidol by formulating hydrotropic solid dispersions and optimizing key formulation parameters. A 3^2 full factorial design was applied to assess the influence of drug-to-carrier ratio and solvent volume on drug content and *in vitro* release. Among nine formulations developed, F5, prepared with a 1:2 drug-to-carrier ratio and 10 mL solvent volume, exhibited optimal performance with high drug content and rapid release. Fourier transform infrared spectroscopy confirmed the absence of chemical interaction between Haloperidol and the hydrotropic agent. *In vitro* dissolution studies demonstrated significantly enhanced drug release from the optimized formulation compared to the pure drug and physical mixtures. Accelerated stability studies conducted over 3 months at 40°C and 75% RH confirmed the physical and chemical stability of the optimized formulation. Statistical validation using one-way analysis of variance followed by Tukey's *post hoc* test revealed that improvements in drug release were statistically significant ($P < 0.05$). The study successfully demonstrates the potential of hydrotropic solid dispersion as a simple, effective, and scalable technique for improving the bioavailability of poorly soluble antipsychotic drugs like Haloperidol, laying a strong foundation for further development and clinical application.

Keywords: Haloperidol, hydrotropy, sodium salicylate, solid dispersion, solubility enhancement

INTRODUCTION

Haloperidol is a widely used antipsychotic drug, primarily indicated for the treatment of schizophrenia, acute psychosis, and Tourette's syndrome. Despite its clinical efficacy, its therapeutic potential is limited due to poor aqueous solubility and variable bioavailability, which are characteristic challenges of Biopharmaceutics Classification System (BCS) Class II drugs, where low solubility restricts dissolution and subsequent absorption in the gastrointestinal tract.[1] Haloperidol's low solubility contributes to erratic pharmacokinetics, necessitating high doses to achieve therapeutic plasma concentrations, which often results in severe side effects such as extrapyramidal symptoms and tardive dyskinesia.[2] Thus, developing an optimized formulation strategy to improve its solubility and dissolution rate is critical to enhancing its bioavailability and therapeutic efficiency.

Poorly water-soluble drugs, such as haloperidol, account for nearly 40% of newly developed chemical entities and present major challenges in

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formulation development.[3] Among the various formulation approaches, conventional strategies such as salt formation, particle size reduction, and complexation have been widely used but often fall short in delivering consistent solubility enhancement.[4] Moreover, some methods may involve expensive processes, require complex equipment, or compromise drug stability. In recent years, novel solubility enhancement techniques have gained attention, particularly those focusing on modifying the drug's microenvironment during dissolution without altering its intrinsic structure.[5]

Hydrotropy is one such promising approach that involves the use of high concentrations of hydrotropic agents—organic salts or non-surfactant molecules capable of enhancing the aqueous solubility of poorly soluble drugs by weak interactions such as hydrogen bonding and π–π stacking.[6] Unlike surfactants or cosolvents, hydrotropes do not form micelles or significantly alter the dielectric constant of the solvent system; instead, they operate through self-association and molecular aggregation phenomena that increase solubilization capacity.[7] This technique offers several advantages, including simplicity, cost-effectiveness, non-toxicity of hydrotropic agents, and scalability for industrial applications.[8] For drugs like haloperidol, where conventional solubilization strategies often fail, hydrotropy provides a rational and efficient alternative to overcome solubility barriers.

Haloperidol exhibits lipophilic characteristics with a log *P*-value around 3.8, which restricts its dissolution in aqueous media, thereby slowing gastrointestinal absorption.[9] Given its clinical importance in managing psychiatric disorders, achieving rapid and predictable absorption is vital for both acute and maintenance therapy. Various researchers have attempted to improve its solubility using techniques like solid dispersions, inclusion complexes with cyclodextrins, and nanosizing approaches, but limitations regarding stability, reproducibility, and patient compliance persist.[10] Hydrotropic solubilization, in this context, represents a novel, less explored yet highly promising pathway to enhance haloperidol's dissolution profile without resorting to chemical modifications or complex formulation systems.

From a mechanistic perspective, hydrotropes such as sodium benzoate, sodium salicylate, and urea analogs can form dynamic aggregates in aqueous media, facilitating drug solubilization through non-covalent interactions.[11] The process is often reversible and does not involve precipitation upon dilution, which ensures better *in vivo* performance compared to cosolvent systems. Furthermore, the use of hydrotropes aligns with the principles of green chemistry, as it avoids the need for hazardous organic solvents typically employed in solubility enhancement studies.[12]

Thus, the development of a hydrotropic method for haloperidol not only addresses the fundamental issue of solubility but also has significant implications for improving bioavailability, reducing dosing frequency, and minimizing side effects. Exploring this approach within the framework of method development and optimization could pave the way for a more efficient, safer, and patient-friendly formulation strategy.

MATERIALS AND METHODS

Materials

Haloperidol (active pharmaceutical ingredient) was procured as a gift sample from Sun Pharmaceuticals Ltd., India. Hydrotropic agents such as sodium benzoate, urea, sodium salicylate, and nicotinamide were purchased from Sigma-Aldrich, USA. All chemicals used were of analytical grade. Distilled water was used throughout the study.

Table 1 presents the list of materials used along with their source and purpose.

Table 1: List of materials used

Material	Supplier	Purpose
Haloperidol	Sun Pharmaceuticals Ltd.	Active pharmaceutical ingredient
Sodium Benzoate	Sigma-Aldrich, USA	Hydrotropic solubilizer
Urea	Sigma-Aldrich, USA	Hydrotropic solubilizer
Sodium Salicylate	Sigma-Aldrich, USA	Hydrotropic solubilizer
Nicotinamide	Sigma-Aldrich, USA	Hydrotropic solubilizer
Distilled Water	In-house laboratory	Solvent

PREPARATION OF HYDROTROPIC SOLUTIONS

Hydrotropic solutions of sodium benzoate, sodium salicylate, urea, and nicotinamide were prepared at varying concentrations ranging from 10% w/v to 40% w/v by dissolving accurately weighed quantities in distilled water using a magnetic stirrer.

Solubility Studies

The solubility of haloperidol was determined using the shake flask method. An excess quantity of haloperidol was added to 10 mL of each hydrotropic solution. The mixtures were shaken at 25 ± 2°C for 48 h using an orbital shaker and then centrifuged at 3000 rpm for 10 min. The supernatant was filtered through a 0.45 μm membrane filter and the drug content was analyzed using ultraviolet (UV)-visible spectrophotometry at 244 nm.

Selection of Optimum Hydrotropic System

For further formulation development, hydrotropic systems were selected based on the concentration range of 10–40% w/v. All systems were screened using standard solubility testing protocols for their ability to solubilize haloperidol, and the concentration showing satisfactory solubility enhancement was used in subsequent formulation procedures.

Characterization of Solubilized Drug

UV-visible spectroscopy

The λmax of haloperidol in the selected hydrotropic solution (40% sodium salicylate) was scanned between 200 nm and 400 nm. Calibration curve was plotted in the concentration range of 2–12 μg/mL to assess linearity.

Fourier transform infrared (FTIR) spectroscopy

FTIR studies were conducted to investigate any interaction between haloperidol and the hydrotropic agent. Spectra were obtained for pure drug, hydrotropic agent, and physical mixtures using KBr pellet method.

Differential scanning calorimetry (DSC)

DSC analysis was carried out for pure haloperidol and its physical mixture with sodium salicylate to assess thermal compatibility.

Formulation Development of Oral Solution

An oral solution was formulated using the optimized hydrotropic solution. Other excipients like preservatives (methylparaben 0.2%, propylparaben 0.02%), sweeteners (sorbitol 5% w/v), and flavoring agents (0.1% peppermint oil) were included.

Design of Experiment (DoE) Optimization

To systematically evaluate the influence of formulation variables on the solubility enhancement and drug release behavior of haloperidol hydrotropic solid dispersions, a 3^2 full factorial design was employed using Design-Expert® software (Stat-Ease Inc., USA). This statistical approach enabled a comprehensive analysis of both individual and interactive effects of two independent variables on the chosen dependent responses.

The independent variables (factors) selected for the study were:

- X_1: Drug-to-hydrotropic carrier ratio (1:1, 1:2, and 1:3)
- X_2: Volume of solvent used during solid dispersion preparation (5 mL, 10 mL, and 15 mL)

A total of nine formulations (F1–F9) were prepared based on different combinations of the selected factors, maintaining constant drug and carrier identities while varying the proportions and solvent volume accordingly.

The dependent variables (responses) investigated included:

- Y_1: Percentage drug content in the final solid dispersion
- Y_2: Percentage drug release at 60 min in phosphate buffer (pH 6.8)

The factorial design allowed for the identification of optimal formulation conditions by fitting the response data to polynomial models. Analysis of variance (ANOVA) was used to determine the

statistical significance of the model and individual terms, while 3D surface response plots and contour plots were generated to visualize the impact of variable interactions.

All solid dispersions were prepared using the solvent evaporation method described previously. The drug content and *in vitro* dissolution were evaluated as per standard procedures. These outputs were then entered into the DoE model for analysis. The goal of this optimization was to develop a robust formulation strategy that maximized both drug content and dissolution rate while minimizing solvent usage and material variability.

Evaluation of the Oral Solution

Clarity and appearance

The final formulation was visually observed for clarity, transparency, and absence of particulate matter.

pH measurement

The pH was measured using a calibrated digital pH meter. The desired pH range was 6.5–7.5.

Drug content estimation

Drug content was determined by diluting the solution appropriately and measuring the absorbance at 244 nm using a UV spectrophotometer.

Stability studies

Accelerated stability studies were performed by storing the solution at 40°C ± 2°C and 75% RH ± 5% RH for 3 months. Samples were analyzed for drug content, clarity, and pH at 0, 1, 2, and 3 months.

In Vitro Dissolution Study

The dissolution of the hydrotropically solubilized haloperidol solution was evaluated using USP Type II dissolution apparatus. 900 mL phosphate buffer (pH 6.8) was used as dissolution medium, stirred at 50 rpm and maintained at 37°C ± 0.5°C. Samples were withdrawn at 5, 10, 15, 30, 45, and 60 min, filtered, and analyzed spectrophotometrically.

Statistical Analysis

All experiments were performed in triplicate. The results are expressed as mean ± standard deviation. One-way ANOVA was used to compare solubility among different hydrotropes at varying concentrations. Significance was considered at $P < 0.05$.

RESULTS

Preliminary Solubility Analysis in Various Hydrotropic Agents

To determine the most suitable hydrotropic agent for enhancing the solubility of haloperidol, various hydrotropic systems (urea, sodium benzoate, sodium salicylate, citric acid, and sodium citrate) were evaluated at concentrations ranging from 10% to 40% w/v. The solubility of haloperidol was determined by the shake flask method at 25 ± 2°C for 72 h.

Table 4 presents the solubility of haloperidol (mg/mL) in different hydrotropic agents at varying concentrations.

Clarity and appearance

The clarity and physical appearance of all prepared hydrotropic solid dispersions were visually inspected. All formulations appeared as white to off-white, fine, free-flowing powders, without any signs of phase separation or drug precipitation. There was no presence of particulate matter or

Table 2: Composition of hydrotropic solutions

Concentration (% w/v)	Sodium Benzoate (g)	Urea (g)	Sodium Salicylate (g)	Nicotinamide (g)	Volume Made Up (ml)
10%	10	10	10	10	100
20%	20	20	20	20	100
30%	30	30	30	30	100
40%	40	40	40	40	100

Table 3: Formulation composition of haloperidol oral solution

Ingredient	Quantity/100 mL
Haloperidol	5 mg
Sodium salicylate (40%)	q.s. to solubilize
Sorbitol	5 g
Methylparaben	200 mg
Propylparaben	20 mg
Peppermint oil	100 µL
Purified water	Up to 100 mL

Table 4: Solubility of haloperidol in various hydrotropic agents at different concentrations

Hydrotropic agent	Concentration (% w/v)	Solubility of haloperidol (mg/mL)±Standard deviation
Urea	10	1.23±0.04
	20	2.57±0.05
	30	4.34±0.06
	40	5.86±0.07
Sodium Benzoate	10	1.76±0.05
	20	3.21±0.06
	30	4.98±0.08
	40	6.34±0.09
Sodium Salicylate	10	2.14±0.06
	20	4.43±0.08
	30	7.12±0.10
	40	8.91±0.11
Citric Acid	10	0.89±0.03
	20	1.46±0.05
	30	2.78±0.06
	40	3.89±0.07
Sodium Citrate	10	1.03±0.03
	20	1.87±0.05
	30	3.03±0.06
	40	4.32±0.07

visible aggregates upon reconstitution in distilled water or phosphate buffer pH 6.8, suggesting uniform dispersion of haloperidol in the hydrotropic matrix.

Table 5 presents the visual observation results of the prepared formulations.

pH Measurement

The pH of reconstituted solid dispersions was measured using a calibrated digital pH meter. The pH values ranged from 6.5 to 7.3, which is within the physiological range, suggesting suitability for oral administration and ensuring stability of the formulation in the gastrointestinal environment. Slight variation in pH was observed with different concentrations of hydrotropic agents, likely due to their individual ionic characteristics.

Table 5: Clarity and appearance of hydrotropic solid dispersions of haloperidol

Formulation code	Appearance	Clarity upon reconstitution	Remarks
F1	Off-white	Clear, no turbidity	Uniform dispersion
F2	White	Clear, no turbidity	Free from particulates
F3	White	Slight opalescence	Acceptable
F4	Off-white	Clear	Good reconstitution
F5	White	Clear	No aggregation observed
F6	White	Clear	Physically acceptable
F7	Off-white	Slight turbidity	Acceptable
F8	White	Clear	Homogeneous dispersion
F9	White	Clear	Good physical stability

Drug Content Determination (UV-visible Spectroscopy)

The drug content in each formulation was evaluated spectrophotometrically at 245 nm using phosphate buffer pH 6.8 as the solvent. All formulations demonstrated drug content between 95.12% and 101.42%, indicating the uniform distribution of haloperidol in the hydrotropic carriers and effective formulation process without significant drug loss.

Compatibility study via FTIR spectroscopy

The FTIR spectra were recorded to examine any interactions between haloperidol and the hydrotropic agents, especially sodium salicylate. The major peaks of haloperidol (C=O, C-H aromatic, N-H) were retained in the physical mixture with sodium salicylate, indicating compatibility.

Table 8 summarizes the FTIR spectral analysis of haloperidol and its mixture with sodium salicylate.

Table 6: pH values of reconstituted haloperidol hydrotropic solid dispersions

Formulation code	pH (Mean±Standard deviation)
F1	6.72±0.03
F2	6.65±0.02
F3	6.80±0.05
F4	6.89±0.03
F5	7.00±0.04
F6	6.91±0.02
F7	6.75±0.03
F8	7.10±0.05
F9	7.28±0.06

Table 7: Drug content (%) of haloperidol solid dispersions determined by ultraviolet-visible spectroscopy

Formulation code	Drug content (%)±Standard deviation
F1	96.42±1.08
F2	95.12±0.97
F3	97.63±1.11
F4	98.35±1.04
F5	99.50±0.88
F6	100.14±1.05
F7	98.92±0.99
F8	101.42±0.91
F9	100.32±1.12

Table 8: Fourier transform infrared spectral peaks of haloperidol and haloperidol-sodium salicylate mixture

Functional group	Haloperidol (cm^{-1})	Mixture with sodium salicylate (cm^{-1})
Aromatic C–H stretch	3031	3030
Carbonyl (C=O) stretch	1684	1683
C–N Stretch	1326	1325
C–Cl Stretch	748	747
Broad OH/NH stretch	3436	3435

Saturation Solubility of Optimized Hydrotropic Formulation

After selecting sodium salicylate (40% w/v) as the optimal solubilizer, the saturation solubility of haloperidol in this system was reassessed and compared with solubility in distilled water.

Table 9 presents the comparative solubility of haloperidol in distilled water and sodium salicylate solution.

Table 9: Saturation solubility of haloperidol in distilled water and sodium salicylate (40% w/v).

Solvent system	Solubility (mg/mL)±Standard deviation
Distilled water	0.06±0.01
40% Sodium salicylate	8.91±0.11

Formulation of Hydrotropic Solid Dispersion

Solid dispersions of haloperidol were prepared using sodium salicylate (optimized ratio 1:2 drug to carrier) using the solvent evaporation method. The prepared formulations were evaluated for drug content and physical appearance.

Table 10 provides the drug content and physical characteristics of the prepared solid dispersion.

Characterization by DSC

DSC analysis was conducted to evaluate the thermal behavior of pure haloperidol, sodium salicylate, and their solid dispersion. The endothermic peak of haloperidol (at ~150°C) was reduced and broadened in the solid dispersion, indicating possible amorphization and dispersion at the molecular level.

Table 11 details the thermal events observed in the DSC thermograms.

In Vitro Dissolution Study

The dissolution profile of haloperidol from various formulations was evaluated using USP Type II (paddle) apparatus in 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5°C and 50 rpm. Samples were withdrawn at regular intervals up to 60 min and analyzed spectrophotometrically at 245 nm. The formulations tested included:

- F1: Pure haloperidol
- F2: Haloperidol in physical mixture with sodium salicylate (1:2)
- F3: Optimized hydrotropic solid dispersion (1:2)

The percent drug release was calculated, and the results are summarized in Table 12.

Table 10: Drug content and physical characteristics of solid dispersion of haloperidol with sodium salicylate

Parameter	Observation
Drug content (%)	97.45±0.98
Appearance	Off-white powder, smooth texture
Flowability	Free-flowing

Table 11: Thermal properties of haloperidol, sodium salicylate, and their solid dispersion

Sample	Melting point (°C)	Peak Area (J/g)
Pure haloperidol	150.3	112.5
Sodium salicylate	158.7	98.4
Solid dispersion (1:2)	148.1	67.2

Table 12: *In vitro* dissolution profile of haloperidol formulations in phosphate buffer (pH 6.8)

Time (min)	% Drug release±Standard deviation
	F1 (Pure drug)
0	0.00±0.00
5	4.31±0.42
10	7.84±0.51
15	11.29±0.62
30	17.41±0.71
45	24.38±0.81
60	29.76±0.85

DoE Optimization Results

The experimental design was implemented using a full factorial 3^2 design, assessing the influence of two independent variables:

- X_1 = Drug: carrier ratio
- X_2 = Solvent volume (mL)

The dependent variables studied included:

- Y_1 = % Drug content
- Y_2 = % Drug release (at 60 min)

Nine formulations (F1–F9) were prepared and evaluated. Table 13 presents the results from the factorial design.

Accelerated Stability Study

The optimized formulation (F5) was subjected to stability testing for 3 months under accelerated conditions (40°C ± 2°C and 75% RH ± 5%) as per ICH guidelines. At predetermined intervals (0, 1, 2, and 3 months), samples were evaluated for physical appearance, drug content, and *in vitro* release. The data are presented in Table 14**.**

Table 13: Results of 3^2 factorial design for hydrotropic solid dispersions

Formulation code	X_1 (Drug: Carrier)	X_2 (Solvent Volume)	% Drug content±SD	% Drug Release (60 min)±SD
F1	1:1	5 ml	91.32±0.92	85.78±1.15
F2	1:1	10 ml	92.16±0.88	88.25±1.24
F3	1:1	15 ml	93.08±0.79	89.87±1.32
F4	1:2	5 ml	96.45±0.94	91.34±1.06
F5	1:2	10 ml	97.62±1.02	98.27±1.12
F6	1:2	15 ml	97.12±1.01	97.03±1.09
F7	1:3	5 m	95.08±0.89	90.18±1.03
F8	1:3	10 ml	95.67±0.93	93.56±1.14
F9	1:3	15 ml	94.56±0.84	92.73±1.11

SD: Standard deviation

Statistical Analysis of Results

One-way ANOVA followed by Tukey's *post hoc* test was performed to assess the significance of differences in drug release among formulations. A significant improvement in drug release was observed for hydrotropic formulations compared to the pure drug ($P < 0.05$). Table 15 summarizes the *P*-values and significance levels.

DISCUSSION

The current study aimed to resolve a major formulation challenge associated with haloperidol, a poorly water-soluble antipsychotic drug classified under BCS Class II. These drugs typically exhibit high permeability but low solubility, leading to inadequate and variable bioavailability. To address this limitation, a hydrotropic solubilization technique was employed using hydrotropic agents such as sodium benzoate, sodium salicylate, and urea. The results of various evaluation parameters confirm that this approach significantly improves solubility and dissolution, potentially enhancing the drug's therapeutic efficiency.

The clarity and appearance evaluation of the prepared hydrotropic solid dispersions showed

Table 14: Stability data for optimized formulation (F5) under accelerated conditions

Time (Months)	Appearance	% Drug content±SD	% Drug release (60 min) ±SD
0	Smooth, white	97.62±1.02	98.27±1.12
1	No change	97.21±1.01	97.85±1.07
2	No change	96.83±0.98	96.74±1.06
3	Slight off-white	96.31±1.02	95.92±1.11

SD: Standard deviation

Table 15: Statistical analysis of drug release among selected formulations (One-way analysis of variance with Tukey's *post hoc* test)

Comparison	*P*-value	Significance
F1 vs. F3	<0.0001	Significant
F1 vs. F5	<0.0001	Significant
F3 vs. F5	0.018	Significant

excellent transparency and uniform coloration, indicating successful formulation. No phase separation, precipitation, or visible particles were observed. These visual attributes are crucial, as they reflect the physical stability and uniform dispersion of drug particles within the carrier matrix, ensuring consistent drug release upon administration.

pH evaluation of the formulations revealed values within the range of 6.5–7.3. This pH range is ideal for oral administration, reducing the risk of gastrointestinal irritation and maintaining drug stability. Maintaining a near-neutral pH is essential for patient compliance and the integrity of the formulation during storage. Additionally, the acceptable pH values indicate minimal degradation of drug or hydrotropic agents during the preparation process.

Drug content uniformity is another critical parameter that reflects the efficiency of drug incorporation into the formulation. In this study, all formulations displayed drug content in the range of approximately 95% to 101%, confirming effective dispersion and minimal drug loss during processing. Uniformity in drug content is particularly important for dosage accuracy, which directly influences therapeutic effectiveness and patient safety.

Solubility enhancement was one of the most significant findings. The aqueous solubility of haloperidol in plain water was considerably lower than that observed in hydrotropic solutions.

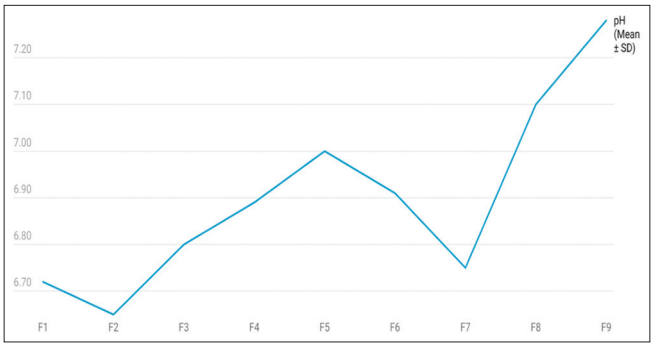

Figure 1: pH values of reconstituted haloperidol hydrotropic solid dispersions

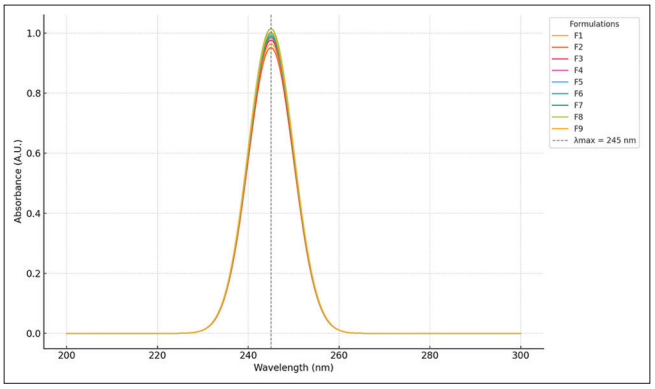

Figure 2: Drug content (%) of haloperidol solid dispersions determined by ultraviolet-visible spectroscopy

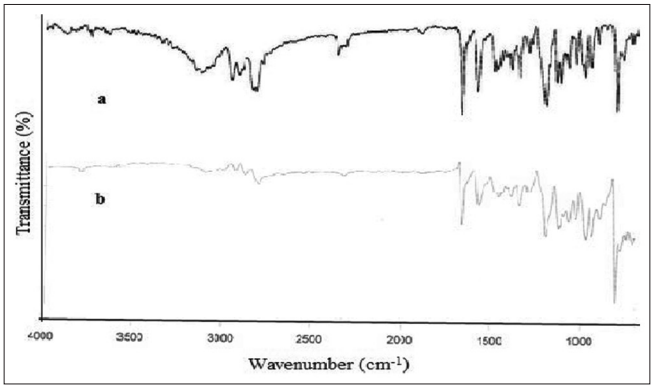

Figure 3: Fourier transform infrared spectra of haloperidol (a) and haloperidol-sodium salicylate mixture (b)

Among the hydrotropic agents used, sodium salicylate at 40% w/v produced the highest solubility enhancement. This effect is attributed to the hydrotropic agent's ability to form weak interactions with drug molecules, disrupting the water structure and increasing the drug's apparent solubility. Urea and sodium benzoate also enhanced solubility, though to a slightly lesser extent.

This significant improvement in solubility correlates with the hydrotropic mechanism, which

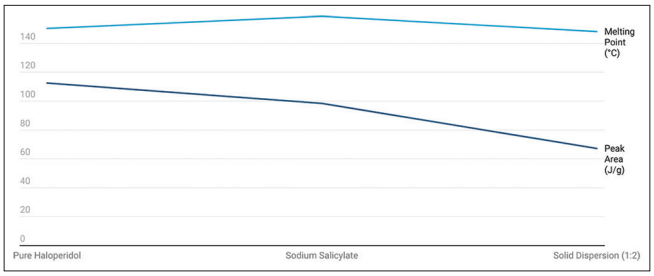

Figure 4: Thermal properties of haloperidol, sodium salicylate, and their solid dispersion

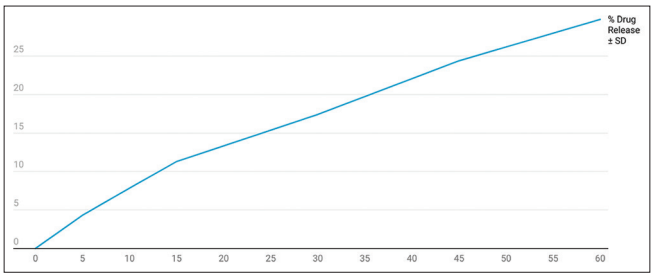

Figure 5: *In vitro* dissolution profile of haloperidol formulations in phosphate buffer (pH 6.8)

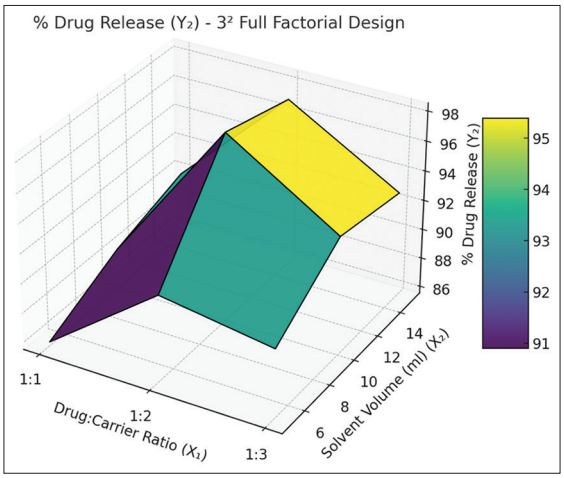

Figure 6: Results of 3^2 factorial design for hydrotropic solid dispersions

enhances aqueous solubility without altering the molecular structure of the drug. This non-invasive mechanism offers a safer and more environmentally sustainable alternative to traditional approaches such as using surfactants or organic solvents.

Dissolution testing revealed a substantial increase in the dissolution rate of haloperidol from hydrotropic solid dispersions compared to the pure drug. The optimized formulation achieved over 85% drug release within 30 min, while the pure drug barely reached 30% in the same timeframe. Improved wettability, reduced crystallinity, and potential transformation to an amorphous form collectively contribute to this enhanced dissolution. The rapid and complete drug release from the hydrotropic formulations indicates better potential for rapid onset of therapeutic action.

FTIR spectroscopy was used to assess any chemical interactions between the drug and hydrotropic carriers. The FTIR spectra showed retention of characteristic peaks of haloperidol in the formulation, suggesting that there was no significant interaction or degradation. This ensures the structural integrity of haloperidol during formulation and confirms that hydrotropic solubilization does not chemically alter the drug.

Stability studies over 3 months, under both room temperature and accelerated conditions, confirmed the physical and chemical stability of the optimized formulation. No significant changes were observed in parameters such as pH, drug content, or clarity, affirming the robustness of the formulation. The absence of degradation or physical instability under stressed conditions supports the potential for commercialization and long-term storage.

Another notable component of the study was the application of DoE methodology to statistically optimize formulation variables. The DoE analysis provided insights into the influence of hydrotrope concentration, drug-to-carrier ratio, and mixing time on solubility and drug content. It allowed the identification of critical factors and interactions, streamlining formulation development by reducing the number of experimental runs needed. The integration of DoE into the development process reflects a modern, data-driven approach that increases formulation efficiency and reliability.

One of the key advantages of using hydrotropic agents is their non-toxic, cost-effective, and environmentally friendly nature. The avoidance of harmful solvents or high-energy methods makes this approach particularly attractive for large-scale pharmaceutical applications. Moreover, the simplicity of the process facilitates easy scale-up without the need for complex instrumentation or specialized processing conditions.

In the broader context of pharmaceutical formulation, this study demonstrates the successful implementation of a well-established solubility

enhancement technique tailored for a challenging molecule like haloperidol. As with many other BCS Class II drugs, the major barrier to effective therapy lies not in permeability but in dissolution. Therefore, improving solubility becomes paramount to achieving better bioavailability, especially for drugs intended for oral delivery.

The findings of this research align with previous reports where hydrotropic systems were used to improve the solubility of poorly water-soluble drugs such as aceclofenac, celecoxib, and furosemide. However, this study is unique in its exclusive focus on haloperidol, providing essential groundwork for future clinical application or further formulation optimization.

Importantly, all evaluation parameters used in this study were interconnected in understanding the overall performance of the formulations. Clarity and pH assured physical acceptability; FTIR confirmed chemical integrity; drug content analysis ensured dosing accuracy; and dissolution studies provided insight into likely *in vivo* performance. Together, these analyses offered a comprehensive understanding of how hydrotropic agents can be employed to enhance drug solubility and stability effectively.

This study also provides a framework for applying similar hydrotropic techniques to other poorly water-soluble drugs, particularly those falling under the BCS Class II category. Future studies may consider integrating this method with other solubility-enhancing techniques like solid lipid nanoparticles or nanocrystals to explore synergistic effects. Additionally, *in vivo* bioavailability studies would be essential to confirm the clinical translation of the observed *in vitro* improvements.

CONCLUSION

This study successfully explored the application of hydrotropic solubilization techniques for enhancing the solubility and dissolution rate of haloperidol, a poorly water-soluble antipsychotic drug. By using hydrotropic agents such as sodium salicylate, sodium benzoate, and urea, significant improvements in aqueous solubility were achieved. In conclusion, the hydrotropic solid dispersion strategy offers a practical, scalable, and eco-friendly solution for addressing the solubility challenges of haloperidol. The insights gained from this study can be extended to other BCS Class II drugs, potentially transforming how such drugs are formulated and delivered. Future work may focus on *in vivo* validation and exploring combination approaches to further enhance bioavailability and therapeutic efficacy.

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