RESEARCH PAPER

Development, Optimization, and Comprehensive Characterization of Eudragit RL 100-Based Amisulpride Microspheres for Sustained Oral Drug Delivery: Process Parameter Optimization and Comparative In-Vitro Evaluation

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ABSTRACT

Amisulpride is an atypical antipsychotic drug characterized by poor aqueous solubility and variable oral bioavailability, necessitating the development of an effective controlled-release delivery system. The present study reports the development and optimization of amisulpride-loaded Eudragit RL 100 microspheres incorporated into a microsphere-based tablet for sustained oral drug delivery. Microspheres were prepared using the solvent evaporation technique. The critical formulation parameters, including drug-to-polymer ratio, internal phase volume, stabilizer concentration, stirring speed, and stirring time, were systematically optimized. Preformulation studies confirmed drug purity and compatibility through melting point determination, UV spectrophotometric analysis (λmax 252 nm), and FT-IR studies.

The optimized formulation (drug: polymer ratio of 1:10, 10 mL DCM, 1% PVA, 1500 rpm, and 90 min) exhibited high entrapment efficiency (90.94 ± 2.35%), percentage yield (89.62 ± 1.36%), and drug content (86.94 ± 2.25%), with a statistically significant improvement ($p < 0.05$) compared to the preliminary batches. SEM analysis revealed spherical and uniform microspheres with acceptable micromeritic properties. In vitro drug release studies demonstrated sustained release behavior, achieving 89.67 ± 1.26% drug release over 6 h, significantly higher than that of the marketed formulation (51.47 ± 1.37%, $p < 0.05$). Drug release kinetics followed the Higuchi model, indicating diffusion-controlled release, as further supported by the Korsmeyer–Peppas analysis, which suggested non-Fickian transport. The microspheres were successfully compressed into tablets, which exhibited acceptable hardness (3.3 kg/cm2), low friability (0.18%), and uniform drug content (90.45 ± 2.35%). Stability studies confirmed no significant changes in the physicochemical properties over 30 days.

In summary, the developed microsphere-based tablet demonstrated enhanced encapsulation efficiency, controlled drug release, and improved performance compared to conventional formulations, highlighting its potential as an effective sustained-release oral drug delivery system for amisulpride.

Keywords: Amisulpride, Microspheres, Eudragit RL 100, Solvent Evaporation, optimization, characterization, Controlled Release, Tablet Formulation.

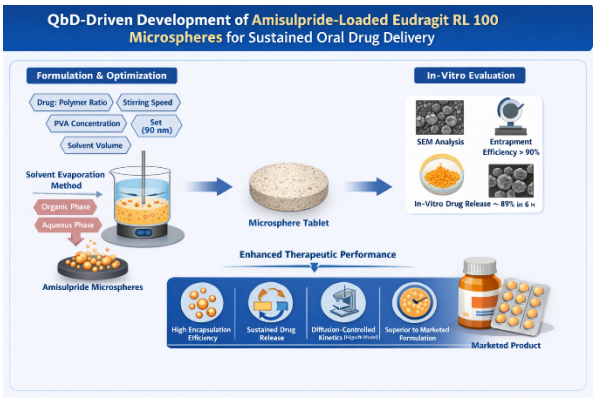
How to cite this article: Bokada A, Patani M, Nangha B, Chaudhari P, Patel A, Sonawane H, Upadhyay S. Development, Optimization, and Comprehensive Characterization of Eudragit RL 100-Based Amisulpride Microspheres for Sustained Oral Drug Delivery: Process Parameter Optimization and Comparative In-Vitro Evaluation. Int J Drug Deliv Technol. 2026;16(19s): 443-461. DOI: 10.25258/ijddt.16.19s.53

Source of support: Nil

Conflict of interest: None

Graphical Abstract

Schematic representation of the development, optimization, and evaluation of amisulpride-loaded Eudragit RL 100 microspheres for sustained oral drug delivery



Highlights

- Developed Amisulpride-loaded Eudragit RL 100 microspheres using solvent evaporation technique
- Optimized formulation achieved high entrapment efficiency (~90%) and yield (~89%)
- Microspheres exhibited uniform spherical morphology with good flow properties
- Sustained drug release (~89% in 6 h) significantly higher than marketed formulation
- Drug release followed diffusion-controlled mechanism (Higuchi model)
- Microsphere-loaded tablets showed acceptable mechanical strength and stability
- Formulation demonstrated superior performance compared to conventional dosage form

INTRODUCTION

Amisulpride is a second-generation (atypical) antipsychotic that is widely prescribed for the management of schizophrenia and related psychotic disorders owing to its selective antagonism of dopamine D_2/D_3 receptors, which contributes to its efficacy against both positive and negative symptoms [1,2]. However, its poor aqueous solubility and limited permeability result in variable oral bioavailability and inconsistent therapeutic outcomes [3]. Such pharmacokinetic limitations necessitate the development of advanced drug delivery systems capable of improving dissolution behavior and maintaining sustained plasma drug levels [4].

In recent years, polymer-based drug delivery systems have emerged as an effective approach to enhance the performance of poorly soluble drugs. Among these, polymeric microspheres have gained considerable attention because of their ability to efficiently encapsulate drugs, protect drug molecules from degradation, and provide controlled and sustained release profiles [5–8]. The release behavior from microspheres is primarily governed by diffusion through the polymer matrix and can be modulated by formulation and process parameters. Consequently, the systematic optimization of these variables is critical to achieve reproducible and efficient drug delivery systems [9].

Eudragit RL 100, a copolymer containing quaternary ammonium groups, is widely utilized in sustained-release formulations because of its permeability and swelling characteristics, which facilitate controlled drug diffusion [11]. In combination, hydrophobic polymers, such as ethyl cellulose, contribute to matrix formation and retard drug release, thereby enhancing sustained delivery [12]. Solvent evaporation is one of the most reliable and scalable methods for preparing polymeric microspheres, offering advantages such as controlled particle size, high encapsulation efficiency, and reproducibility [13].

Recent advancements in drug delivery systems, including microsponges, proniosomes, nanoemulgels, and floating insitu gels, have demonstrated significant improvements in drug targeting, release modulation, and therapeutic performance [10,14,15,18]. Nanocarrier systems, such as niosomes based on non-ionic surfactants, have shown promising potential in improving drug solubility, stability, and bioavailability, particularly for poorly soluble drugs [19]. These studies highlight the growing emphasis on innovative carrier systems and formulation strategies in modern pharmaceutical research.

Despite these advancements, only a limited number of studies have focused on the development of a combined microsphere-based tablet system for amisulpride that integrates both enhanced dissolution and sustained drug release. Furthermore, comprehensive optimization of formulation and process parameters, along with

comparative evaluation against marketed formulations, has not been adequately explored.

Therefore, the present study aimed to develop and optimize amisulpride-loaded Eudragit RL 100 microspheres using the solvent evaporation technique and to incorporate them into a microsphere-based tablet dosage form. The optimized formulation was systematically evaluated for its physicochemical properties, drug release kinetics, and stability, and comparatively assessed against a marketed formulation to establish its potential as an improved sustained-release oral drug delivery system.

MATERIALS AND METHODS

Materials

Amisulpride was procured from a certified pharmaceutical supplier and used as received. Eudragit RL 100 and ethyl cellulose were obtained from commercial sources. Dichloromethane (DCM) was used as the organic solvent. Polyvinyl alcohol served as the stabilizer in the aqueous phase. Mannitol, hydroxypropyl methylcellulose, talc, and magnesium stearate were used for tablet formulation. Sodium hydroxide and potassium dihydrogen orthophosphate were used to prepare a phosphate buffer (pH 7.4). All reagents were of analytical grade, and distilled water was used throughout the study.

Preformulation Studies

Organoleptic properties, including color, odor, and physical appearance, were assessed visually. The melting point was determined using the capillary method.

Solubility studies were performed in water, ethanol, acetone, chloroform, ether, and phosphate buffer (pH 7.4) using the equilibrium solubility method. The samples were filtered and analyzed using a UV–Vis spectrophotometer.

The wavelength of maximum absorbance (λmax) was determined by scanning drug solutions between 200 and 400 nm. A calibration curve was constructed in phosphate buffer (pH 7.4) by plotting concentration versus absorbance.

Drug–polymer compatibility was evaluated using Fourier transform infrared (FT-IR) spectroscopy. Thermal analysis was performed using differential scanning calorimetry (DSC). The particle size of pure drug was determined using optical microscopy and a particle size analyzer.

Preparation of Amisulpride Microspheres

Microspheres were prepared using the solvent evaporation technique. The drug and polymer were dissolved in dichloromethane to form the internal organic phase. This solution was added dropwise to an aqueous phase containing polyvinyl alcohol under continuous mechanical stirring to form an oil-in-water emulsion.

Stirring was maintained for a predetermined time to allow solvent evaporation and solidification of the microspheres. The formed microspheres were collected by filtration, washed with distilled water to remove residual stabilizer, and dried in a hot air oven.

Experimental Design and Optimization (QbD Approach)

A quality-by-design (QbD)-based approach was employed to systematically optimize the formulation and process parameters affecting microsphere characteristics. A three-factor, three-level Box–Behnken design (BBD) was utilized to evaluate the influence of independent variables, including drug-to-polymer ratio (X_1), stirring speed (X_2), and stabilizer concentration (X_3), on critical quality attributes, such as entrapment efficiency, percentage yield, and drug release.

The experimental design and statistical analysis were performed using Design-Expert (version 13; Stat-Ease Inc., USA). Polynomial equations were generated to evaluate the relationship between independent and dependent variables, and response surface plots were constructed to identify optimal formulation conditions.

The optimized formulation was selected based on the desirability function criteria to achieve maximum entrapment efficiency, controlled drug release, and an acceptable yield.

Optimization of Formulation Variables

The formulation variables, including drug-to-polymer ratio, internal phase volume, external phase stabilizer concentration, stirring speed, and stirring time, were systematically varied. Each batch was evaluated for percentage yield, entrapment efficiency, and drug content. The optimized formulation was selected based on a comparative evaluation of these parameters.

Characterization of Microspheres

The mean particle size was determined by measuring randomly selected particles using optical microscopy. The surface morphology was examined using scanning electron microscopy (SEM). Entrapment efficiency was determined by dissolving microspheres in a phosphate buffer (pH 7.4) and analyzing the drug concentration spectrophotometrically.

Micromeritic properties, including the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, were evaluated.

In-vitro Drug Release Study

In vitro drug release studies were conducted using a USP Type II (paddle) dissolution apparatus in phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C and stirred at 100 rpm. Samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 252 nm.

Drug Release Kinetics Modeling

To elucidate the mechanism of drug release, the in-vitro dissolution data of the optimized formulation were fitted to various kinetic models.

- **Zero-order model:** evaluates constant drug release over time
- **First-order model:** describes concentration-dependent release
- **Higuchi model:** explains drug release as a diffusion process based on square root of time
- **Korsmeyer–Peppas model:** characterizes the mechanism of drug release using release exponent (n)

The model that best fit the release data was selected based on the highest regression coefficient (R^2) value. The Korsmeyer–Peppas model was used to interpret the release mechanism (Fickian or non-Fickian diffusion).

Formulation of Microsphere-Loaded Tablets
The optimized microspheres were blended with mannitol, HPMC, talc, and magnesium stearate. The powder blend was evaluated for its pre-compression parameters. The tablets were prepared by direct compression using a tablet compression machine**.**

Evaluation of Tablets
Tablets were evaluated for physical appearance, thickness, weight variation, hardness, friability, and drug content according to standard pharmacopoeial procedures.

In-vitro dissolution studies were performed under conditions similar to those used for microsphere evaluation and compared with a marketed formulation.

Stability Studies
Stability studies were conducted by storing the optimized formulation at room temperature for 30 days. The samples were evaluated at predetermined intervals for hardness, weight variation, friability, and drug content.

Statistical Analysis
All experiments were performed in triplicate (n = 3), and results are expressed as the mean ± standard deviation. Statistical significance was evaluated using one-way ANOVA, and a p-value < 0.05 was considered statistically significant.

RESULTS

Preformulation Studies of Amisulpride
Preformulation studies confirmed the suitability of amisulpride for microsphere formulation. The drug exhibited a melting point in the range of 126–128°C, consistent with reported standards, indicating purity. The λmax was observed at 252 nm (Figure 1), and the calibration curve demonstrated good linearity (Figure 2), confirming compliance with Beer–Lambert law.

FT-IR analysis (Figure 3 and Table 1) confirmed the presence of characteristic functional groups without any significant shift in peak positions, indicating compatibility between the drug and selected polymers. Particle size analysis (Figure 4) revealed a crystalline morphology, supporting the need for formulation modification.

Organoleptic Characteristics
Amisulpride was observed as a white crystalline solid with a characteristic odor. The uniform appearance and absence of discoloration or foreign particles indicated acceptable physical purity and suitability for formulation development.

Melting Point Determination
The melting point of amisulpride was determined using a capillary tube method and was found to be in the range of 126–128°C. This value corresponds closely with the reported pharmacopoeial data, confirming the identity and purity of the drug and indicating the absence of significant degradation or impurities.

Solubility Study
Solubility profiling demonstrated that amisulpride is very slightly soluble in water, confirming its poor aqueous solubility. However, improved solubility was observed in a phosphate buffer (pH 7.4) and in organic solvents, such as ethanol, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF). The enhanced solubility in buffered and organic media supports the selection of the solvent evaporation technique for microsphere preparation and justifies the use of polymer-based controlled-release systems to overcome solubility-related limitations.

Identification and Determination of Wavelength Maxima (λmax)
The absorption maximum (λmax) of amisulpride was determined using UV-Vis spectrophotometry to establish a reliable analytical wavelength for quantitative estimation. A stock solution (1000 µg/mL) was prepared in methanol and subsequently diluted to obtain a working concentration of 10 µg/mL. The solution was scanned over the wavelength range of 200–400 nm.

Amisulpride exhibited a distinct absorption maximum at 252 nm. This value is consistent with reported pharmacopoeial data, confirming the identity of the drug and validating the selected wavelength for subsequent analytical procedures. The sharp and well-defined peak indicates the adequate sensitivity and specificity of the method for routine quantitative analysis. Figure 1 illustrates the UV absorption spectrum of Amisulpride showing the characteristic peak at 252 nm.

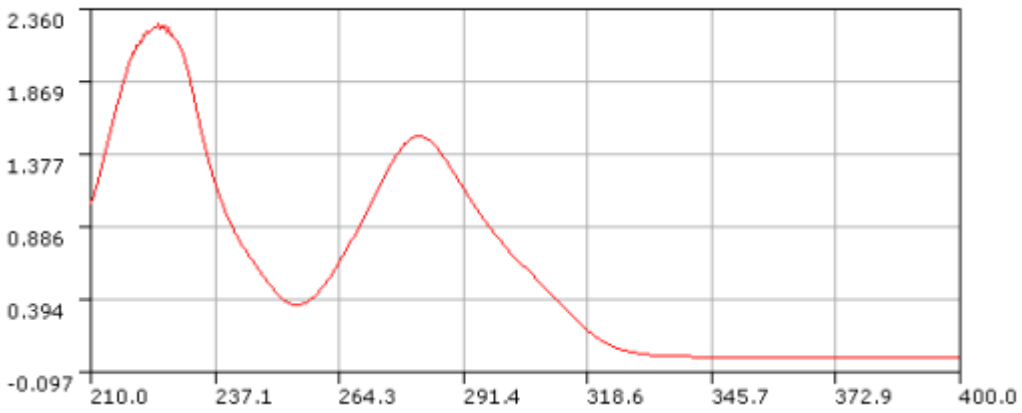


Figure 1: Wavelength max (λmax) of Amisulpride

Preparation of Calibration Curve of Amisulpride

A calibration curve was constructed to establish the linear relationship between concentration and absorbance for quantitative estimation of Amisulpride. Standard solutions were prepared in a phosphate buffer (pH 7.4) within the concentration range of 0–10 µg/mL. The absorbance of each solution was measured at 252 nm using a UV–Vis spectrophotometer.

The absorbance values increased proportionally with increasing drug concentration, demonstrating a direct concentration-dependent response. The calibration plot of concentration versus absorbance exhibited linear behavior over the studied range, indicating compliance with Beer–Lambert's law. The regression analysis confirmed the suitability of the method for accurate and reproducible quantification of Amisulpride in subsequent formulation and release studies. Figure 2 represents the calibration curve of Amisulpride in phosphate buffer pH 7.4.

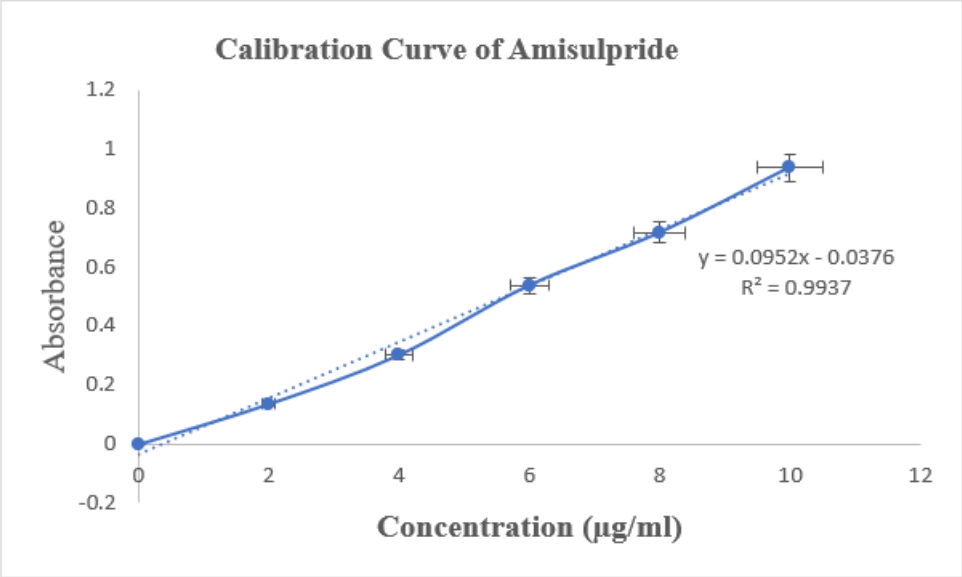


Figure 2: Calibration Curve of Amisulpride

Identification of Amisulpride by FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) spectroscopy was performed to confirm the structural identity of Amisulpride and to verify the integrity of its functional groups. The sample was prepared using the potassium bromide (KBr) pellet method by compressing approximately 1 mg of drug with dry KBr using a hydraulic pellet press. The spectrum was recorded over the range of 4000–400 cm^{-1}.

The obtained spectrum exhibited characteristic absorption bands corresponding to the functional groups present in the molecular structure of Amisulpride. A prominent peak observed at 1685.49 cm^{-1} corresponds to the amide carbonyl (C=O) stretching vibration. The band at 1350.48

cm^{-1} is attributed to sulfonamide (S=O) stretching, while the peak at 1510.35 cm^{-1} falls within the aromatic ring stretching region. The methoxy (C–O) stretching vibration was observed at 1275.68 cm^{-1}. Additionally, the N–H stretching vibration appeared at 3256.67 cm^{-1}.

All observed peaks are in close agreement with the reported standard wavenumber ranges for Amisulpride, confirming the presence of key functional groups and supporting the structural authenticity and purity of the drug. No additional peaks indicating degradation or impurity-related functional groups were detected. Figure 3 shows the FT-IR spectrum of Amisulpride, and Table 1 summarizes the characteristic absorption peaks.

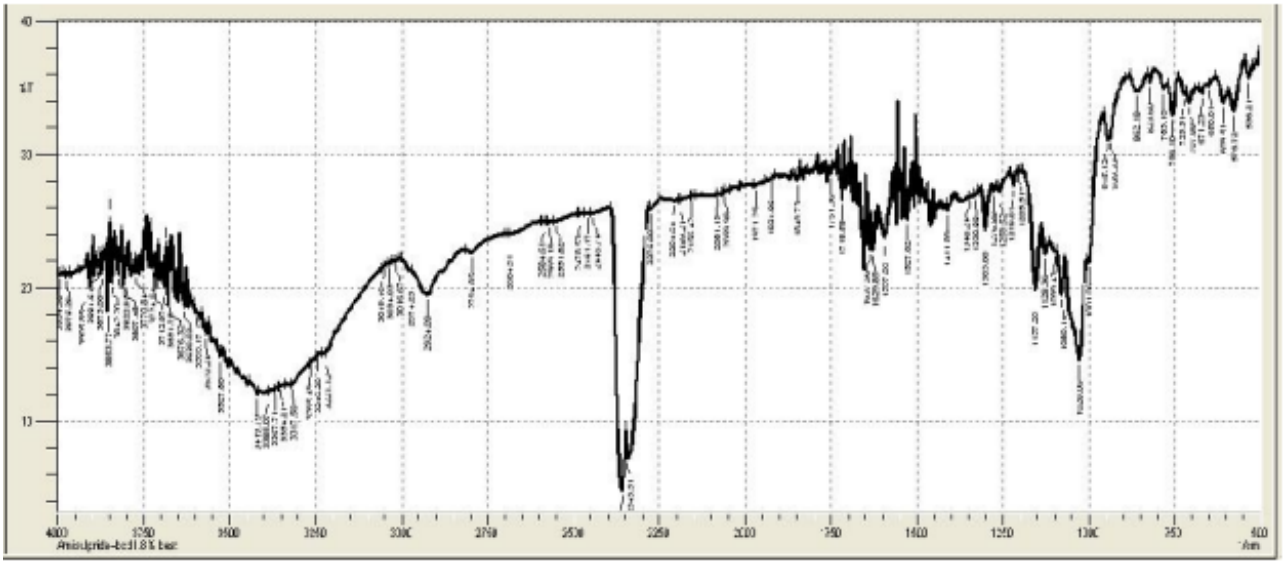


Figure 3: FTIR of Amisulpride

Table: 1: Characteristic FTIR Peaks of Amisulpride

Type of Vibration	Standard Wave Number (Cm-1)	Observed Wave Number (Cm-1)
Aromatic Ring	1400-1600	1510.35
Amide Group (C=O)	1650–1700	1685.49
Sulfonamide Group (S=O)	1335–1370	1350.48
Methoxy Group (C-O)	1000-1300	1275.68
N-H	3300-3500	3256.67

The obtained FT-IR spectrum complies with standard data which further confirms the drug identity and purity.

Particle Size Study of Amisulpride

Particle size analysis of pure Amisulpride was performed to evaluate its physical characteristics prior to formulation. The study was conducted using optical microscopy and particle size analysis techniques, as described in the methodology section. The observed particles exhibited an irregular crystalline morphology, consistent with the physical nature of the drug.

The measured particle size distribution indicated that Amisulpride existed in the micrometer range, confirming its crystalline particulate form. Particle size is a critical parameter influencing dissolution behavior, surface area, and formulation performance. The relatively large crystalline particle size observed supports the need to formulate microspheres to enhance surface characteristics and modulate drug release. Figure 4 illustrates the representative particle size distribution of pure Amisulpride.

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 817.67	Peak 1:	4169	49.4	1038
PdI: 0.940	Peak 2:	612.2	44.5	265.8
Intercept: 0.169	Peak 3:	5.281	6.1	1.334

Result quality : Refer to quality report

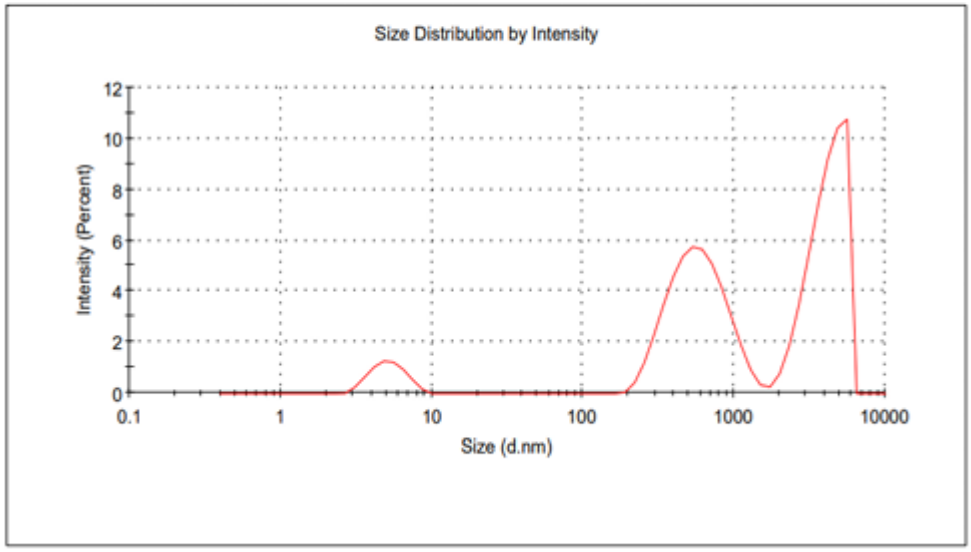


Figure 4: Particle Size Study

Effect of Drug-to-Polymer Ratio on Microsphere Characteristics

The drug-to-polymer ratio significantly influenced the microsphere characteristics, including percentage yield, entrapment efficiency, and drug content ($p < 0.05$), as presented in **Table 3**.

An increase in polymer concentration improved encapsulation efficiency owing to enhanced matrix formation, which reduced drug diffusion into the external phase. Among all the formulations, the 1:10 ratio (ASMS5) demonstrated optimal performance. The comparative trend is illustrated in **Figure 5**, which shows maximum performance at an intermediate polymer concentration.

Table 2: Preliminary Trail Batch for Selection of Drug: Polymer Ratio

Batch	Polymer	Drug: Polymer ratio	Type of Internal phase	Vol. of Internal Phase (ml)	Conc. of external phase (%)	Stirring Speed R.P.M	Stirring Time (Mins)
ASMS1	Ethyl cellulose	1:5	DCM	10	1	1500	90
ASMS2		1:10	DCM	10	1	1500	90
ASMS3		1:15	DCM	10	1	1500	90
ASMS4	Eudragit RL 100	1:5	DCM	10	1	1500	90
ASMS5		1:10	DCM	10	1	1500	90
ASMS6		1:15	DCM	10	1	1500	90

The performance parameters of the prepared microspheres, including percentage yield, entrapment efficiency, and drug content, are summarized in Table 3. A gradual improvement in encapsulation characteristics was

observed with increasing polymer concentration. For the ethyl cellulose-based formulations (ASMS1–ASMS3), increasing the drug-to-polymer ratio from 1:5 to 1:15 enhanced yield and entrapment efficiency, indicating improved matrix formation and reduced drug diffusion into the external phase during emulsification.

Eudragit RL 100-based formulations (ASMS4–ASMS6) demonstrated comparatively superior performance. Among all batches, ASMS5 (drug:polymer ratio of 1:10) exhibited the highest percentage yield (76.48 ± 1.26%), entrapment efficiency (84.37 ± 1.59%), and drug content (92.34 ± 1.35%). The enhanced performance of this batch may be attributed to the optimal polymer concentration, which provided sufficient viscosity for droplet stabilization while maintaining efficient drug incorporation within the polymeric matrix.

Table 3: Effect of Drug: Polymer Ratio

Batch	% Yield (Mean ± S.D.) (n = 3)	Entrapment Efficiency (%) (Mean ± S.D.) (n = 3)	% Drug Content (Mean ± S.D.) (n = 3)
ASMS1	67.43±2.26	68.44±1.26	73.53±2.05
ASMS2	71.88±1.25	72.81±1.24	76.55±1.24
ASMS3	73.45±1.26	76.43±1.02	80.41±1.26
ASMS4	69.09±2.24	77.81±1.34	84.79±2.02
ASMS5	76.48±1.26	84.37±1.59	92.34±1.35
ASMS6	71.70±1.02	81.20±1.78	88.65±1.26

Increasing the polymer concentration to 1:15 ASMS6) resulted in a slight decline in the performance parameters, possibly due to increased internal phase viscosity affecting emulsification efficiency and resulting in partial drug loss. The comparative trends in formulation performance are illustrated in Figure 5, which highlights the optimal behavior at the 1:10 ratio. Based on these findings, a drug-to-polymer ratio of 1:10 using Eudragit RL 100 was selected for subsequent optimization studies.

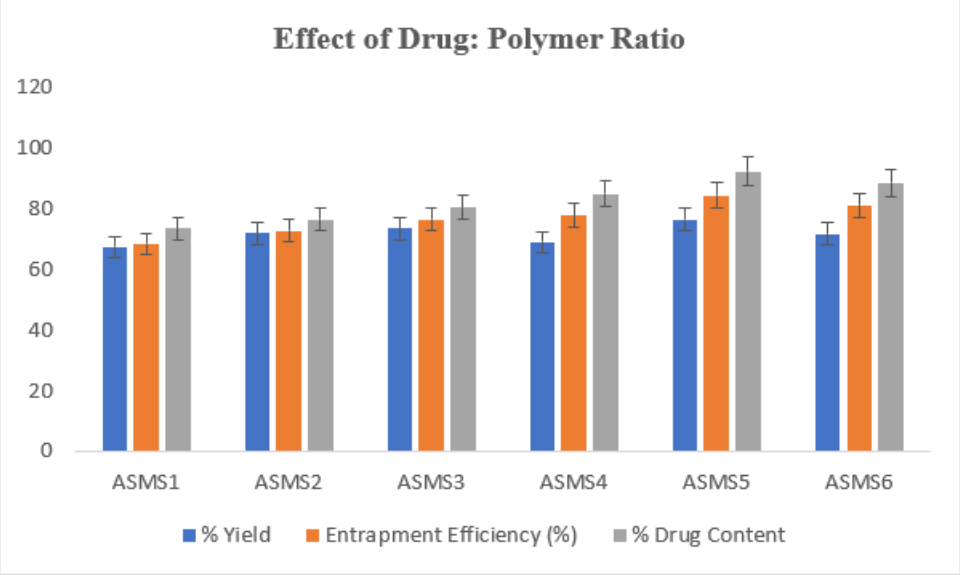


Figure 5: Effect of Drug: Polymer Ratio

Effect of Internal Phase Volume on Microsphere Characteristics

The influence of the internal phase volume on microsphere characteristics is presented in Table 5. Increasing the

volume from 5 to 10 mL improved encapsulation efficiency and yield owing to the optimal viscosity facilitating uniform droplet formation. However, further increasing the volume to 15 mL resulted in decreased performance. This trend is clearly depicted in Figure 6, indicating that an excessive solvent volume negatively affects emulsification stability.

Table 4: Preliminary Trail Batch for Selection of Internal Phase Volume

Batch	Polymer	Drug: Polymer Ratio	Type of Internal phase	Vol. of Internal Phase (ml)	Conc. of external phase (%)	Stirring Speed R.P.M	Stirring Time (Mins)
ASMS7	Eudragit RL 100	1:10	DCM	5	1	1500	90
ASMS8		1:10	DCM	10	1	1500	90
ASMS9		1:10	DCM	15	1	1500	90

The corresponding performance parameters are presented in Table 5, and the comparative trend is illustrated in Figure 6. The internal phase volume markedly influenced the microsphere characteristics. Increasing the solvent volume from 5 mL (ASMS7) to 10 mL (ASMS8) resulted in a substantial improvement in the percentage yield, entrapment efficiency, and drug content. Batch ASMS8 demonstrated the highest yield (85.34 ± 2.21%), entrapment efficiency (82.44 ± 1.34%), and drug content (90.09 ± 1.25%). The improved performance at 10 mL internal phase may be attributed to the optimal viscosity of the organic phase, which facilitates uniform droplet formation and efficient drug entrapment during emulsification. However, further increasing the solvent volume to 15 mL (ASMS9) resulted in a reduction in yield and encapsulation parameters. This decline may be due to excessive dilution of the polymer concentration, leading to unstable droplet formation and increased diffusion of the drug into the external aqueous phase. Based on these observations, 10 mL was selected as the optimal internal phase volume for further studies.

Table 5: Effect of Internal Phase Volume

Batch	% Yield (Mean ± S.D.) (n = 3)	Entrapment Efficiency (%) (Mean ± S.D.) (n = 3)	% Drug Content (Mean ± S.D.) (n = 3)
ASMS7	72.24±1.2	70.54±1.26	78.51±1.20
ASMS8	85.34±2.21	82.44±1.34	90.09±1.25
ASMS9	75.48±1.35	76.45±1.59	82.34±1.24

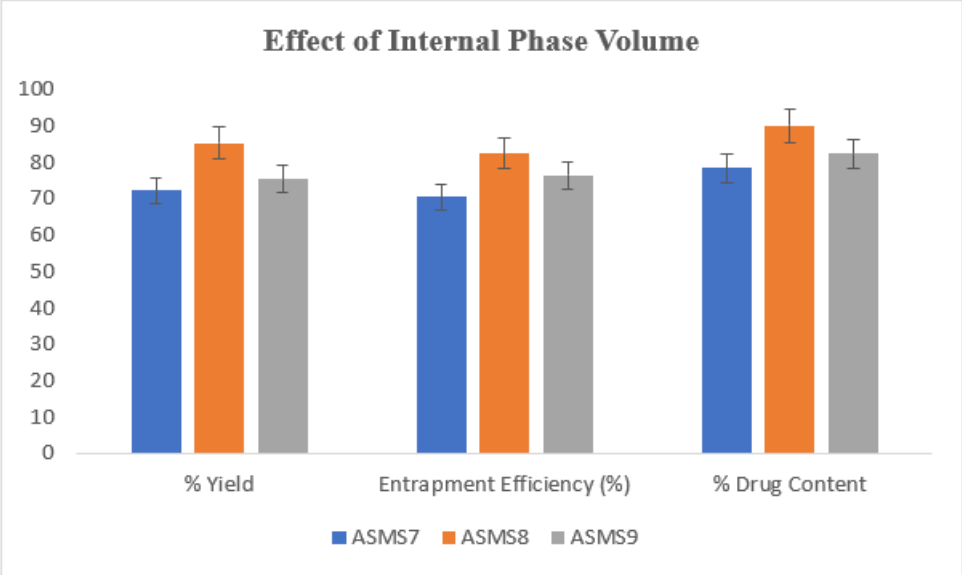


Figure 6: Effect of Internal Phase Volume

Effect of External Phase Concentration on Microsphere Characteristics

The effects of the stabilizer concentration on microsphere properties are summarized in **Table 7**. Increasing the PVA concentration up to 1% significantly improved the entrapment efficiency and yield ($p < 0.05$). At a higher concentration (1.5%), a decline in performance was observed. The comparative effects are shown in **Figure 7**, which highlights the optimal stabilizer concentration required for efficient microsphere formation.

Table 6: Preliminary Trail Batch for Selection of External phase Concentration

Batch	Polymer	Drug: Polymer Ratio	Type of Internal phase	Vol. of Internal Phase (ml)	Conc. of external phase (%)	Stirring Speed R.P.M	Stirring Time (Mins)
ASMS10	Eudragit RL 100	1:10	DCM	10	0.5	1500	90
ASMS11		1:10	DCM	10	1	1500	90
ASMS12		1:10	DCM	10	1.5	1500	90

The resulting microsphere characteristics, including percentage yield, entrapation efficiency, and drug content, are summarized in Table 7, and the comparative trend is illustrated in Figure 7. The data indicate that the stabilizer concentration plays a critical role in emulsification efficiency and particle stabilization.

Increasing the PVA concentration from 0.5% (ASMS10) to 1% (ASMS11) resulted in a substantial improvement in yield and encapsulation efficiency. Batch ASMS11 demonstrated the highest percentage yield (82.43 ± 1.26%), entrapment efficiency (84.97 ± 2.15%), and drug content (91.43 ± 2.45%). This enhancement may be attributed to improved interfacial stabilization at the oil–water interface, which reduces droplet coalescence and minimizes drug diffusion into the external aqueous phase during solvent evaporation. However, further increasing the stabilizer concentration to 1.5% (ASMS12) led to a slight decline in the performance parameters. The reduction may be associated with an increased viscosity of the external phase, which can interfere with efficient solvent diffusion and may result in irregular particle formation or partial drug leakage.

Overall, the results demonstrated that a 1% external phase concentration provided optimal stabilization during emulsification, promoting efficient microsphere formation, and enhanced drug encapsulation. Therefore,

this concentration was selected for subsequent optimization studies.

Table 7: Effect of External Phase Concentration

Batch	% Yield (Mean ± S.D.) (n = 3)	Entrapment Efficiency (%) (Mean ± S.D.) (n = 3)	% Drug Content (Mean ± S.D.) (n = 3)
ASMS10	72.90±1.34	74.48±2.24	78.88±2.58
ASMS11	82.43±1.26	84.97±2.15	91.43±2.45
ASMS12	78.43±1.57	80.57±2.34	82.54±2.67

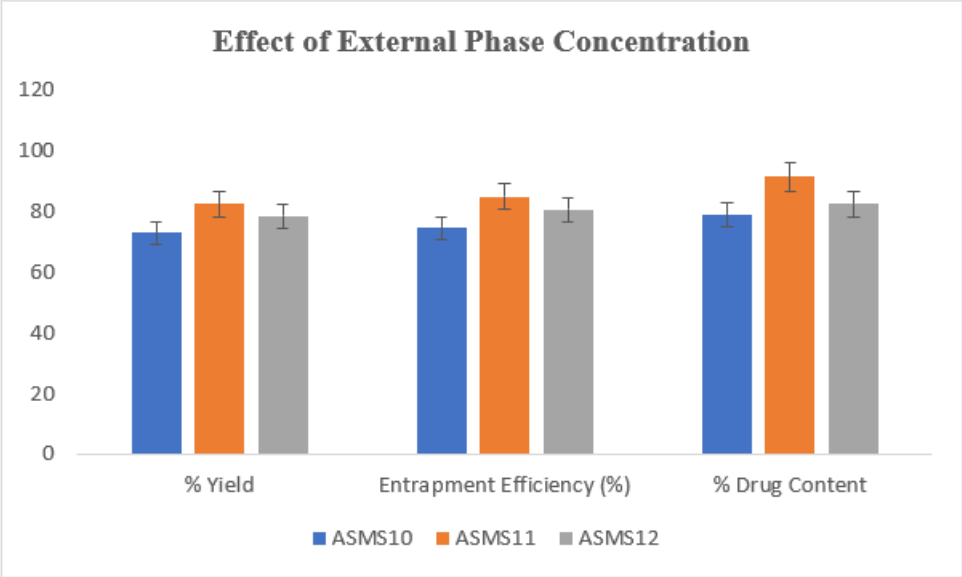


Figure 7: Effect of External Phase Concentration

Effect of Stirring Speed on Microsphere Characteristics

The influence of stirring speed is presented in Table 9. Increasing the speed from 1000 to 1500 rpm improved encapsulation efficiency owing to better droplet formation. However, increasing the speed to 2000 rpm resulted in reduced performance. The trend is illustrated in Figure 8, which indicates that excessive shear leads to drug loss.

Table 8: Preliminary Trail Batch for Selection of Stirring Speed

Batch	Polymer	Drug: Polymer Ratio	Type of Internal phase	Vol. of Internal Phase (ml)	Conc. of external phase (%)	Stirring Speed R.P.M	Stirring Time (Mins)
ASMS13		1:10	DCM	10	1	1000	90

ASMS14	Eudragit	1:10	DCM	10	1	1500	90
ASMS15	RL 100	1:10	DCM	10	1	2000	90

The resulting performance parameters, including percentage yield, entrapment efficiency, and drug content, are summarized in Table 9, and the comparative trend is illustrated in Figure 8. The stirring speed significantly influenced the emulsification efficiency and microsphere characteristics.

Increasing the stirring speed from 1000 rpm (ASMS13) to 1500 rpm (ASMS14) resulted in improved yield and encapsulation efficiency. Batch ASMS14 exhibited the highest percentage yield (79.83 ± 1.16%), entrapment efficiency (85.40 ± 1.35%), and drug content (89.10 ± 2.15%). The enhancement observed at 1500 rpm may be attributed to the sufficient shear force facilitating uniform droplet formation, leading to improved polymeric matrix solidification and reduced drug diffusion into the external phase.

However, further increasing the stirring speed to 2000 rpm (ASMS15) resulted in a decline in the yield and encapsulation parameters. Excessive agitation may produce very fine droplets with an increased surface area, potentially enhancing drug diffusion into the aqueous phase during solvent evaporation and reducing entrapment efficiency.

An overall stirring speed of 1500 rpm provided an optimal balance between droplet size reduction and stable microsphere formation. Therefore, 1500 rpm was selected as the optimized stirring speed for subsequent formulation development.

Table 9: Effect of Stirring Speed

Batch	% Yield (Mean ± S.D.) (n = 3)	Entrapment Efficiency (%) (Mean ± S.D.) (n = 3)	% Drug Content (Mean ± S.D.) (n = 3)
ASMS13	74.58±1.35	77.51±1.25	81.60±2.35
ASMS14	79.83±1.16	85.40±1.35	89.10±2.15
ASMS15	70.43±1.57	73.50±1.56	76.09±2.48

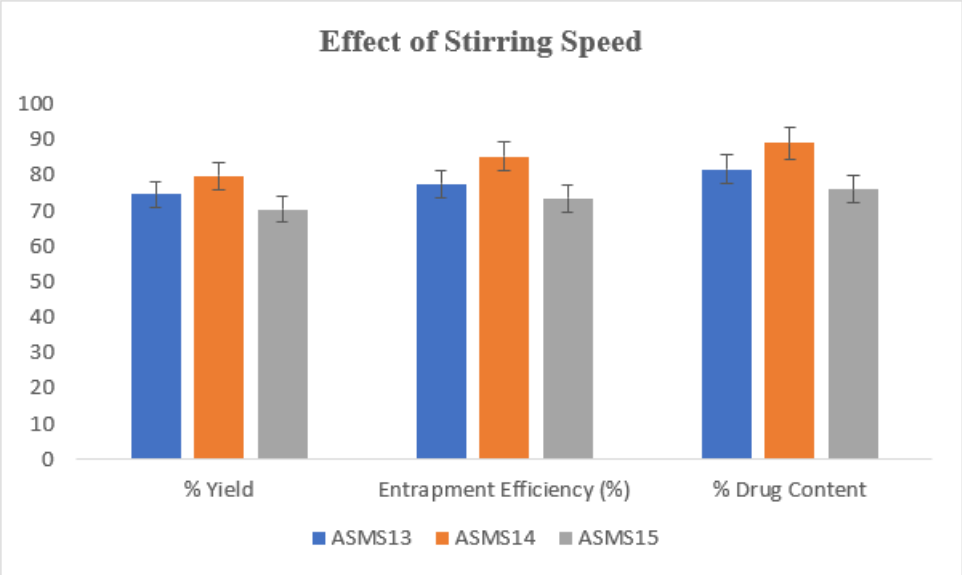


Figure 8: Effect of Stirring Speed

Effect of Stirring Time on Microsphere Characteristics
The effects of stirring time on microsphere characteristics are summarized in Table 11. An optimal duration of 90 min provided maximum encapsulation efficiency and yield. Shorter or longer durations resulted in reduced performance. This trend is shown in Figure 9, confirming the importance of an optimized stirring time.

Table 10: Preliminary Trail Batch for Selection of Stirring Time

Batch	Polymer	Drug: Polymer Ratio	Type of Internal Phase	Vol. of Internal Phase (ml)	Conc. of external phase (%)	Stirring Speed R.P.M	Stirring Time (Mins)
ASMS16	Eudragit RL 100	1:10	DCM	10	1	1500	60
ASMS17		1:10	DCM	10	1	1500	90
ASMS18		1:10	DCM	10	1	1500	120

The performance parameters of the resulting microspheres are summarized in Table 11, and the comparative trends are illustrated in Figure 9. Stirring time affected the production yield, entrapment efficiency, and drug content.

An increase in stirring time from 60 to 90 min (ASMS16 to ASMS17) resulted in improved yield and encapsulation efficiency. Batch ASMS17 exhibited the highest percentage yield (76.85 ± 1.26%), entrapment efficiency (78.53 ± 1.25%), and drug content (90.81 ± 2.26%). The improvement observed at 90 min may be attributed to sufficient time for complete solvent evaporation and proper solidification of the polymeric droplets, leading to stable microsphere formation and enhanced drug entrapment.

However, extending the stirring time to 120 min (ASMS18) resulted in a slight decline in the yield and encapsulation parameters. Prolonged stirring may promote drug diffusion into the external phase or cause partial erosion of the formed microspheres, thereby reducing the overall encapsulation efficiency.

Overall, a stirring time of 90 min provided optimal conditions for solvent evaporation and microsphere stabilization; therefore, it was selected as the optimized stirring time for the formulation.

Table 11: Effect of Stirring Time

Batch	% Yield (Mean ± S.D.) (n = 3)	Entrapment Efficiency (%) (Mean ± S.D.) (n = 3)	% Drug Content (Mean ± S.D.) (n = 3)
ASMS16	69.41±1.35	73.48±1.26	76.77±2.35
ASMS17	76.85±1.26	78.53±1.25	90.81±2.26
ASMS18	74.63±1.24	75.47±1.23	80.43±2.24

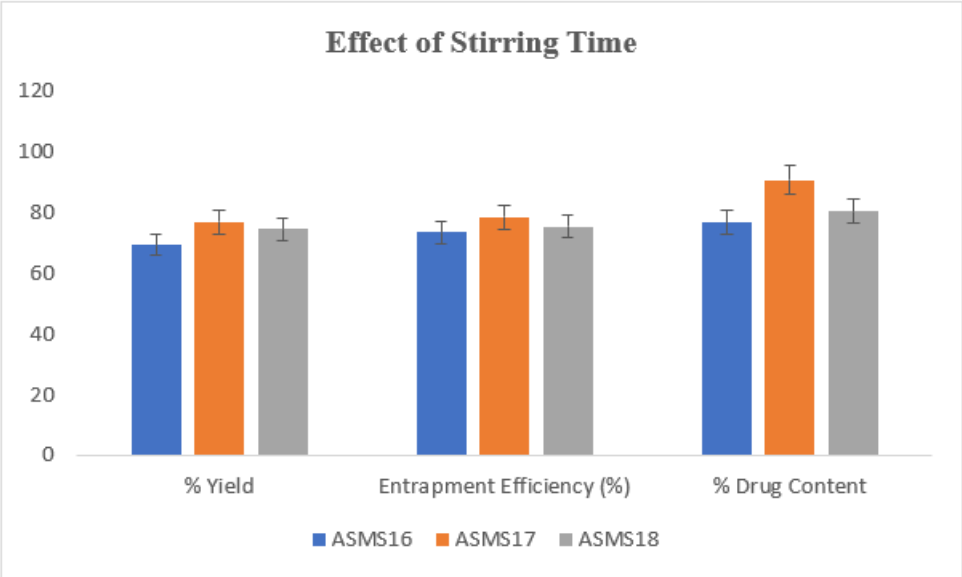


Figure 9: Effect of Stirring Time

Selection of Optimized Batch

Based on the systematic optimization of the formulation variables, the optimized microsphere formulation comprised a drug-to-polymer ratio of 1:10 using Eudragit RL 100, dichloromethane as the internal organic phase (10 mL), 1% polyvinyl alcohol as the external phase stabilizer, a stirring speed of 1500 rpm, and a stirring time of 90 min.

The selected drug-to-polymer ratio provided sufficient polymer matrix density to enhance drug encapsulation while minimizing drug diffusion into the external aqueous phase during emulsification. Eudragit RL 100 was preferred because of its permeability characteristics and ability to form a stable matrix system. Dichloromethane served as a suitable solvent because of its excellent polymer solubility and volatility, facilitating efficient solvent evaporation and microsphere solidification. An internal phase volume of 10 mL ensured optimal viscosity, promoting uniform droplet formation without excessive coalescence.

The use of a 1% stabilizer concentration provided adequate interfacial stabilization during emulsification, preventing droplet aggregation while maintaining efficient solvent diffusion. Stirring at a speed of 1500 rpm generated sufficient shear force to produce uniform droplets without causing excessive fragmentation. Similarly, a stirring time of 90 min allowed for complete solvent evaporation and proper hardening of the microspheres, resulting in stable particle formation.

Overall, these parameters collectively provided an optimal balance between encapsulation efficiency, production yield, and formulation stability; therefore, they were selected for further characterization.

Characterization of Optimized Microspheres

The optimized microspheres exhibited good micromeritic properties, with an angle of repose of 26.62 ± 1.1°, indicating satisfactory flow behavior. Bulk density and tapped density were found to be 0.614 ± 0.01 g/cm³ and 0.822 ± 0.05 g/cm³, respectively. Carr's index (23.74 ± 1.3%) and Hausner's ratio (1.22 ± 0.24) suggested acceptable compressibility and flowability, confirming suitability for tablet compression.

SEM analysis (Figure 10) revealed spherical, discrete, and uniformly distributed microspheres with smooth surfaces, indicating efficient droplet formation and solvent evaporation. Minor surface irregularities may be attributed to polymer precipitation dynamics.

Particle size analysis (Figure 11) showed a narrow and uniform distribution, supporting reproducible drug release behavior. The optimized formulation demonstrated high entrapment efficiency (90.94 ± 2.35%), percentage yield (89.62 ± 1.36%), and drug content (86.94 ± 2.25%), confirming effective drug incorporation and minimal loss during processing.

Overall, the optimized microspheres exhibited desirable physicochemical and morphological characteristics suitable for controlled-release applications.

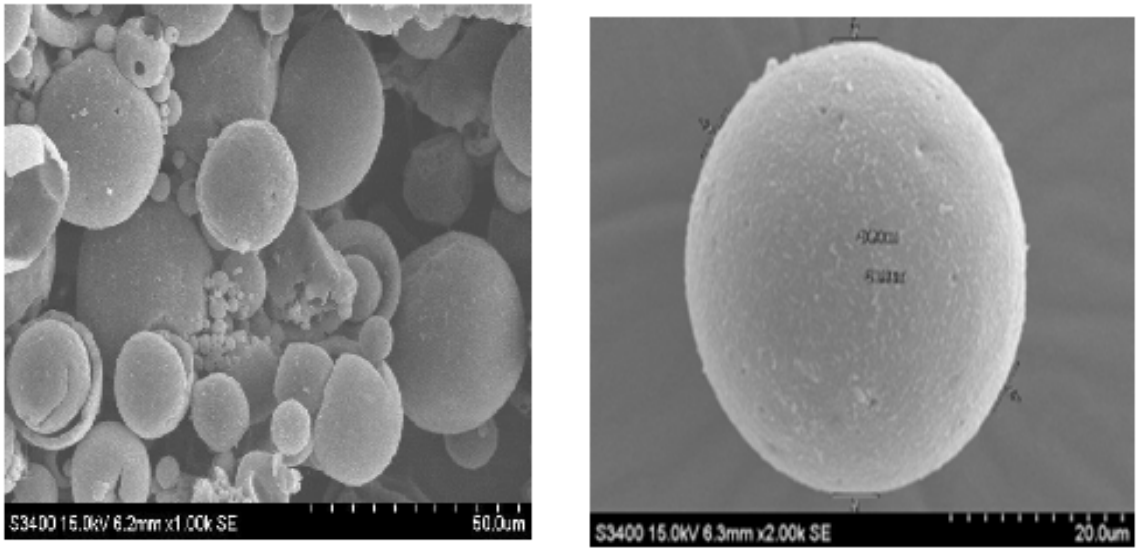


Figure 10: Scanning Electron Microscopy (SEM) of optimized microsphere

Particle Size Analysis of Optimized Microsphere Batch

The particle size distribution of the optimized microsphere formulation was evaluated to assess uniformity and its potential influence on drug release behavior. A representative particle size profile is shown in Figure 11.

The optimized microspheres exhibited a relatively narrow particle size distribution, indicating uniform droplet formation during the emulsification process. Controlled stirring speed and optimized internal phase volume contributed to consistent droplet breakup and stable polymer solidification, resulting in homogeneous microsphere formation.

Particle size plays a critical role in determining the surface area, drug diffusion path length, and release kinetics. The uniform distribution observed in the optimized batch supports reproducible drug release behavior and efficient encapsulation. The absence of excessive fines or oversized aggregates further confirms effective process optimization and stable microsphere formation.

Overall, the particle size characteristics of the optimized formulation were consistent with the selected processing parameters and supported its suitability for controlled-release applications.

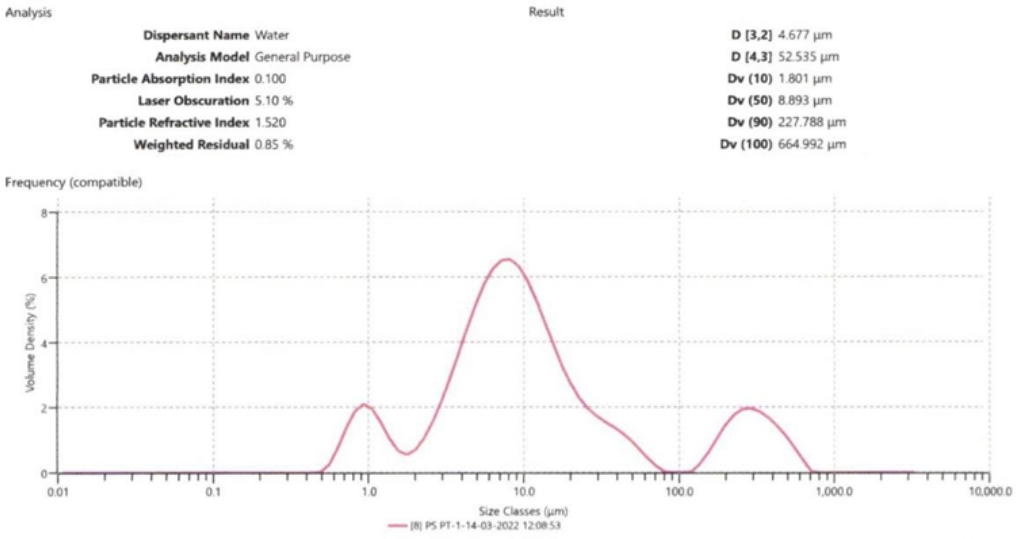


Figure 11: Particle Size Analysis of optimized microsphere batch

Formulation of Optimized Microsphere-Loaded Tablets

Formulation of Microsphere-Loaded Tablets

The optimized microspheres were successfully formulated into tablets containing 20 mg Amisulpride (22.31 mg microspheres). Mannitol was used as a diluent, HPMC as a binder and release modifier, talc as a glidant, and magnesium stearate as a lubricant.

This formulation ensured adequate compressibility, uniformity, and mechanical integrity, supporting its suitability as a sustained-release oral dosage formulation.

Evaluation of Microsphere-Loaded Tablets

Physical Appearance

The prepared tablets were white, odorless, tasteless, and round. The uniform appearance without visible defects or discoloration indicates homogenous blending of microspheres and excipients. The absence of odor and taste enhances patient acceptability and compliance.

Precompression Properties

The powder blend exhibited an angle of repose of 25.41 ± 1.1°, indicating acceptable flow behavior. The bulk and tapped densities were 0.523 ± 0.01 and 0.724 ± 0.05 g/cm³, respectively. The calculated Carr's index (22.47 ± 1.3%) and Hausner's ratio (1.34 ± 0.24) suggested fair flowability with moderate compressibility. These results confirm that the blend possessed suitable characteristics for direct compression without the need for extensive flow enhancers.

Post-Compression Evaluation

The compressed tablets demonstrated a thickness of 2.1 ± 0.02 mm and a mean weight of 298.5 ± 3 mg, indicating uniform die filling and consistent compression. The hardness was 3.3 ± 0.02 kg/cm², reflecting adequate mechanical strength to withstand handling and packaging. Friability was 0.18 ± 0.01%, well below the pharmacopoeial limit of 1%, confirming structural robustness.

The drug content of the tablets was 90.45 ± 2.35%, indicating a uniform distribution of amisulpride within the dosage form and consistent dose delivery.

Overall, the optimized microsphere-loaded tablets exhibited acceptable pharmaceutical quality attributes, including mechanical strength, uniformity, and drug content consistency, supporting their suitability for sustained-release oral administration.

In-Vitro Drug Release Study of Amisulpride Microsphere-Loaded Tablets

The in vitro dissolution profile (**Figure 12**) demonstrated markedly improved and sustained drug release from the optimized microsphere-loaded tablets compared with the marketed formulation. The optimized batch exhibited an initial release of 73.50 ± 1.26% at 1 h, which may be attributed to the surface-associated drug and enhanced wettability.

Thereafter, controlled and sustained release was observed, reaching 89.67 ± 1.26% at 6 h, which was significantly higher than that of the marketed formulation (51.47 ± 1.37%, $p < 0.05$). This behavior confirms effective drug encapsulation and diffusion through the polymeric Eudragit matrix.

The release data were fitted to kinetic models, yielding R^2 values of 0.91 (zero-order), 0.94 (first-order), 0.98 (Higuchi), and 0.96 (Korsmeyer–Peppas). The best fit with the Higuchi model indicates diffusion-controlled release, whereas the Peppas model suggests a non-Fickian mechanism involving both diffusion and polymer relaxation.

The similarity factor was calculated as **f2 = 32.45**, confirming a significant difference between the optimized and marketed formulations and demonstrating improved sustained-release performance.

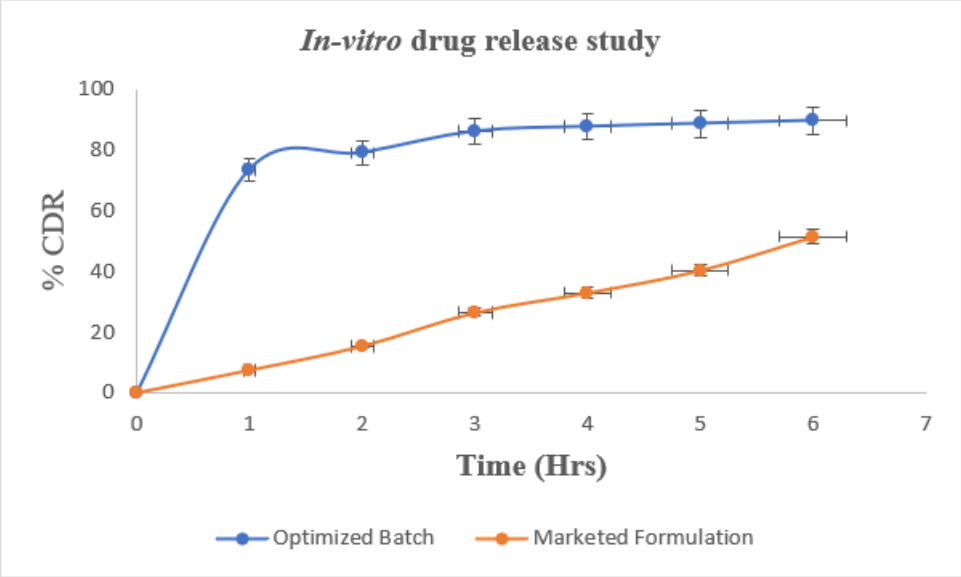


Figure: 12: In-vitro drug release study

Drug Release Study and Kinetics

The in vitro drug release profile (Figure 12) demonstrated sustained release behavior, with 89.67 ± 1.26% drug release over 6 h, which was significantly higher than that of the marketed formulation ($p < 0.05$).

The release data were fitted to various kinetic models, yielding R^2 values of 0.91 (zero-order), 0.94 (first-order), 0.98 (Higuchi), and 0.96 (Korsmeyer–Peppas). The highest correlation with the Higuchi model ($R^2 = 0.98$) indicated that drug release was predominantly diffusion-controlled through the polymeric matrix. The Korsmeyer–Peppas model further suggests a non-Fickian (anomalous) mechanism involving both diffusion and polymer relaxation.

Comparison with Marketed Formulation

The comparative release profile (Figure 12) revealed a significant difference between the optimized and marketed formulations. The similarity factor was calculated as f2 = 32.45, confirming that the optimized formulation exhibits a distinct and improved sustained drug release profile.

Stability Study

Stability studies conducted over 30 days showed no observable changes in tablet appearance. The mechanical properties remained consistent, with a maintained hardness of 3.3 kg/cm², and no significant variations in weight or friability were observed. The drug content remained stable at 90.45%, indicating the absence of degradation.

Overall, the formulation exhibited good physicochemical stability under the storage conditions.

DISCUSSION

The present study successfully developed and optimized Amisulpride-loaded polymeric microspheres to address the challenges associated with poor aqueous solubility and variable oral bioavailability [3]. Polymeric encapsulation has been widely recognized as an effective strategy for improving drug release characteristics and therapeutic performance [4–6].

Preformulation studies confirmed the identity, purity, and compatibility of the drug, supporting its suitability for formulation development. Optimization studies revealed that formulation variables, such as drug-to-polymer ratio, internal phase volume, stabilizer concentration, stirring speed, and stirring time, significantly influenced microsphere characteristics. Increasing the polymer concentration enhanced matrix formation and reduced drug diffusion into the external phase, consistent with the established principles of microsphere preparation using solvent evaporation techniques [7,13].

Eudragit RL 100 demonstrated superior performance compared to ethyl cellulose, likely due to its permeability and swelling properties, which facilitate controlled drug diffusion [11]. Similar findings have been reported in advanced delivery systems, such as microsponges and proniosomes, wherein the polymer composition plays a crucial role in determining encapsulation efficiency and release kinetics [9,10,15].

Process optimization played a critical role in achieving uniform particle size, high entrapment efficiency, and stable microsphere formation. These findings are in agreement with previous studies, which emphasize the importance of systematic optimization and QbD-based approaches in formulation development [5,9].

The optimized formulation exhibited sustained drug release behavior, which can be attributed to diffusion-controlled release through the polymeric matrix, as described in controlled drug delivery models [16,17]. Comparable advanced delivery systems, such as nanoemulgels and in situ gels, have also demonstrated improved drug release profiles and enhanced patient compliance [14,18].

Furthermore, emerging nanocarrier systems, such as niosomes, have shown significant potential in improving drug delivery efficiency and therapeutic outcomes, particularly for chronic and complex diseases [19]. These advancements support the integration of novel drug delivery approaches with conventional polymer-based systems.

Stability studies confirmed that the optimized formulation maintained its physicochemical properties and drug content over time, indicating good stability and suitability for long-term storage [8,20]. Overall, the developed microsphere-based system demonstrated improved encapsulation efficiency, controlled drug release, and better performance than conventional formulations.

CONCLUSION

This study successfully developed and optimized Amisulpride-loaded polymeric microspheres using the solvent evaporation method and formulated them into microsphere-based tablets. The optimized formulation demonstrated high entrapment efficiency, satisfactory yield, uniform drug content, and sustained drug release compared to the marketed product. The tablets exhibited acceptable mechanical properties and stability under storage conditions. Overall, the developed system shows potential as an effective controlled-release oral delivery platform for Amisulpride.

Limitations and Future Perspectives

The present work is limited to in vitro evaluation, and in vivo pharmacokinetic studies are necessary to confirm the therapeutic benefits. Extended stability studies and release kinetic modeling would further strengthen the scientific basis of the formulation. Future research should focus on in vitro–in vivo correlation (IVIVC), scale-up feasibility, and comprehensive stability assessment to support clinical and industrial applications.

Conflict of Interest

The authors declare no conflicts of interest related to the publication of this study.

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