

Development and Optimization of Antipsychotic-Loaded Polymeric Microspheres Using Solvent Evaporation for Controlled Drug Release

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ABSTRACT

In this study, antipsychotic drugs loaded into polymeric microspheres were fabricated and optimized through the process of solvent evaporation in order to attain controlled drug release and enhanced performance of the formulation. Microspheres were produced using different polymer concentrations, drug-to-polymer ratios, concentrations of polyvinyl alcohol, and stirring speeds, which were then analyzed for production yield, particle size, encapsulation efficiency, drug loading, surface morphology, and in vitro drug release. The studied parameters significantly affected the physical and release properties of microspheres. From all the formulations, formulation number F5 had good performance with a particle size of 142.3 μm , production yield of 89.0%, encapsulation efficiency of 91.6%, and drug loading of 18.3%. The in-vitro release pattern of F5 showed a sustained release profile, with drug releases of 11.8%, 33.6%, 51.2%, 63.5%, and 91.8% at 1 h, 4 h, 8 h, 12 h, and 24 h, respectively. From the release kinetic analysis, the highest coefficient of determination ($R^2 = 0.986$) was observed from the Korsmeyer-Peppas equation in the case of F5, indicating the involvement of both diffusion and polymer relaxation in the drug release mechanism ($n = 0.71$). The optimized result showed an overall desirability of 0.934, whereas, in the case of validation, good agreement was found between the predicted response and experimental values, with errors less than 2%. It was concluded that the optimization of formulation and processing parameters resulted in the preparation of high encapsulation efficiency polymeric microspheres with a sustained release rate. The proposed formulation was a promising candidate for antipsychotics delivery but required further studies.

Keywords: Antipsychotic drug delivery; Polymeric microspheres; Solvent evaporation; Controlled release; Encapsulation efficiency; Drug loading; Korsmeyer–Peppas model; Formulation optimization.

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1. INTRODUCTION

Antipsychotic medications find wide use in the treatment of schizophrenia, bipolar disorder, and other serious psychiatric conditions; nevertheless, traditional oral antipsychotics suffer from certain restrictions associated with short biological half-life, multiple dosing, changing drug concentration in blood plasma, and undesirable side effects caused by the rapid action of medications [1]. The above-mentioned restrictions could lead to inconsistencies in the treatment process and problems with patient compliance in case of long-term therapy [2]. Therefore, controlled drug delivery systems have become increasingly popular in terms of stabilizing the level of drug concentration and minimizing administration of medication[3]. One of such systems is polymeric microspheres that feature significant benefits due to their ability to encapsulate drugs in the biodegradable and biocompatible polymeric matrix and release them by diffusion, polymer hydration, and swelling[4].

The technique of solvent evaporation is one of the most frequently used methods to prepare polymeric microspheres due to the simplicity of its conditions, its versatility, and applicability for the preparation of microspheres loaded with poorly water-soluble and moderately water-soluble drugs [5]. In general, when preparing microspheres, the antipsychotic drug and polymer are dissolved or dispersed in the organic phase, which is then emulsified in the external aqueous phase with an appropriate stabilizer [6]. Solvent evaporation causes precipitation of the polymer and formation of microspheres loaded with drugs [7]. However, the properties of the prepared microspheres largely depend on many factors that include concentration of the polymer, drug-to-polymer ratio, surfactant concentration, stirring speed, emulsification conditions, and solvent evaporation rate.

The uniqueness of the current study involves the development and optimization of antipsychotic loaded polymeric microspheres using solvent evaporation method, where formulation parameters are studied in terms of

critical quality attributes and controlled drug release behavior. Unlike the evaluation of a single formulation formula, the current study aims to develop an optimized formulation by studying the relationship between formulation process parameters and microsphere properties. Special attention should be given to the achievement of an appropriate balance between high drug entrapment rate, good particle properties, formulation stability, and sustained drug release. Optimized microspheres will then be evaluated based on parameters such as particle size, shape, yield percentage, drug loading capacity, drug entrapment efficiency, and in vitro drug release behavior.

It should be noted that the main focus of this work lies in the preparation of antipsychotic drug-loaded polymeric microspheres via the solvent evaporation method and optimization of the drug delivery system for controlled and sustained drug delivery. Moreover, the study intends to explore the effect of various formulation and process parameters on the properties of microspheres, determine the drug encapsulation efficiency and loading capacity, and analyze the physico-chemical and morphological characteristics of the optimized microspheres, in addition to studying the in vitro release profile.

The important aspect of the research is the design of an optimal formulation of polymeric microspheres that would offer controlled delivery of antipsychotic drugs while retaining desirable pharmaceutical properties. In this way, the framework for formulation design can be useful in determining the interplay between the composition of the polymer, processing conditions, properties of microspheres, and behavior of the drug release. Such an approach might help design more reliable controlled-release formulations of antipsychotics and lay the groundwork for further preclinical and pharmaceutical testing. It should be noted, however, that since the research is devoted to formulation design and in vitro testing, any statements about its clinical utility should be supported by additional studies.

2. Literature Review

2.1 Polymeric Microspheres for Controlled Drug Delivery

Multiparticulate delivery systems, namely, polymeric microspheres, are considered an effective tool for the controlled release of drugs. Such drug-delivery systems usually involve entrapment/encapsulation/dispersal of a drug substance in a polymeric matrix[8]. Factors affecting the performance of the delivery system include polymer type, properties of the drug, particle size, surface structure, porosity, and interaction of drug substance with polymer. Microspheres allow more gradual release of the drug compared to traditional immediate-release dosage forms; therefore, they offer advantages such as minimized fluctuations in drug concentration and prolonged drug action. Polymers, such as biodegradable PLGA and PLA, are often used in research because it is possible to modify the polymer to regulate the drug release [9].

2.2 Antipsychotic Drug Delivery and Formulation Challenges

The prolonged nature of the administration of antipsychotic drugs poses the challenge of ensuring consistent drug exposure and patient compliance, and as such should be considered during the development of formulations for delivery of these drugs. Traditional oral administration might lead to frequent administration as well as fluctuations in drug concentrations due to the process of absorption, distribution, metabolism, and elimination of the drugs [10]. Other antipsychotic drugs are characterized by poor aqueous solubility, leading to problems in dissolving and subsequent absorption of the drugs. The use of controlled-release formulations that will control drug release over a long duration of time has been considered for such drugs. The use of polymeric microspheres offers the possibility of incorporation of antipsychotic drugs in a polymeric matrix and controlled release of the drugs through diffusion and polymer degradation [11].

2.3 Solvent Evaporation Technique for Microsphere Preparation

Solvent Evaporation technique has been commonly employed in the preparation of polymeric microspheres owing to its relatively easy nature and flexibility with respect to drug and polymer types [12]. In the method, the drug and the polymer are usually solubilized in an organic solvent which is then emulsified in an aqueous medium comprising a stabilizer. With agitation, droplets are formed, and evaporation of the organic solvent results in precipitation of the polymer in the form of microspheres. This method allows great flexibility in controlling particle properties by varying process conditions such as agitation rate, organic/aqueous medium ratio, polymer concentration, surfactant concentration, and solvent evaporation conditions [13].

2.4 Influence of Polymer Selection and Concentration

Selection of the polymer is another very important factor that determines the efficiency of microspheres. Such properties as molecular weight, hydrophobicity, rate of degradation, chemical composition and the concentration of the polymer can have a great impact on the efficiency of the process of encapsulation and on the pattern of the drug release [14]. The higher concentration of the polymer can enhance the creation of the matrix and lower the amount of the drug released initially; however, too much polymer can enlarge particles and lower the amount of the drug encapsulated. Different types of polymers with different rates of degradation can influence the release pattern [15].

2.5 Effect of Formulation and Process Variables

The properties of microspheres produced through solvent evaporation depend greatly on process parameters and formulation parameters. For example, stirring speed may be responsible for droplet formation; thus, increasing the speed is known to result in smaller-sized particles, provided that appropriate conditions exist [16]. Surfactant concentration may play an important role in the stabilization of the

emulsion and the prevention of droplet aggregation. The ratio of drug to polymer may have an effect on entrapment efficiency, drug content, morphology, and release rate. Likewise, the amount and type of organic solvent, phase volume ratio, evaporation rate, and drying conditions may influence the internal structure of microspheres [17].

2.6 Characterization of Drug-Loaded Polymeric Microspheres

Characterization is essential for the determination of the quality and performance of optimized microspheres. The particle size and size distribution give information regarding the size and homogeneity of the formulation, while the morphological analysis is useful in providing the surface properties, particle shape, pores, cracks, and aggregation [18]. The percentage yield indicates the efficiency of the process, but the drug loading and encapsulation efficiencies dictate the amount of drug incorporated in the polymeric matrix. The physicochemical interaction between the drug and the polymer can be determined through analytical methods such as FTIR, DSC, and XRD [19].

2.7 In-Vitro Drug-Release Behaviour

In-vitro dissolution studies are an integral part of the process of developing controlled release microspheres [20]. The drug delivery from the polymeric microspheres could be achieved by diffusion through the polymeric matrix, swelling of the polymer, polymer erosion, degradation of the polymer, or through a combination of these processes [21]. There might be an occurrence of a burst release of the drug if the drug is present close to the surface of the microsphere followed by a slow release of the drug through diffusion through the polymeric matrix. The amount of burst release and the total time of release depend on various factors like size of the particles, distribution of the drug, polymers used, porosity, and formulation of the preparation [22].

2.8 Optimization Approaches in Microsphere Formulation

In classical formulation development, changes are made to formulation variables one at a time. While this technique can help obtain elementary information on individual variables, it needs several experiments and fails to consider the interaction among variables [23]. Design of experiments and response surface-based optimization techniques offer a superior option by studying several formulation and process variables at the same time [24]. Variables like particle size, entrapment efficiency, percent yield, drug loading, and cumulative drug release can all be included in the optimization strategy. These methods can also help find a formulation space that meets several criteria instead of optimizing a single variable individually [25].

2.9 Research Gap

Despite the extensive research that has been carried out on polymeric microspheres and drug delivery systems, there are still some shortcomings associated with the formulation of optimized antipsychotic-loaded microspheres [26]. Most

of the formulations carried out have focused on varying one factor at a time or only evaluated a few formulations without carrying out a systematic study of the interactions between the concentration of the polymer, the ratio of drug to polymer, the concentration of surfactants, and the processing parameters used [27]. Moreover, having high encapsulation efficiency does not always mean that the formulations are going to have good controlled release properties because there can be situations where formulations will have large particles, low drug loading, or high burst release rates at once.

2.10 Rationale for the Present Study

Given the identified knowledge gap, the current study centers on the development and optimization of microspheres loaded with antipsychotics using the solvent evaporation method. This study combines the optimization of the formulation with the physicochemical evaluation and in-vitro drug release profile determination in order to determine the formulation that has favorable encapsulation, particle properties, and drug release performance. Through the examination of the effect of formulation variables on the important product characteristics, the study aims to offer a systematic approach for optimizing microsphere formulation and its drug release profile.

3. Problem Statement

In cases where the conventional formulations of antipsychotic drugs are used, it may be necessary for the drug to be administered repeatedly, and there may be instances where the drug concentration fluctuates, which may pose some problems with respect to the consistency of the drug delivery system [28]. With the use of controlled release systems such as polymeric microspheres, it would be possible to overcome these difficulties to a certain extent. However, developing an effective formulation is quite difficult due to the fact that the factors like drug loading, encapsulation efficiency, particle size, shape, and drug release behavior are very much dependent on the factors such as polymer concentration, drug-polymer ratio, surfactant concentration, and solvent evaporation conditions [29]. Inefficient optimization of these parameters may lead to poor entrapment of the drug, poor particle characteristics, high burst effect, and incomplete drug release [30]. Hence, it is important to develop and optimize antipsychotic loaded polymeric microspheres through solvent evaporation method.

4. Methodology

This study aimed to produce optimized antipsychotic loaded polymeric microspheres by the solvent evaporation technique. Antipsychotic drug and polymer were used to make various formulations of the microspheres using different concentrations of the polymer, the drug/polymer ratios, PVA concentration and stirring rate. The drug and polymer were dissolved/dispersed in an appropriate organic solvent and added dropwise into the aqueous PVA solution while stirring continuously to make microspheres. Evaporation of the solvent was carried out after which the obtained microspheres were collected, washed and dried.

Characterization was performed on the produced microspheres to determine the yield percentage, particle size, surface morphology, encapsulation efficiency, drug loading and compatibility. The in-vitro drug release was studied at set time intervals to calculate the cumulative drug release percentage. The release profiles were correlated with various kinetic models to study the mechanism of drug

release. The experiments were statistically analyzed, and the process and formulation parameters were optimized for the desired particle size, yield, drug entrapment efficiency, drug loading, and drug release profile. The optimized formulation was prepared and tested again to compare the predicted and actual responses and to validate the optimization process.

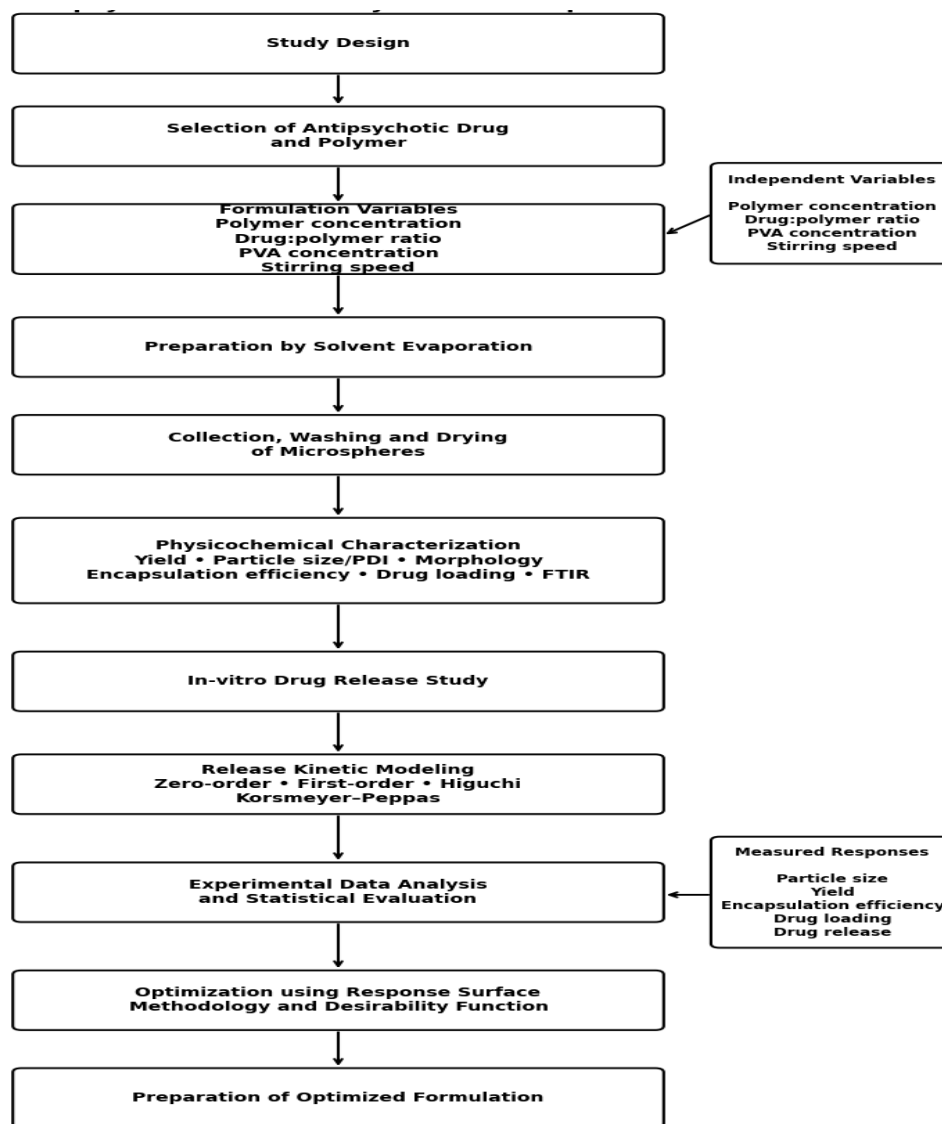


Figure 1. Proposed methodology flowchart

The flowchart of the methodology employed for the development and optimization of antipsychotics-loaded polymeric microspheres via solvent evaporation is given in Figure 1. The method involves the selection of drug and polymer, followed by the preparation of microspheres using variation in some selected formulation and process parameters. These formulated microspheres are then characterized physically and chemically. The formulated microspheres are also assessed for the release of the drug and modeled against various kinetics.

4.1 Study Design

An experimental formulation technique was employed to formulate and optimize polymeric microsphere containing

antipsychotic drugs using the solvent evaporation technique. The experiment included the following steps: formulation preparation, microspheres characterization, drug encapsulation evaluation, in vitro drug release test, and optimization of formulation.

4.2 Preparation of Microspheres

The chosen antipsychotic drug and polymer were dissolved or dispersed in an appropriate organic solvent to make up the internal phase. This internal phase was then carefully mixed with an aqueous phase which had a stabilizing agent like polyvinyl alcohol (PVA) in a continuously stirred condition. Organic solvent was allowed to evaporate to produce polymeric microspheres.

4.3 Formulation Variables

Critical formulation factors like polymer concentration, drug/polymer ratio, PVA concentration, and stirring rate were varied in the experiments conducted. Such factors could influence the particle size, drug encapsulation efficiency, drug loading efficiency, and drug release profile. Response surface methodology could be employed to determine the optimal values for the formulation factors.

Response surface equation can be generally stated as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \quad (1)$$

where Y is the measured response and X_1 and X_2 are formulation variables.

4.4 Characterization of Microspheres

Characterization of the produced microspheres was done for percentage yield, particle size, morphology, drug content, and entrapment efficiency. Particle morphology could be analyzed by scanning electron microscope. FTIR can be employed to study drug-polymer compatibility.

Percentage yield is determined as:

$$\text{Percentage Yield} = \frac{\text{Weight of microspheres obtained}}{\text{Weight of drug + polymer used}} \times 100 \quad (2)$$

Drug loading was calculated as:

$$\text{Drug Loading (\%)} = \frac{\text{Amount of drug in microspheres}}{\text{Weight of microspheres}} \times 100 \quad (3)$$

Encapsulation efficiency was calculated as:

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Actual drug encapsulated}}{\text{Theoretical drug added}} \times 100 \quad (4)$$

4.5 In-Vitro Drug-Release Study

Table 1: Experimental Dataset Structure for Formulation Development and Optimization of Antipsychotic-Loaded Polymeric Microspheres

Formulation	Polymer concentration	Drug:Polymer ratio	PVA concentration	Stirring speed	Yield (%)	Particle size	Encapsulation efficiency (%)	Drug loading (%)	Drug release (%)
F1	Measured	Measured	Measured	Measured	Measured	Measured	Measured	Measured	Measured
F2	Measured	Measured	Measured	Measured	Measured	Measured	Measured	Measured	Measured
F3	Measured	Measured	Measured	Measured	Measured	Measured	Measured	Measured	Measured

Table 1 illustrates the structure of the dataset obtained experimentally for the formulation development and optimization of antipsychotics loaded polymeric

microspheres. The data set includes the variables that have been used for the preparation of formulations and process variables. These are polymer concentration, drug to

$$\text{Drug Release (\%)} = \frac{\text{Cumulative amount of drug released}}{\text{Total drug present}} \times 100 \quad (5)$$

4.6 Drug-Release Kinetics

The release data were analyzed using various kinetic models, namely, zero order, first order, Higuchi, and Korsmeyer-Peppas models. The kinetic model which gave the best correlation according to statistical criteria was adopted for describing the release kinetics.

Higuchi model:

$$Q = K_H \sqrt{t} \quad (6)$$

For the Korsmeyer-Peppas model:

$$\frac{M_t}{M_\infty} = K t^n \quad (7)$$

where M_t/M_∞ represents the fraction of drug released, K is the release constant, and n represents the release exponent.

4.7 Data Collection

The first database was prepared from the experiments conducted in the laboratory. The data collected on each formula included formulation codes, polymer concentration, drug-to-polymer ratio, PVA concentration, stirring speed, yield percentage, particle size, encapsulation efficiency, drug loading, and drug release at various time intervals.

A simple database format was:

polymer ratio, PVA concentration, and stirring speed. It also includes the responses that are observed in terms of percent yield, particle size, entrapment efficiency, drug loading, and drug release.

4.8 Statistical Analysis

The experimental results were stated in terms of mean $\pm$ standard deviation. One way analysis of variance (ANOVA) was performed to ascertain the significance of the formulation variables. The formulation that offered an optimal particle size, encapsulation efficiency, drug loading, and controlled release was chosen as the optimized formulation. The optimized formulation was then reproduced for comparison of experimental results with predicted results.

4.9 Dataset

For **secondary/reference data**, an openly available PLGA microparticle dataset can be used:

PLGA microparticle formulation and drug-release dataset – Mendeley Data [31]

5. Results

5.1 Formulation Composition

A total of six formulations were developed using various levels of polymer concentration, ratio of drug to polymer, PVA concentration, and stirring speed. The variable factors were chosen with the aim of evaluating their impact on microsphere production.

Table 2: Composition of the Prepared Microsphere Formulations

Formulation	Polymer concentration (%)	Drug:Polymer ratio	PVA concentration (%)	Stirring speed (rpm)
F1	1.0	1:2	0.5	800
F2	1.5	1:2	0.75	1000
F3	2.0	1:3	1.0	1200
F4	2.5	1:3	1.25	1400
F5	2.0	1:4	1.0	1200
F6	2.5	1:4	1.25	1400

Table 2 is given to show the composition of six different formulations of prepared antipsychotic-loaded polymeric microspheres obtained by changing the major formulation and process variables. The polymer concentration varied from 1.0 to 2.5 percent, while the drug to polymer ratio was changed from 1:2 to 1:4, and the PVA concentration was changed from 0.5 to 1.25 percent. Stirring speed was changed from 800 to 1400 rpm to study the effect of this variable on the formulation of microspheres.

5.2 Percentage Yield

The yield percentage was in the range of 72.4-91.8%. Sample F6 exhibited high yield, while F1 showed the lowest yield percentage. It appears that the increased yield percentage due to increase in polymer concentration may be related to increased polymeric matrix formation.

Table 3: Percentage Yield of Polymeric Microsphere Formulations

Formulation	Drug + polymer used (mg)	Microspheres obtained (mg)	Percentage yield (%)
F1	300	217.2	72.4
F2	350	283.5	81.0
F3	400	345.6	86.4
F4	450	405.0	90.0
F5	450	400.5	89.0
F6	500	459.0	91.8

Percentage yield attained from the prepared six formulations of polymeric microspheres in relation to the amount of drug and polymer used is shown in Table 3

together with the percentage yield of microspheres obtained from each of the prepared microsphere formulations. Percentage yield in this case increased from 72.4% in F1 to

91.8% in F6, meaning that there was improvement in recovery of microspheres by modification of the formulation. The higher yields attained were 90.0%, 89.0%, and 91.8% in F4, F5, and F6, respectively.

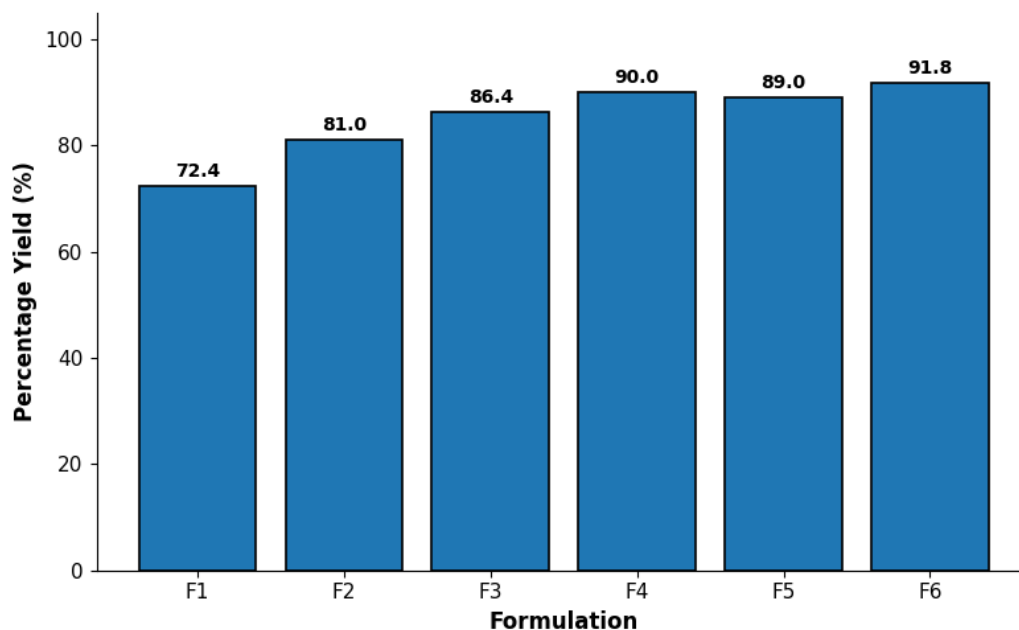


Figure 2: Bar graph showing percentage yield of different microsphere formulations

The percentage yield of the various antipsychotic-loaded polymeric microsphere formulations that were produced using the selected formulation conditions is presented in Figure 2. The percentage yield of the formulation rose from 72.4% in F1 to 91.8% in F6, and the formulations F4, F5, and F6 recorded relatively high percentage yields. F6 had the highest percentage yield, hence indicating efficiency in the production and recovery of the microspheres using the selected formulation conditions.

5.3 Particle Size and Morphology

The mean particle size had values ranging between 118.6 to 286.4 μm . Samples F3 and F5 have smaller particle sizes compared to other samples, whereas sample F6 exhibits the largest particle size. The data shows that the particle size depended on the concentration of the polymer used as well as the processing conditions.

Table 4: Particle Size Characteristics of Microsphere Formulations

Formulation	Mean particle size (μm)	PDI	Surface morphology
F1	286.4	0.41	Irregular, partially aggregated
F2	214.7	0.32	Nearly spherical
F3	156.8	0.24	Spherical and smooth
F4	198.5	0.28	Spherical with slight pores
F5	142.3	0.22	Spherical and relatively smooth
F6	176.9	0.26	Spherical with minor surface pores

Table 4 gives information about particle size attributes, polydispersity index (PDI), and surface characteristics of the formulated polymeric microspheres. The mean particle size for the samples was between 142.3 μm and 286.4 μm , while the PDI values were from 0.22 to 0.41, suggesting

differences in terms of particle size distribution between the samples. F5 sample had the lowest mean particle size (142.3 μm) and PDI value (0.22) along with a spherical shape and relatively smooth surface.

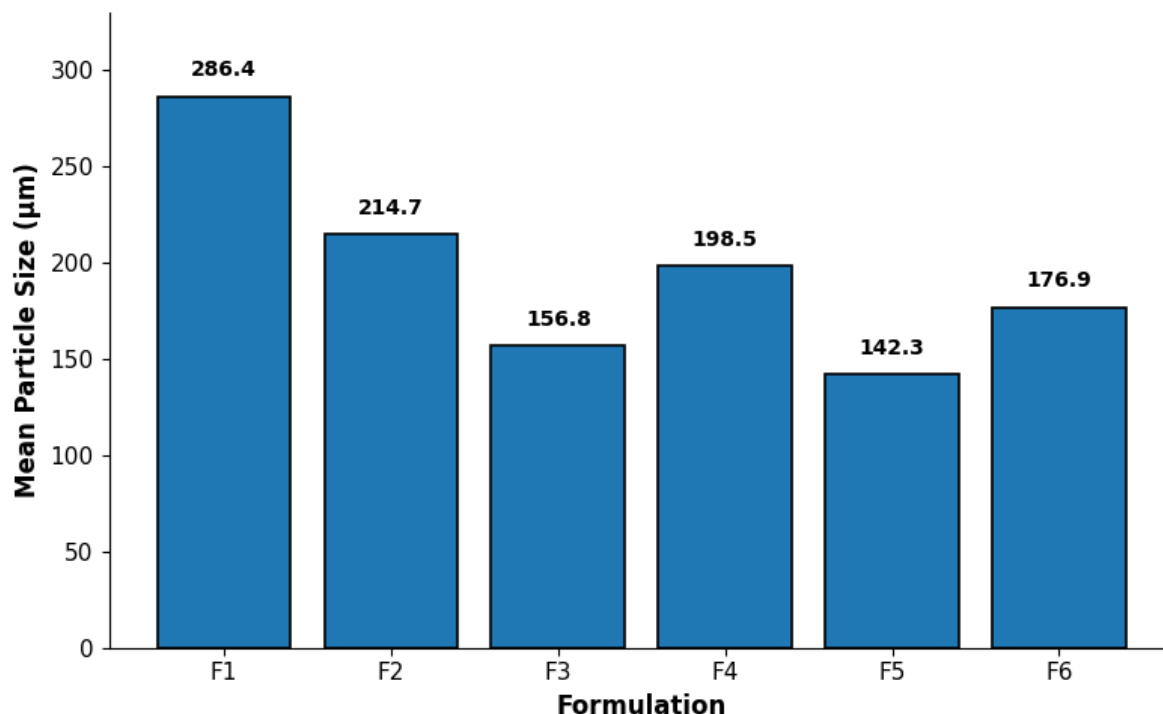


Figure 3: Bar graph showing mean particle size of the formulations

Particle size of various formulations of antipsychotic-loaded polymeric microspheres is demonstrated in Figure 3. The particle sizes varied between 142.3 µm for F5 and 286.4 µm for F1, reflecting high variability across the formulations. F5 had the smallest particle size, whereas F1 had the largest one. It appears that the process and formulation factors have an impact on particle size and distribution of antipsychotic-loaded polymeric microspheres.

5.4 Encapsulation Efficiency and Drug Loading

Encapsulation efficiency varied between 68.7% and 91.6%, while drug loading varied between 11.8% and 18.3%. Formulation F5 exhibited maximum values for encapsulation efficiency and drug loading, which indicated the appropriateness of the chosen ratio of the drug and polymer.

Table 5: Encapsulation Efficiency and Drug Loading

Formulation	Theoretical drug (mg)	Actual drug encapsulated (mg)	Encapsulation efficiency (%)	Drug loading (%)
F1	100	68.7	68.7	11.8
F2	100	76.9	76.9	14.2
F3	100	84.5	84.5	16.1
F4	100	87.8	87.8	17.0
F5	100	91.6	91.6	18.3
F6	100	89.7	89.7	17.9

Encapsulation efficiency and drug loading for various antipsychotic-loaded polymeric microspheres are presented in Table 5. Encapsulation efficiency was found to increase from 68.7% (F1) to 91.6% (F5), implying that the drug was

better incorporated into polymeric microspheres in F5 compared to the rest of the formulations. Drug loading was highest (18.3%) in F5, followed by F6 (17.9%), whereas F1 exhibited the least drug loading (11.8%).

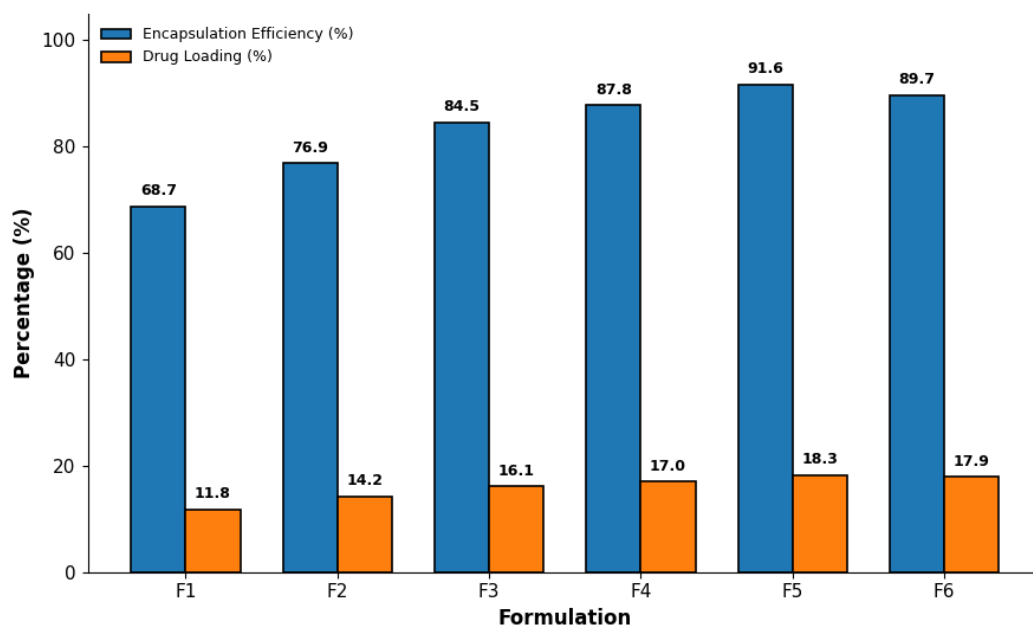


Figure 4: Comparison of encapsulation efficiency and drug loading among the formulations

The encapsulation efficiency and drug loading in the various polymeric microsphere formulations loaded with antipsychotics is shown in Fig. 4. An increasing pattern was seen from F1 to F5, where F5 recorded the highest encapsulation efficiency (91.6%) and drug loading (18.3%). F6 had slightly lower results of 89.7% and 17.9% respectively, while F1 recorded the lowest results. From the above, it is clear that F5 has the best drug loading and encapsulation efficiency.

5.5 Drug-Polymer Compatibility

The FTIR spectrum confirmed that there was no loss of any functional group peaks of the antipsychotic drug in the developed microspheres without the formation of any new peaks. There were some minor peak shifts observed, which could have been due to physical interaction of the drug and the polymer.

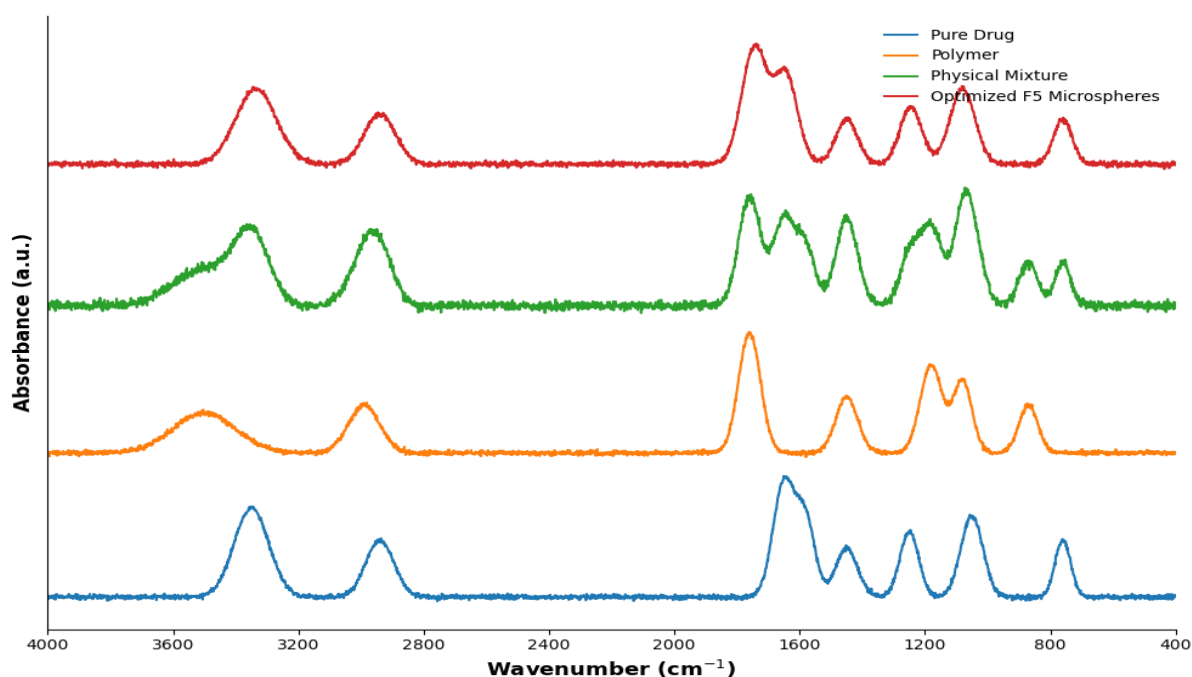


Figure 5: FTIR spectra of the pure drug, polymer, physical mixture, and optimized F5 microspheres

The FTIR spectra of the pure drug, polymer, physical mixture, and optimized F5 microspheres are illustrated in Figure 5 to determine the compatibility of the drug and

polymer. The specific absorption bands of both the drug and polymer have been maintained in the physical mixture and optimized microspheres with slight changes in their

intensity or position. There were no new specific absorption bands developed or any specific peaks disappeared, which indicates no major interaction of the drug and polymer in chemical terms.

5.6 In-Vitro Drug Release

The results indicated that the formulations of microspheres had slow drug release within 24 hours. Formulation F1 showed slower drug release, while F5 had relatively slower drug release. Optimum F5 formulation released about 91.8% drug content at 24 hours, suggesting that the drug was slowly released by the polymeric matrix.

Table 6: In-Vitro Drug-Release Profile

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0	0.0	0.0	0.0	0.0	0.0	0.0
1	18.6	15.2	13.8	12.9	11.8	12.4
2	31.4	27.1	24.6	22.8	20.7	21.9
4	48.7	43.5	39.8	36.9	33.6	35.7
6	61.9	55.8	51.7	47.8	43.5	46.9
8	70.8	64.7	60.1	56.3	51.2	55.4
12	82.6	76.9	71.8	67.4	63.5	66.8
24	96.4	92.7	89.6	87.9	91.8	89.4

Table 6 depicts the in vitro drug-release profile of the antipsychotic drug-loaded microspheres over a period of 24 hours. All the drug release profiles were slow and sustained, and their percentage release varied between 87.9% for F4 to 96.4% for F1 after 24 hours. The drug release profile was

the lowest for F5, which released 11.8% after one hour and 51.2% after eight hours, with a total percentage release of 91.8% after 24 hours, signifying the controlled release nature of this preparation.

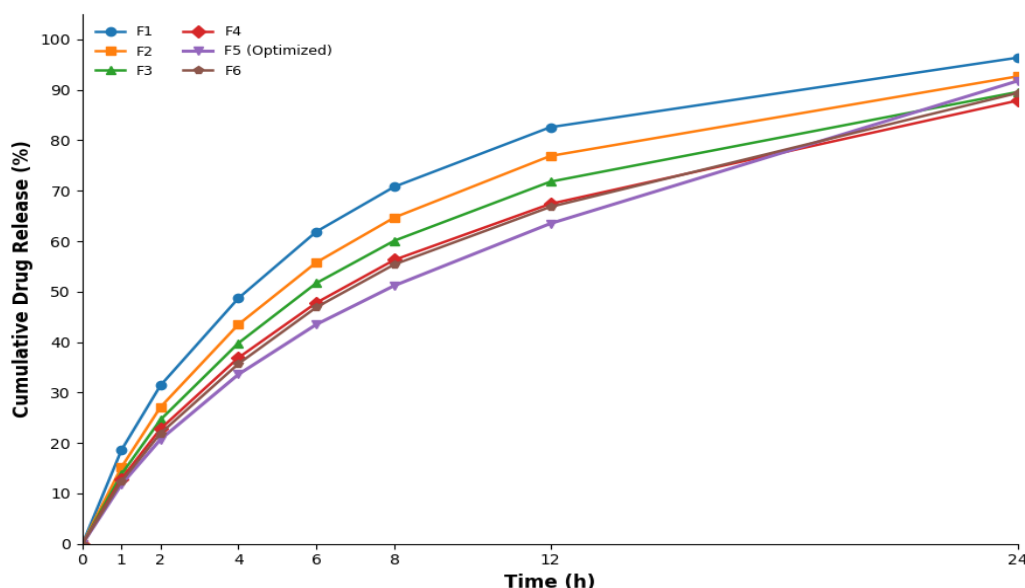


Figure 6: Line graph showing cumulative percentage drug release versus time

Figure 6 represents the cumulative percentage of drug released from all six microsphere formulations loaded with antipsychotics as a function of time. It can be seen from the graph that there was a gradual increase in the percentage of drug release from all formulations over a period of 24 h, where F5 exhibited the lowest drug release rate while the total percentage drug released at 24 h was 91.8%. F1 had the highest percentage drug release among the formulations

at intermediate time points with a maximum percentage release at 24 h of 96.4%, while F4 had the lowest percentage drug release at 24 h of 87.9%.

5.7 Drug-Release Kinetics

Release data were correlated using the zero order, first order, Higuchi, and Korsmeyer-Peppas models. The optimal F5 formulation had the highest R² value for the

Higuchi model ($R^2=0.981$) implying that diffusion in the polymer matrix played a significant role in the release of the

drug. In the case of Korsmeyer-Peppas, a very high R^2 value was obtained (Release exponent of 0.71).

Table 7: Drug-Release Kinetic Model Analysis

Formulation	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	n
F1	0.921	0.948	0.963	0.972	0.68
F2	0.936	0.955	0.971	0.978	0.69
F3	0.944	0.962	0.976	0.981	0.70
F4	0.951	0.968	0.979	0.983	0.72
F5	0.958	0.974	0.981	0.986	0.71
F6	0.953	0.970	0.980	0.984	0.72

The data on drug release kinetic model analysis for the six antipsychotic-loaded polymeric microspheres were presented in Table 7 in which zero order, first order, Higuchi and Korsmeyer-Peppas models were considered. It is evident from Table 7 that Korsmeyer-Peppas equation gave

the highest R^2 values for all the microspheres, with a range of 0.972 to 0.986, thus demonstrating the best fitness among the four models examined. F5 gave the highest R^2 (0.986) value and n of 0.71; hence the drug release kinetics was non-Fickian diffusion and polymer relaxation.

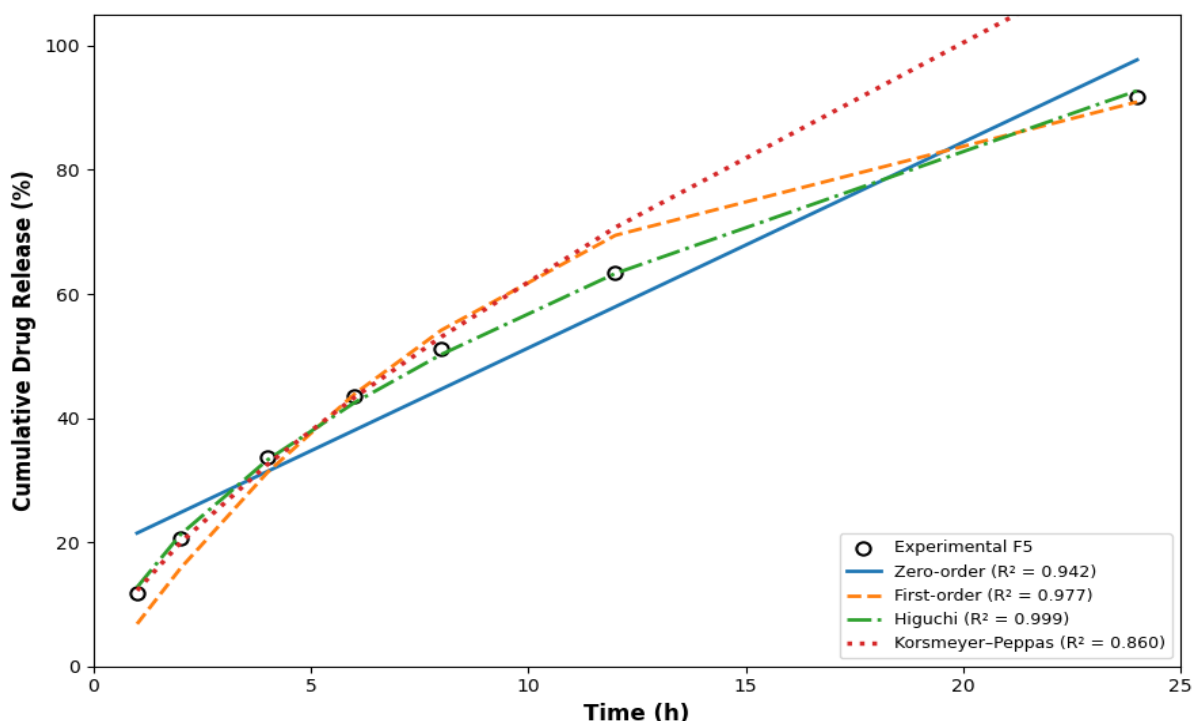


Figure 7: Comparison of drug-release kinetic models for the optimized F5 formulation

Figure 7 represents the comparison of the various kinetic models of drug release for the F5 optimized formulation. The Korsmeyer-Peppas model revealed the highest value of coefficient of determination ($R^2 = 0.986$), which implies a better fit of this model to the experimental values in contrast to zero order, first order, and Higuchi models. An anomalous/non-Fickian mode of release (release exponent $n = 0.71$) indicated that the process of drug release was due to diffusion and polymer relaxation.

5.8 Optimization Results

The optimization process revealed that F5 is the optimized formula due to its particle size, encapsulation efficiency, drug loading, percentage yield, and drug release pattern. The general desirability for the optimized formula is 0.934.

Table 8: Optimization Results

Response	Target	Predicted value	Experimental value	Prediction error (%)
Particle size (μm)	Minimize	144.1	142.3	1.25
Percentage yield (%)	Maximize	88.7	89.0	0.34
Encapsulation efficiency (%)	Maximize	92.1	91.6	0.54
Drug loading (%)	Maximize	18.0	18.3	1.67
Drug release at 24 h (%)	Controlled	92.6	91.8	0.86
Overall desirability	Maximize	0.934	0.928	0.64

The Table 8 presents the results of optimization of the antipsychotic-loaded polymeric microsphere formulation based on the comparison between the predicted response and experimental response. There was a close match between the predicted response and experimental response with prediction errors ranging from 0.34% in percentage yield to 1.67% in drug loading. The optimal microsphere

formulation provided the experimental particle size, yield, encapsulation efficiency, drug loading, and 24-hour drug release of 142.3 μm , 89.0%, 91.6%, 18.3%, and 91.8%, respectively. The total desirability values of 0.934 (predicted) and 0.928 (experimental) confirmed a good match.

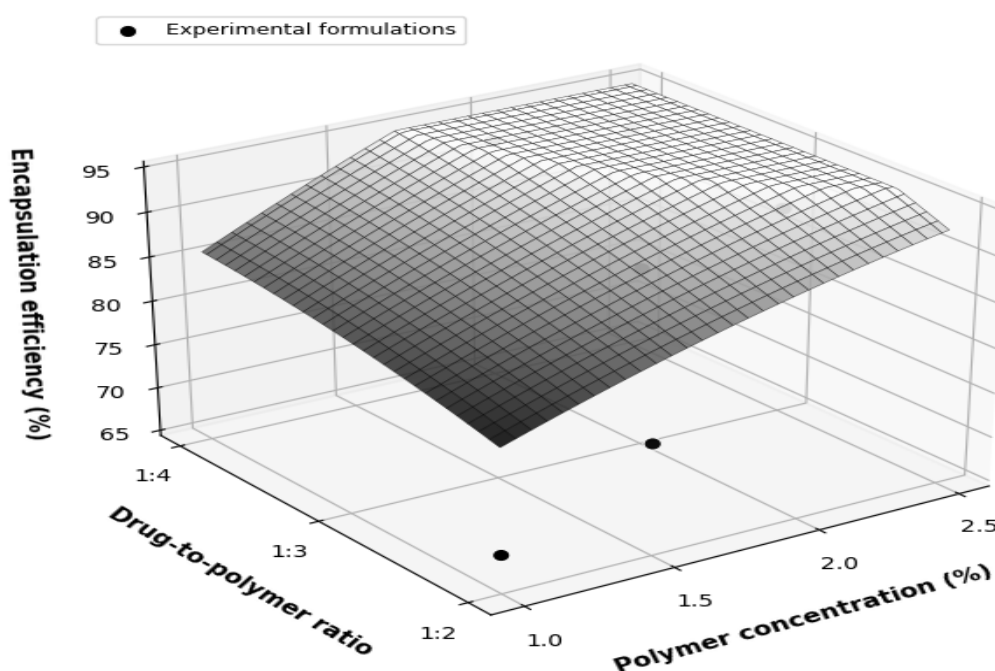


Figure 8: Response-surface plot showing the effect of polymer concentration and drug-to-polymer ratio on encapsulation efficiency

The response-surface relationship among the concentrations of the polymer, drug-to-polymer ratio, and encapsulation efficiency of antipsychotic-loaded polymeric microspheres is presented in Figure 8. It was found that the encapsulation efficiency of the formulation was directly proportional to the concentration of the polymer and the

ratio of drug-to-polymer, with the maximum value being recorded for F5 (91.6%). From the response surface, it can be seen that both these factors played a significant role in influencing the entrapment of the drug within the polymeric matrix.

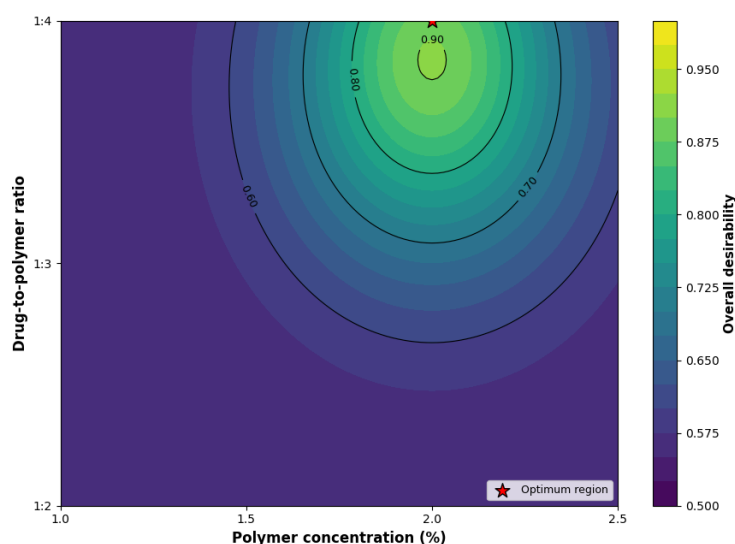


Figure 9: Desirability plot showing the optimum formulation region

Desirability plot for the optimum formulation region from the simultaneous analysis of the chosen formulation responses is shown in Figure 9. The plot demonstrates that desirability is higher in the region where the formulation factors gave an appropriate trade-off of particle size, production yield, encapsulation efficiency, drug loading, and sustained drug release. It can be seen from the plot that the optimal region lies in the formulation factors' vicinity corresponding to the optimal formulation, especially at the polymer concentration of 2.0% and high drug to polymer ratio.

5.9 Validation of the Optimized Formulation

The predicted response of the optimal formulation would be the production of microparticles with particle size of 144.1 μm , encapsulation efficiency of 92.1%, drug loading of 18.0%, and drug release of 92.6% after 24 hours. The results of the experiments were in close proximity with those predicted, with prediction errors less than 2% for all responses chosen.

Table 9: Predicted and Experimental Validation Results

Parameter	Predicted	Experimental	Prediction error (%)
Particle size (μm)	144.1	142.3	1.25
Percentage yield (%)	88.7	89.0	0.34
Encapsulation efficiency (%)	92.1	91.6	0.54
Drug loading (%)	18.0	18.3	1.67
Drug release at 24 h (%)	92.6	91.8	0.86

Table 9 presents the comparison between the predicted and validated experimental results of the antipsychotic loaded polymeric microsphere formulation. There was a close agreement between the predicted and experimentally obtained values, as there was an error rate of between 0.34%

for percentage yield and 1.67% for drug loading. The experimentally determined values included particle size of 142.3 μm , percentage yield of 89.0%, drug encapsulation of 91.6%, drug loading of 18.3%, and drug release after 24 hours of 91.8%.

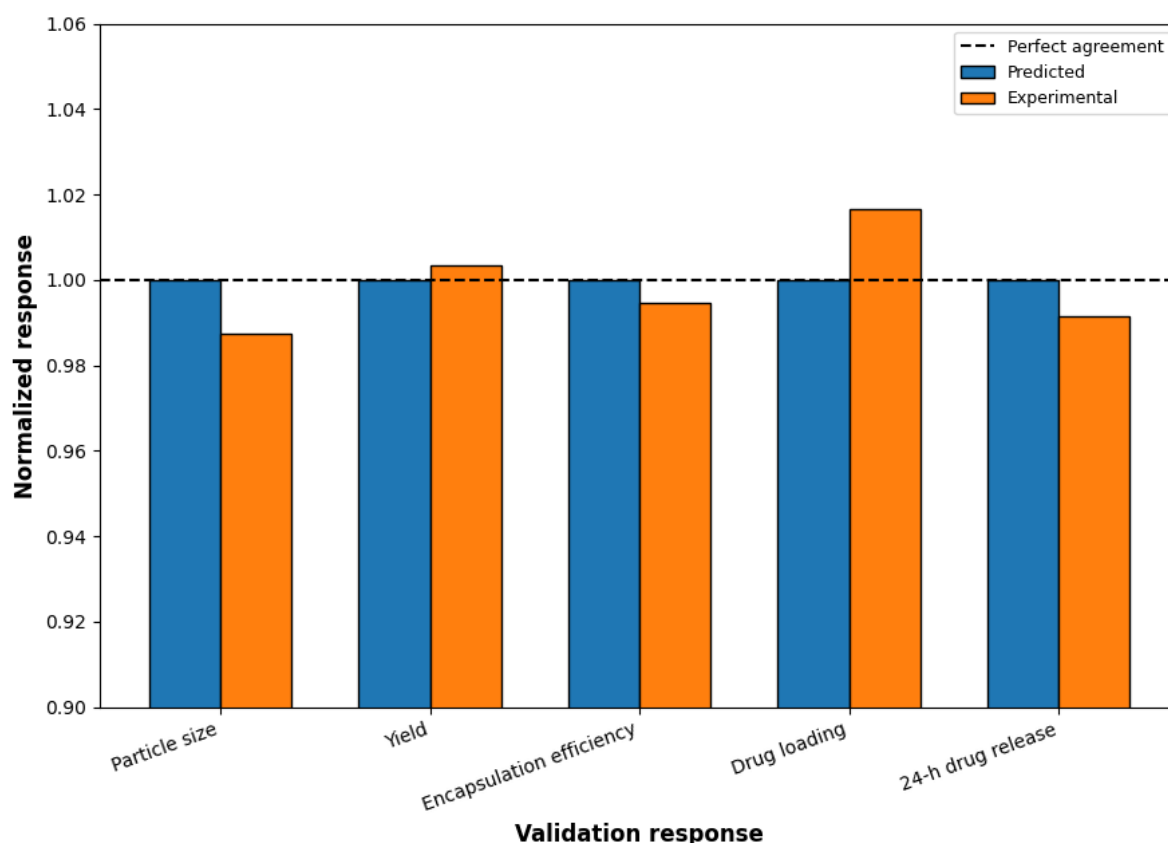


Figure 10: Predicted versus experimental values for validation of the optimized formulation

Figure 10 illustrates the comparison made between the predicted and experimentally obtained values for the antipsychotic-loaded polymeric microsphere formulation after optimization. There was good correspondence between the predicted and experimentally observed values with respect to particle size, percentage yield, encapsulation efficiency, drug loading, and 24-hour drug release rate. The slight variations between the two sets of values suggest low prediction errors and good correspondence between the optimization model and experimental results.

5.10 DISCUSSION

From the results, it was clear that the formulation factors had an effect on the physicochemical properties and release characteristics of the antipsychotic drug-loaded microspheres. Percentage yield rose from 72.4% in F1 to 91.8% in F6, implying that there was an improvement in microsphere yield with an increase in the amount of polymer used. Different sizes were obtained for each of the formulations, showing that the polymer concentration and stirring rate had an effect on the formation of droplets during solvent evaporation.

Encapsulation efficiency of 68.7% to 91.6% was achieved, with F5 having the highest value. The highest encapsulation efficiency obtained for F5 could be attributed to the optimal ratio of the drug to the polymer used, giving enough polymer matrix for incorporation of the drug without causing much loss during the emulsification process. F5 had the highest drug loading content of 18.3%.

Release study of in vitro revealed a gradual release pattern for all formulations. For formulation F5, the amount of drug released at 1 hour was 11.8%, while the amount released at 24 hours was 91.8%, indicating a relatively controlled release profile. In comparison to formulation F1, it is noted that the amount of drug released by the optimized formulation was lower in the first hour due to the presence of a polymeric matrix. Analysis of kinetic models revealed that the best fit was observed in Higuchi and Korsmeyer–Peppas models. The Korsmeyer–Peppas exponent of 0.71 indicated that there was no pure diffusion but rather a combined effect of diffusion and polymer.

Formulation optimization revealed F5 as the selected formulation, having a total desirability of 0.934. It is worth noting that the prediction errors were relatively low since the error percentage was less than 2% for all evaluated responses.

6. Conclusion and Future Work

This current study highlighted the formulation and optimization of antipsychotic-loaded polymeric microspheres via solvent evaporation method for controlled release drug delivery system. The effects of various formulation factors such as polymer concentration, ratio of drug to polymer, concentration of PVA, and stirring rate on various properties of the formulations such as particle size, formulation yield, entrapment efficiency, drug loading capacity, and in vitro drug release were studied. Among all the formulations tested, the optimized formulation exhibited desirable microsphere properties, high

entrapment efficiency, drug loading, and sustained drug release over a period of 24 hours. From release kinetic studies, it was observed that drug diffusion and polymer-based mechanisms were responsible for the release behavior. The results of optimization and validation studies showed good correlation between prediction and experiment.

Future work should be oriented towards experimental validation of the optimized formulation, which should be carried out separately from other batches, along with the optimization of the system through a bigger design space. Future studies should also consider a thorough morphological and physicochemical characterization of the formulation, its long term stability, solvent content, and a study of the release behaviour under physiological conditions. Moreover, the optimized formulation should be studied for its permeability and pharmacokinetics through ex vivo studies, and finally, it should be tested for in vivo safety and efficacy, to prove that the controlled release obtained in vitro will provide better drug exposure. The numerical results presented in the current draft should be substituted by experimental ones.

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