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Formulation and evaluation of microspheres-loaded capsule of duloxetine HCL by extrusion-spheronization techniques

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Abstract

The present Investigation focuses on the formulation; optimization and evaluation of a microsphere-loaded capsule containing Duloxetine HCl; aimed at enhancing its oral bioavailability and therapeutic efficacy. Duloxetine HCl; a selective serotonin and norepinephrine reuptake inhibitor (SNRI); exhibits limited water solubility and is unstable in acidic pH; leading to reduced absorption and erratic bioavailability. The goal was to develop a controlled-release multiparticulate dosage form to improve therapeutic efficacy and patient compliance. A series of formulations were prepared by varying the polymer type and drug-to-polymer ratios; and the process parameters were optimized with a particular focus on spheronization speed (fixed at 1200 rpm) and spheronization time. Optimization was guided by evaluating key parameters such as micromeritic properties (bulk density; tapped density; Carr's index); particle size distribution; percentage yield; drug entrapment efficiency; and drug release. In vitro drug release studies were conducted over 12 hours to assess sustained-release behavior. Among the prepared batches; the formulation using Sodium Alginate in a 1:2 drug-to-polymer ratio demonstrated optimal performance; exhibiting high entrapment efficiency (above 85%); favorable spherical morphology; and sustained drug release following Higuchi diffusion kinetics. Surface morphology observed under Scanning Electron Microscopy (SEM) confirmed well-formed; discrete; and spherical microspheres. Among the various formulations; batch F6 demonstrated superior performance with excellent flow properties; high entrapment efficiency (85.4 %); and sustained drug release of 83.82% over 12 hours; indicating controlled release behavior.

The study concludes that through systematic optimization of formulation and process parameters; natural polymer-based microspheres of Duloxetine Hydrochloride can be successfully developed for controlled oral delivery. Drug-to-polymer ratio demonstrated optimal performance; exhibiting high entrapment efficiency (above 85%); physicochemical compatibility using Fourier Transform Infrared Spectroscopy (FTIR); favorable spherical morphology; and sustained drug release following Higuchi diffusion kinetics. The study confirms that the developed microsphere-loaded capsule system offers a promising strategy for improving the solubility; stability; and controlled release of Duloxetine HCl; thereby potentially enhancing patient compliance and therapeutic outcomes.

Keywords: Duloxetine HCL; Microspheres; Chitosan; Sodium Alginate; Xanthum Gum; Extrusion-Spheronization Techniques

1. Introduction

Microspheres are small, spherical particles with diameters typically ranging from 1 to 1000 micrometers, often containing a core substance. Ideally, they are designed to be less than 200 micrometers in size. These microspheres are commonly made from proteins or biodegradable synthetic polymers and are often in the form of free-flowing powders. The extrusion-spheronization technique, first introduced by Nakahara in 1966, is a widely used method for producing microspheres in the pharmaceutical industry. Microspheres offer several advantages over single-unit dosage forms,

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making them highly preferred. These benefits include: a) Consistent GI Tract Transport, b) Reduced GI Irritation, c) Controlled Release Potential, d) Improved Content Uniformity, e) High Drug Loading Capacity. [1,2]

Duloxetine hydrochloride (DLX) is a type of antidepressant known as a serotonin-norepinephrine reuptake inhibitor (SNRI). It works by specifically blocking the reabsorption (reuptake) of serotonin and norepinephrine in the brain, which helps regulate mood and relieve symptoms of depression. It also mildly inhibits dopamine reuptake but doesn't significantly affect other receptors, such as histamine, dopamine, or adrenergic receptors. The recommended daily dose of duloxetine HCL is typically 40–60 mg, which can be taken either twice or three times a day. It is commonly available in 20 mg, 30 mg, and 60 mg delayed-release capsules and tablets. Duloxetine HCL has an oral bioavailability of about 50%, meaning only half of the drug reaches the bloodstream after administration. [3]

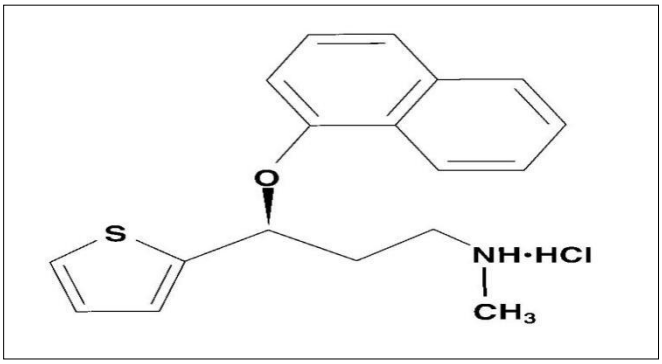

Figure 1 Chemical Structure of Duloxetine HCL

In addition to treating depression, duloxetine is commonly prescribed for diabetic peripheral neuropathy a condition that causes nerve pain in the hands, legs, and feet and for managing urinary incontinence. It is considered a newer and more favorable antidepressant due to its dual mechanism of action, good tolerability, safety profile, quicker onset of therapeutic effects, and reduced side effects compared to older drugs. Moreover, it has a low affinity for other neuronal receptors, which further reduces unwanted interactions. [4]

However, duloxetine has one drawback it breaks down easily in acidic environments, like the stomach, which can reduce its effectiveness. To address this, a controlled release formulation is often used to protect the drug from stomach acid and ensure it is released properly in the intestines. This approach helps maintain a steady concentration of the drug in the bloodstream, which is essential for effective and consistent treatment results.

In Present study, efforts were made to incorporate Duloxetine HCL in Chitosan, Sodium alginate along with Xanthum gum polymer by applying Extrusion-Spheronization techniques. [5]

The research aims to develop, optimize, and formulate Duloxetine HCL microsphere-loaded capsules using extrusion-spheronization to enhance its poor water solubility, achieve controlled and sustained drug release, improve bioavailability, allow for potential multi-drug encapsulation, and ensure uniform particle size distribution with high drug loading efficiency for effective treatment of depression and neuropathic pain.

2. Material and methods

2.1. Materials

Duloxetine Hydrochloride gift sample received from Sciquaint Innovations Lab Pune, India, Chitosan, Xanthum gum procured from Sciquaint Innovations Lab Pune, India, Sodium alginate, Calcium chloride received from Pravara Rural College of pharmacy Loni India. All excipients used were of analytical grade.

2.2. Methods

2.2.1. Formulation and Manufacture of Microspheres

Microspheres are prepared by Extrusion-Spheronization techniques. Chitosan, Sodium Alginate, and Xanthan Gum were dispersed in deionized water under continuous stirring for 30 minutes to form a uniform polymer solution. A weighed amount of Drug was thoroughly mixed with the prepared polymer dispersion to obtain a homogeneous drug-polymer

mixture. The homogeneous mixture was fed for an Extrusion process. Extrusion followed immediately using a extruder Anish Extruder-30(AEXT- 30) equipped with 1.0 mm diameter screen and functioning at a speed of 50 rpm. The prepared wet mass extruded through a flat-tip die to form cylindrical extrudates. The extruder settings were optimized to ensure smooth extrusion and uniform extrudate formation. The cylindrical extrudates were transferred to a spheronizer Anish Spheronizer- 200 (ASPH- 200) and spheronized at 1200 rpm for 5–10 minutes. During spheronization, the cylindrical extrudates were broken down and rounded to form spherical microspheres. The formed microspheres were collected and dried in a hot air oven at 60ºC for 3 hours to achieve the desired moisture content.[6]

2.3. Preparation Flowchart

Polymer Dispersion

(Chitosan + Sodium Alginate + Xanthan Gum) in water → 30 min stirring

↓

Drug Incorporation

(Active drug mixed into polymer solution → homogeneous blend) [7]

↓

Extrusion

(AEXT-30 extruder @50 rpm → 1.0 mm screen → cylindrical extrudates)

↓

Spheronization

(ASPH-200 @1200 rpm → 5-10 min → spherical shaping)

↓

Drying

(60°C hot air oven → 3 hrs → final microspheres)

↓

Quality Control

(Size distribution, drug content, moisture analysis) [8]

Table 1 Formulation of Microspheres

Formulation Batch	Duloxetine Hcl	Sodium Alginate	Xanthum Gum	Chitosan	Calcium Chloride
	Mg	Mg	Mg	Mg	Mg
F1	60	250	50	50	0.0029
F2	60	250	50	100	0.0029
F3	60	250	50	150	0.0029
F4	60	250	100	50	0.0029
F5	60	250	100	100	0.0029
F6	60	250	100	150	0.0029
F7	60	250	150	50	0.0029
F8	60	250	150	100	0.0029
F9	60	250	150	150	0.0029

Figure 2 Prepared microsphere

3. Formulation of filling microspheres of Capsule

3.1. Manual Procedure for Filling Microspheres in Capsules

3.1.1. Preparing the Capsules

Start by placing empty capsules into the capsule loading tray, making sure they align properly with the machine's holes. Once aligned, position the loaded tray on the capsule-filling machine.

3.1.2. Separating Capsule Caps from Bodies

Pull the locking handle forward and press down the long lever to separate the capsule caps from the bodies. Carefully remove the tray containing the separated caps and set it aside for later use.

3.1.3. Setting Up for Filling

Place the tray containing the capsule bodies back onto the machine's filling surface. Place the powder or microsphere tray underneath the filling area to catch any excess material and prevent spills.

3.1.4. Filling the Capsules with Microspheres

Pour the required number of microspheres onto the capsule-filling surface. Using a spreader plate, evenly distribute the microspheres over the capsule bodies. Lower the tamper and gently press to compact the microspheres within the capsule. If necessary, add additional microspheres and repeat the tamping process until the capsule reaches the desired fill.

3.1.5. Reassembling the Capsules

Retrieve the tray containing the separated capsule caps and carefully align it with the tray holding the filled capsule bodies. Lower locking plate and secure it in place by locking it. Turn the front knob to the right to ensure everything is properly aligned.

3.1.6. Closing the Capsules

Push the long lever downward to firmly attach the capsule caps onto the filled capsule bodies. This action locks the microspheres inside the capsules, completing the encapsulation process.

3.1.7. Removing the Filled Capsules

Unlock and lift the locking plate to release the filled capsules. Turn the front knob to the left to reset the machine, then lift the tray containing the completed capsules and empty them into a collection container.

3.1.8. Final Inspection and Cleaning

Check the filled capsules to ensure they are properly sealed and free of any defects. Finally, clean the capsule-filling machine thoroughly to remove any remaining powder or microspheres, leaving it ready for the next use. [9,10]

3.2. Calibration curve of Duloxetine hcl

3.2.1. Preparation of Duloxetine Stock and Working Solutions

A quantity of 10 mg of Duloxetine was accurately weighed and dissolved in 95% ethanol. The solution was then diluted to a final volume of 10 mL with ethanol to obtain a stock solution with a concentration of 1000 ppm (parts per million). From the stock solution, 1 mL was taken and further diluted to 10 mL using ethanol. This resulted in a working standard solution with a concentration of 100 ppm. From the 100 ppm working standard solution, aliquots of 0.5 mL, 1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL, and 3.0 mL were taken and diluted as needed to prepare additional solutions. The absorbance of these solutions was measured at a wavelength (λ) of 290 nm determined using a UV-visible spectrophotometer (Shimadzu UV-1800, Japan). The absorbance vs concentration calibration curve was drawn and linear regression equation was determined. The values of coefficient of determination (R^2), slope and y-intercept were calculated [11]

3.3. FTIR Analysis

Fourier transform infrared (FTIR) spectroscopy was used to verify possible interactions of Duloxetine HCL with co-formers. An FTIR spectrometer (Bruker Alpha) with an attenuated total reflection (ATR) accessory was used to analyze samples of pure Duloxetine HCL and physical mixture. About 2 to 3 mg of each sample was placed directly on the diamond crystal and compressed. Spectra were obtained in the range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1}, with 24 scans per spectrum. Characteristic peaks were identified and compared across samples to understand structural changes and intermolecular interactions. Regions near functional groups engaged in hydrogen bonding were given special attention. [12]

3.4. Optimization of Microspheres- loaded Capsule of Duloxetine HCL using 3^2 Full factorial design

Full Factorial Design 3 by 2 was implemented using Design Expert® DX 13.0 software to optimize parameter levels. The experimental setup incorporated two factors – Amount of Xanthan Gum (X1, measured in milligrams), Amount of Chitosan (X2, measured in milligrams), - along with two target responses: R1: Entrapment Efficiency; R2: In vitro Drug Release. 09 distinct experiments with different factor values were designed and optimized.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \ldots\ldots\ldots \quad (1)$$

Response surface methodology (RSM) is characteristically employed to relate a response variable to the levels of the input variables were selected and used to construct a design matrix aimed at identifying the optimal formulations. A statistical model incorporating both interaction and polynomial terms was applied to assess the response outcomes. The responses were then examined using analysis of variance (ANOVA), with individual parameters evaluated through the F-test. For each response, a polynomial equation was derived using multiple linear regression analysis.

A 3^2 full factorial design (which means 3 levels for each of 2 factors, totaling 9 experimental runs) was used to study how Xanthan Gum and Chitosan affect several outcomes: drug entrapment efficiency, drug release after 12 hours(t12). Contour plots and response surface methodology (RSM) plots were created for each response using DESIGN EXPERT softwares 13.0. [13]

Table 2 Variables in factorial design

Independent Variables	**Levels**		
	Low	**Medium**	**High**
X1: Amount of Xanthan gum(mg)	50	100	150
X2: Amount of Chitosan (mg)	50	100	150
Dependent Variables	Goals		
R1: Entrapment efficiency (%)	Maximize		
R2: In Vitro drug Release	Maximize		

Table 3 Design Batches as per 3^2 Factorial design

Batches	Factor 1 A: Xanthan gum(mg)	Factor 2 B: Chitosan(mg)	Response 1 EE (%)	Response 2 Drug release (%)
1	50	50	79.5	72.05
2	50	100	82.1	80.23
3	50	150	84.2	68.32
4	100	50	80.5	75.93
5	100	100	82.5	70.17
6	100	150	85.4	83.82
7	150	50	79.2	71.67
8	150	100	81.8	79.38
9	150	150	83.7	68.17

4. Evaluation of microspheres:

4.1. Percentage yield

The prepared microspheres are weighed after drying and percentage yield was calculated by dividing the weight of the microspheres collected (called the practical yield, Yp) by the total weight of the drug and polymers initially used to prepare the batch (the theoretical yield, Yt), and then multiplying the result by 100.

% Yield = (Practical Yield / Theoretical Yield) × 100[14]

4.2. Determination of flow properties of microspheres

The prepared microspheres were evaluated for flow Properties including bulk density, tapped density, Carr's Index, Hausner's ratio and angle of repose.

4.2.1. Bulk density

It is the ratio of total mass of microspheres to the bulk Volume of microspheres. It was measured by pouring the Weighed microspheres into a measuring cylinder and the Volume was noted. It is expressed in gm/ml and is given by

Bulk density = Mass of microspheres / Bulk volume of microspheres

4.2.2. Tapped density

It is the ratio of the total mass of microspheres to their tapped volume. The tapped volume is determined by tapping the microspheres until a constant volume is achieved. The result is expressed in g/mL.

Tapped density = Mass of microspheres / Tapped Volume of microspheres [15]

4.2.3. Carr's Index

It indicates the ease with which a material can be induced to Flow. It is expressed in percentage and is given by

Carr's Index = Tapped density- Bulk density/ Tapped density × 100

4.2.4. Hausner's ratio

It is an indirect index of ease of flow of microspheres. It is measured by

Hausner's ratio = Tapped density/ Bulk density

Angle of repose (θ)

It is defined as the maximum angle formed between the surface of a powder pile and the horizontal plane. The angle of repose was determined by measuring the height and radius of the heap of microspheres formed. It is measured by

$$Tan\theta = Height/ Radius$$

$$\Theta = \tan{-1}(Height /Radius)$$ [16,17]

4.3. Drug entrapment efficiency

Microspheres (20 mg) were crushed using a glass mortar and pestle, and the resulting powder was suspended in 100 ml of phosphate buffer (pH 7.4). The suspension was sonicated for 1 hour at room temperature, then filtered. The filtrate was subsequently analyzed for drug content. The Duloxetine content in the microspheres was determined by measuring the absorbance of entrapped product at 290 nm by UV spectrophotometrically (1800, Shimadzu). The drug Entrapment efficiency was calculated using the following formula:

Entrapment efficiency: Theoretical drug content/ Practical drug content × 100 [18,19]

4.4. Weight Variation Test

Ten capsules are individually weighed, and then their contents are carefully removed. The empty shells are weighed separately, and the net weight of the contents is calculated by subtracting the weight of the shell from the total weight of each capsule. Using the results from an assay as specified in the respective monograph, the amount of active ingredient present in each capsule is determined.

Formula- Individual wt – Avg.wt / Avg. wt × 100 [20]

4.5. In –Vitro release Study

The dissolution studies were conducted using a USP type II (Paddle) dissolution test apparatus (Electrolab TDT 08-L India). The dissolution medium consisted of 900 ml of phosphate buffer with a pH of 7.4 in sink condition. During the study, the temperature was carefully maintained at 37 ± 2°C, and the stirring speed was set at 100 rpm. A total of nine dissolution vessels were used, each containing one microsphere loaded Capsule.

At specific time intervals, samples were collected, and the withdrawn volume was replaced with a fresh dissolution medium to maintain sink conditions. The collected samples were then filtered using Whatman No. 1 filter paper. Finally, the concentration of Duloxetine HCL in the samples was measured using a UV (Shimadzu UV- 1800, Japan) at a wavelength of 290 nm. [21,22,23]

4.6. Scanning Electron Microscopy

The sample assembly was placed in a microscope and vaccum was applied. SEM works by scanning a focused beam of high-energy electrons over the surface of a sample. These electrons interact with atoms in the sample, producing various signals that can be detected and converted into detailed images. Surface morphology of microspheres examined by scanning electron microscopy (SEM) [24]

5. Result and discussion

5.1. Determination of Lambda max and Calibration curve of Duloxetine HCL with Ethanol: At 290 nm

The calibration curve of Duloxetine HCL exhibited excellent linearity (R^2 = 0.9989) with the equation y = 0.0818x–0.0281, confirming the reliability of the analytical method (Figure 3). The strong linear relationship between concentration and absorbance, coupled with the minimal y-intercept, indicates negligible systematic error, establishing a robust foundation for quantitative determination of Duloxetine HCL in the co-crystal formulation.

Table 4 UV spectrophotometer absorbance of Duloxetine hcl

Sr. No	Concentration	Absorbance
1	0	0.000
2	5	0.369
3	10	0.760
4	15	1.208
5	20	1.582
6	25	2.044

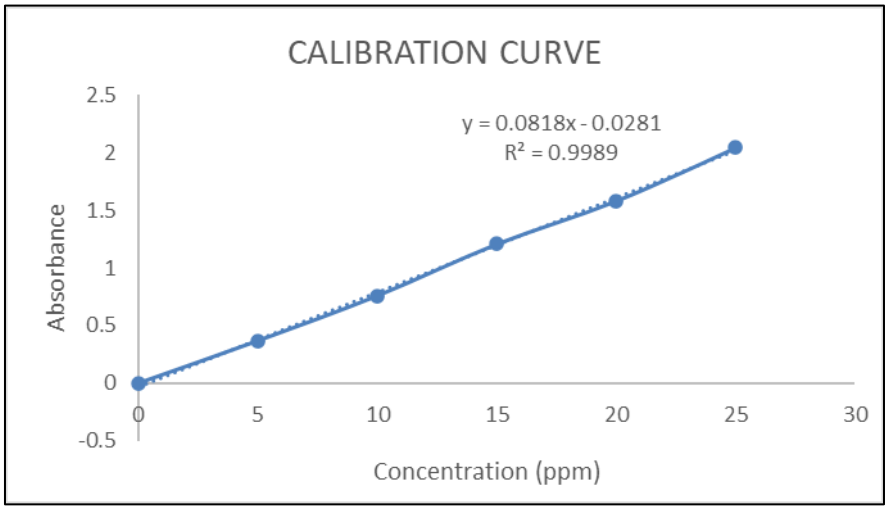

Figure 3 Calibration curve of Duloxetine HCL

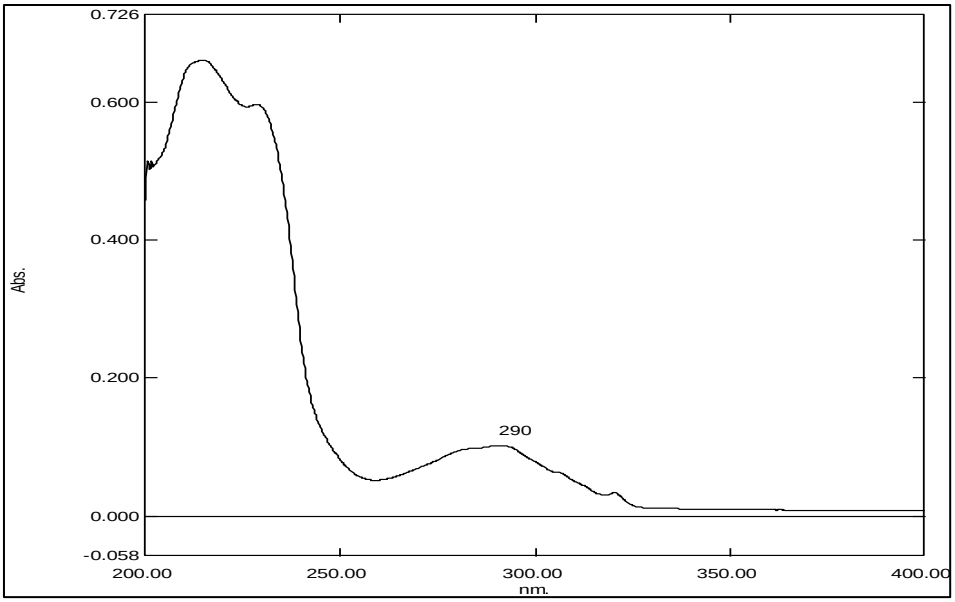

Figure 4 Lambda Max of Duloxetine HCL

6. Results of FTIR analysis

Fourier Transform Infrared (FTIR) spectroscopy was employed to evaluate potential drug-excipient interactions in the physical mixture. The FTIR spectra of Microspheres, Duloxetine hcl, Chitosan and Sodium alginate was recorded in FTIR Spectrophotometer (Brucker Alpha 2). The FT-IR spectrum of DX, presented in Fig. 5 of the supplementary file, displays several characteristic peaks. A weak N–H stretching vibration appears near 3400 cm^{-1}, likely reduced due to hydrogen bonding. A peak above 3000 cm^{-1} corresponds to aromatic C–H stretching, while a band below this region is attributed to alkyl CH_2 stretching. Additional bands related to hydrogen-bonded N–H groups are observed in the 2200–2800 cm^{1} range. The CH_2 bending vibrations are observed at 1450 and 1375 cm^{-1}, while the phenoxy C–O stretching vibration appears around 1200 cm^{-1}.Peakseen 1600 and 1450 cm^{-1} are associated with thiophene and naphthalene rings. Furthermore, a cluster of peaks near 700 cm^{1} corresponds to aromatic C–H bending modes, characteristic of the naphthalene and thiophene structures.

The FT-IR spectra of the Drug-loaded microspheres, Chitosan, Sodium alginate, and API- Duloxetine hcl, are shown in Fig. 5,6,7,8. The persistence of characteristic" peaks" of Duloxetine HCL in the physical mixture with only slight shifts in wavenumbers indicates the absence of significant chemical interactions between the drug and excipients, confirming compatibility for the co-crystal formulation.

A Fourier Transform Infrared Spectroscopy (FT-IR) analysis was carried out to assess the compatibility between the drug, excipients, their physical mixture, and the final optimized formulation. The spectra showed no new peaks or disappearance of existing ones, suggesting no chemical interaction had occurred. This indicates that the selected polymers are compatible with the drug. When comparing the FT-IR spectra, there were no significant differences between the pure Duloxetine HCL and the optimized formulation. This further confirms that there is no interaction between the drug and the polymers used.

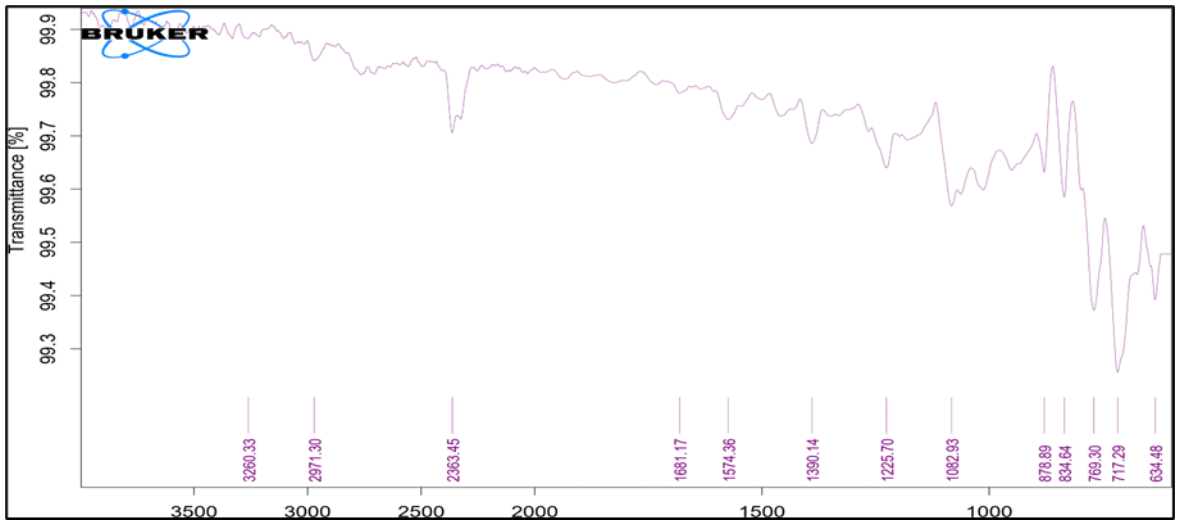

Figure 5 FTIR spectra of Duloxetine Hcl

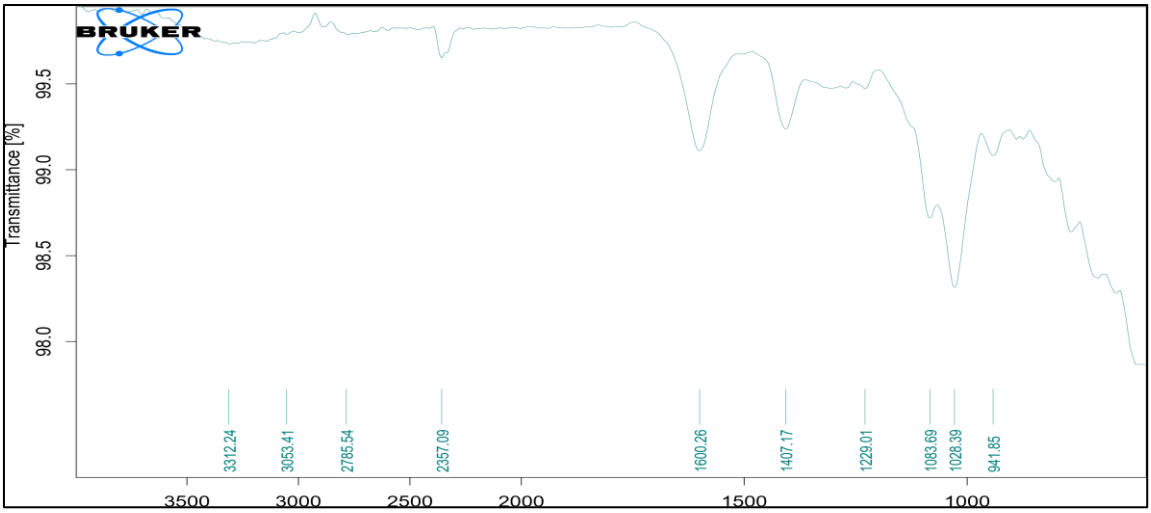

Figure 6 FTIR spectra of API + Sodium alginate

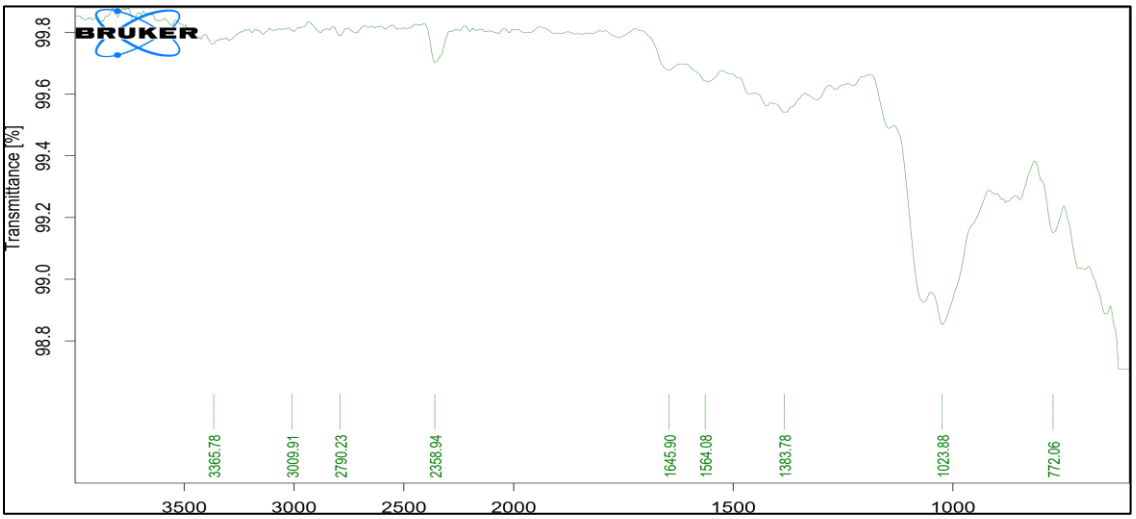

Figure 7 FTIR spectra API + Chitosan

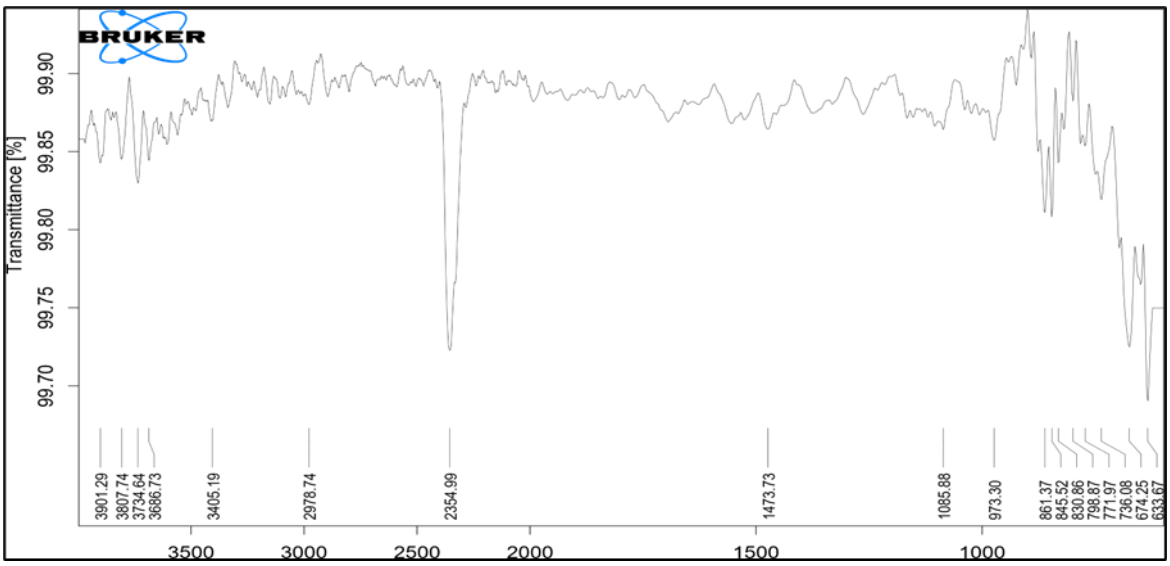

Figure 8 FTIR spectra of prepared microspheres

7. Micromeretics properties

The bulk density of Formulation F1 to F9 containing Sodium alginate, Xanthan gum and Chitosan formulation was in the range of 0.368 to 0.414 gm/ cm3 (as shown in table. 5), tapped density 0.432 to 0.482 and Hausner's ratio 1.08 to 1.20.

The carrs index of formulation F1 to F9 containing Sodium alginate, Xanthan gum and Chitosan 9.09 to 16.6. The angle of repose of formulation F1 to F9 containing Sodium alginate, Xanthan gum and Chitosan formulation was in the range of < 33.1 (as shown in the table.5). The formulation F1 to F9 shows good flow properties.

Table 5 Micromeretics properties of prepared microspheres

Formulation Code	Bulk Density (gm/cm2)	Tapped Density (gm/cm2)	Hausner's Ratio	Carr's Index	Angle of repose
F1	0.395±0.015	0.449±0.012	1.16±0.01	12.0±0.5	27.5±0.7
F2	0.372±0.013	0.462±0.015	1.14±0.01	14.4±0.7	31.8±0.8
F3	0.404±0.013	0.441±0.013	1.20±0.02	16.0±0.8	30.2±0.8
F4	0.392±0.012	0.482±0.011	1.08±0.01	13.5±0.7	29.3±0.8
F5	0.414±0.011	0.453±0.015	1.12±0.01	9.09±0.5	26.8±0.7
F6	0.410±0.012	0.432±0.011	1.16±0.01	10.5±0.6	33.1±0.9
F7	0.374±0.012	0.445±0.013	1.19±0.02	12.6±0.6	28.7±0.6
F8	0.368±0.014	0.451±0.015	1.12±0.01	16.6±0.8	32.6±0.9
F9	0.386±0.011	0.458±0.014	1.17±0.01	15.8±0.5	30.9±0.7

7.1. Percentage Yield and Drug Entrapement Efficiency

The entrapment efficiency of the drug was evaluated by varying the drug concentration in the formulation, using drug-to-polymer concentrations. Percentage yield and Entrapment efficiency of formulation F1 to F9 observed in the range of 81.25 to 94.75% and 79.2 to 85.4 % respectively. The result demonstrates that the Percentage yield and Entrapment efficiency both increase with an increase in polymer concentration.

Table 6 Percentage Yield and Drug Entrapement efficiency

Formulation Code	% Yield	% Drug entrapement efficiency
F1	90.73	79.5
F2	87.60	82.1
F3	81.25	84.2
F4	85.43	80.5
F5	89.01	82.5
F6	90.71	85.4
F7	82.74	79.2
F8	89.21	81.8
F9	94.75	83.7

7.2. Formulation and Optimization

A numerical optimization method based on the desirability approach was utilized to develop an optimized formulation that meets the targeted response criteria. In optimizing the microspheres- loaded capsule of DLX HCl, specific constraints were established for all variables and outcomes.

Table 7 ANOVA for Quadratic Model Entrapment efficiency

Response	Sum of squares	df	Mean square	F- value	P - value	Selection
Model	35.56	5	7.11	75.30	0.0024	Significant
A- Xanthan gum	0.2017	1	0.2017	2.14	0.2401	
B- Chitosan	33.14	1	33.14	350.84	0.0003	
AB	0.0100	1	0.0100	0.1059	0.7663	
A^2	2.21	1	2.21	23.35	0.0169	
B^2	0.0050	1	0.0050	0.0529	0.8328	
Residual	0.2833	3	0.0944			
Cor total	35.84	8				

Table 8 ANOVA for Quadratic Model Drug Release

Response	Sum of squares	df	Mean square	F- value	P - value	Selection
Model	254.40	5	50.88	72.41	0.0025	Significant
A- Xanthan gum	0.3174	1	0.3174	0.4517	0.5496	
B- Chitosan	28.12	1	28.12	40.03	0.0080	
AB	0.0132	1	0.0132	0.0188	0.8996	
A^2	22.27	1	22.27	31.69	0.0111	
B^2	203.68	1	203.68	289.89	0.0004	
Residual	2.11	3	0.7026			
Cor total	256.51	8				

7.3. Factorial equation for Drug entrapment efficiency

Effect of Formulation Variables on Entrapment Efficiency

The polynomial equation generated for Entrapment Efficiency in terms of coded factors was

7.3.1. Entrapment Efficiency

$+73.90000 + 0.082333\ A + 0.053000\ B - 0.000020\ AB - 0.000420\ A^2 - 0.000020\ B^2$

Xanthan gum had a Positive effect (coefficient = +0.0823) on entrapment efficiency compared to chitosan (coefficient = +0.0530), as seen from their linear coefficients. The negative quadratic terms (A^2 = -0.000420, B^2 = -0.000020) indicate a non-linear, suggesting that increasing the polymer concentration a certain point reduces the efficiency. The negative interaction term (AB = -0.000020) suggests a that combining xanthan gum and chitosan at higher levels does not improve entrapment efficiency as much as when used individually at optimal levels.

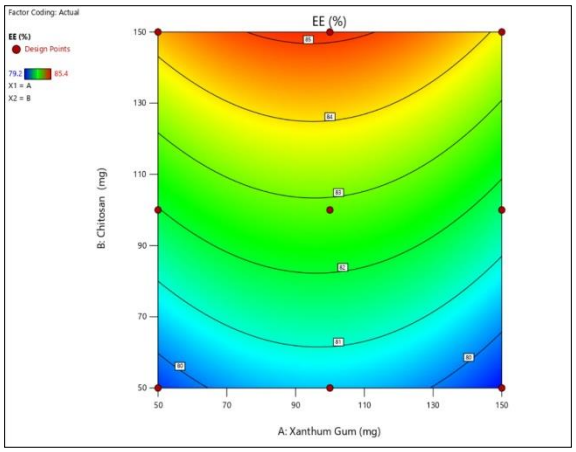

Figure 9 EE 2D

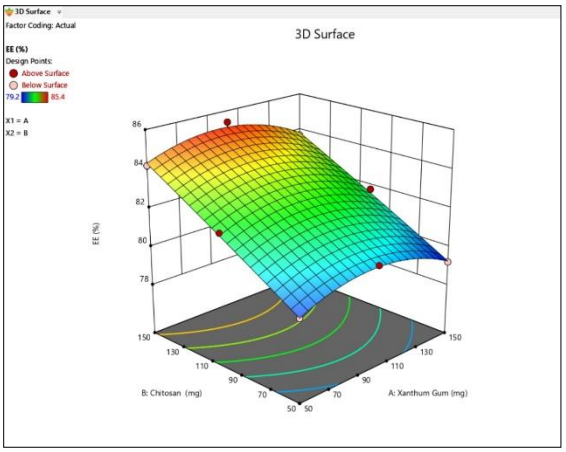

Figure 10 EE 3D

8. Factorial equation for Drug release Study

Effect of Formulation Variables on In Vitro Drug release

The polynomial equation generated In Vitro Drug release in terms of coded factors was

In Vitro Drug release = $34.67444 + 0.260033\ A + 0.761733\ B + 0.000002\ AB - 0.001335\ A^2 - 0.004037\ B^2$

The positive effect of Xanthan gum (A) and Chitoson (B) for A (0.2600) and B (0.7617) indicate that increasing both xanthan gum and chitosan increases drug release. The negative quadratic terms (A^2 = -0.001335, B^2 = -0.004037) suggest a non-linear (concave) relationship. This means that after a certain point, increasing the amount of xanthan gum or chitosan starts to decrease drug release. The very small positive interaction term (AB = 0.000002) indicates almost no synergistic or antagonistic interaction between xanthan gum and chitosan on drug release.

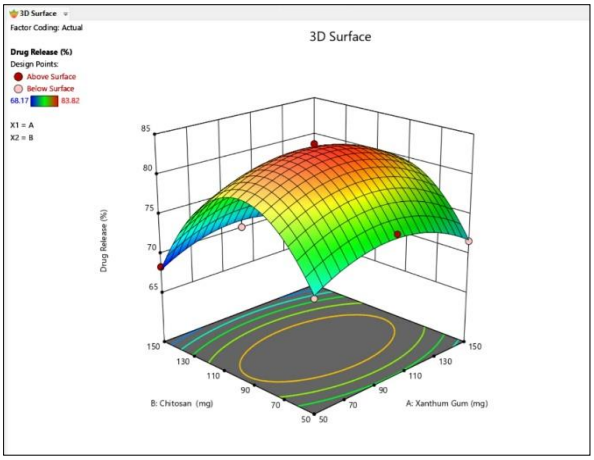

Figure 11 Drug release 2D

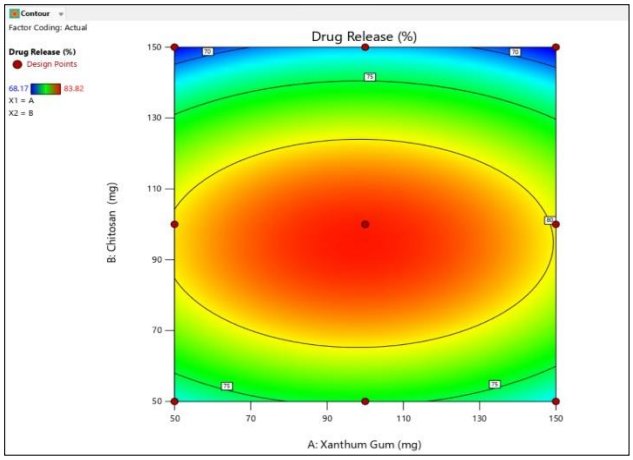

Figure 12 Drug release 3D

8.1. Weight Variation Test

Capsule were evaluated for weight variation test and F6 batch was within the acceptable limit as per IP. The result for the test is given in the table 9.

Table 9 Weight Variation Test

Sr. No	Capsule Shell wt. in (mg)	Net content wt. (mg)	Whole capsule wt. (mg)
1.	95	435	530
2.	94	421	515
3.	97	406	503
4.	89	453	542
5.	98	452	550
6.	95	413	508
7.	89	430	519
8.	93	407	500
9.	93	425	518
10.	96	408	504

Formula- Individual wt – Avg.wt / Avg. wt × 100 = NMT 7.5

453 – 425/ 425× 100= 6.5%

8.2. Drug release study

Dissolution studies for all the formulations (F1 to F9) were performed using a USP Type II (paddle) dissolution apparatus. The in vitro drug release of all formulations was observed at the end of 12 hours. The studies were carried out in a dissolution medium with a pH of 7.4. The In-vitro drug release results for each formulation are summarized in the table below. Additionally, graphs illustrating the cumulative percentage of drug released over time have been provided and the increased in concentration of polymer leads to increased density of polymer matrix into the microspheres which result maximum release of drug. The formulation F6 is the optimized batch which shows the maximum drug release of 83.82% after 12 hours.

Table 10 Cumulative percentage In Vitro drug released from Duloxetine HCL microspheres formulation batch F1- F9

Time (hour)	% drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	13.73	14.45	14.27	13.15	20.83	20.57	11.48	20.35	17.57
2	17.78	17.97	19.08	15.75	22.33	22.23	14.23	27.78	19.65
4	22.97	22.20	24.82	19.08	33.83	33.32	21.27	32.97	25.20
6	34.08	27.83	29.08	24.45	48.15	49.10	24.45	41.47	28.67
8	43.68	30.93	32.23	33.32	50.75	63.72	30.62	57.60	33.75
10	66.48	71.30	47.75	51.30	56.62	78.58	61.32	66.27	47.67
12	72.05	80.23	68.33	75.93	70.17	83.82	71.67	79.38	68.17

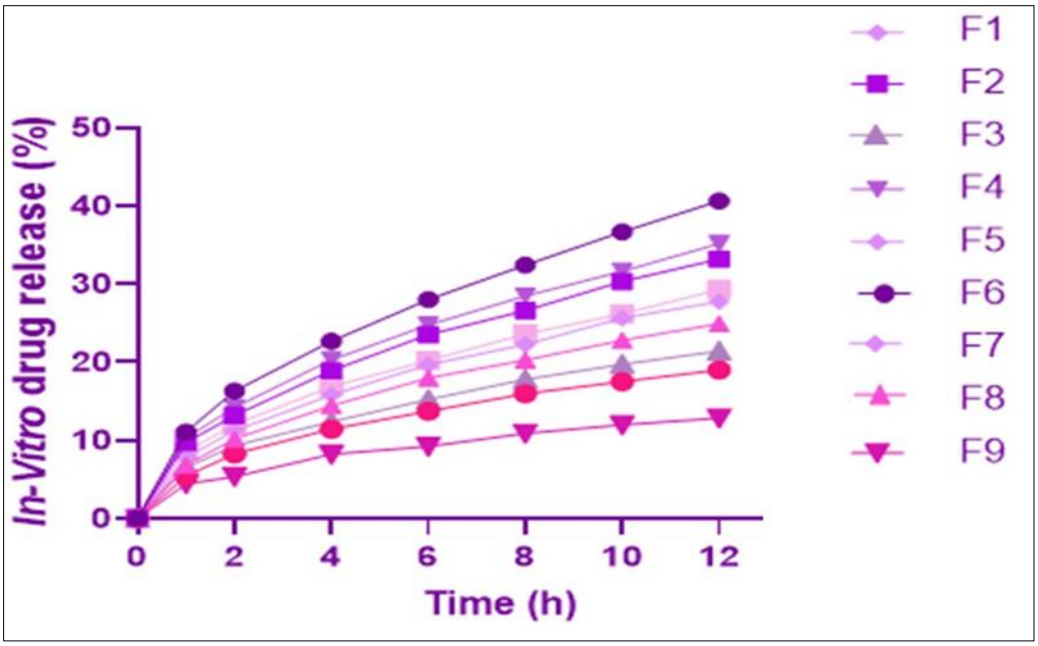

Figure 13 Drug release Study

8.3. Scanning Electron Microscopy Analysis

The surface of the microspheres was examined using scanning electron microscopy (SEM), as shown in the figure 14. The SEM images showed that the microspheres were mostly round, had a clear shape, and could move around easily. Their surfaces looked a bit rough, and small drug crystals were often seen on them. These surface crystals are important because they help with the release of the drug from the microspheres.

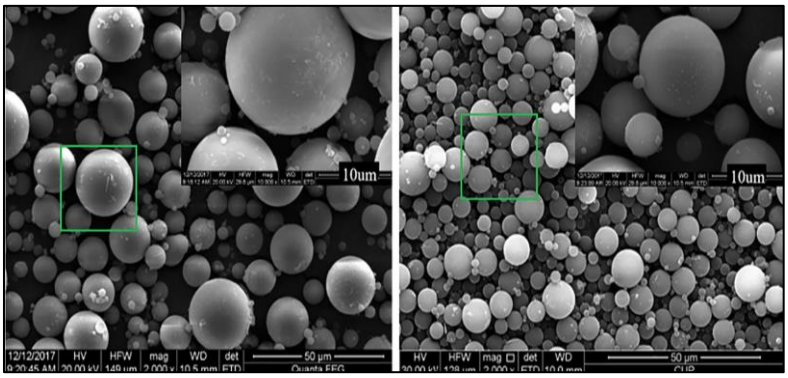

Figure 14 SEM image of Microspheres

9. Discussion

This study was designed to formulate and evaluate microspheres of Duloxetine HCL using extrusion-spheronization with a focus on sustained drug release. Three polymers Chitosan, Sodium Alginate, and Xanthan Gum were selected for their distinct physicochemical and biocompatible properties, each contributing differently to drug encapsulation and release behavior. Drug-Polymer Compatibility is fundamental to ensure the stability and effectiveness of the formulation. FTIR and DSC studies showed no significant changes in the characteristic peaks or thermal behavior of Duloxetine HCL when combined with the selected polymers. This indicates no interaction or degradation, confirming that the polymers are chemically compatible with the drug during formulation and storage. Micromeritics and Flow Behavior, Flow properties of microspheres are crucial for consistent dosing and manufacturability. The formulated microspheres showed: Angle of repose < 30°, indicating excellent flow. Carr's Index < 15% and Hausner's ratio < 1.25, suggesting minimal inter-particle friction and easy packing. These parameters confirm that the microspheres are suitable for encapsulation in hard gelatin capsules, aiding in ease of handling and uniform dosage. Particle Size and Surface Morphology, SEM analysis showed spherical, discrete, and smooth microspheres, essential for uniform flow and

controlled release. The size range between 620–950 µm was optimal for oral administration, providing a balance between surface area and structural integrity. Larger microspheres (e.g., with Xanthan Gum) were associated with slower drug release due to thicker diffusion barriers. Production Yield and Drug Entrapment Efficiency, the production yield of 78.9%–89.5% suggests minimal processing losses and efficient spheronization. The encapsulation efficiency ranged from 68.3%–88.7%, which is notably high. The variation can be attributed to: Polymer type: Xanthan Gum's higher viscosity likely helped retain more drug. Drug-polymer ratio: Increased polymer content typically enhanced drug retention by forming a denser matrix. In-vitro Drug Release Behavior, all formulations exhibited sustained release over 12 hours, making them suitable for once or twice-daily dosing an important benefit for drugs like Duloxetine HCl, which require steady plasma levels for effective depression management. The release mechanism followed: Higuchi model: indicating diffusion-controlled release. In some batches, minor swelling and erosion (particularly in Chitosan and Alginate) may have contributed to dual-release mechanisms. Among all batches, F6 (Xanthan Gum) showed the most prolonged and consistent release profile, making it ideal for sustained delivery. Advantages of the Formulation Approach, The extrusion-spheronization technique enabled uniform microspheres with controlled particle size and good flow. The use of natural and biodegradable polymers like Chitosan, Alginate, and Xanthan Gum provides a safe, non-toxic, and eco-friendly drug delivery approach. The sustained release helps improve patient compliance and reduces side effects associated with peak plasma concentrations.

10. Conclusion

Extrusion-spheronization has shown to be an effective method for producing microspheres containing Duloxetine HCl, a drug known for its low water solubility. The resulting microspheres were nearly spherical, had a consistent size, and possessed suitable hardness and weight. These properties are important because they help ensure even coating, smooth flow during processing, and efficient capsule filling.

Extrusion-spheronization has proven to be an effective technique for formulating controlled-release microspheres of Duloxetine HCl. The prepared microspheres were spherical, uniform in size, and exhibited good flowability and encapsulation efficiency. FTIR and SEM analyses confirmed drug-polymer compatibility and appropriate surface morphology. Among all batches, the F6 formulation demonstrated superior drug entrapment and sustained release, making it the optimized batch. This study confirms that microsphere-loaded capsules can enhance the solubility, stability, and controlled release of Duloxetine HCl, making them a suitable alternative for improving its therapeutic performance in treating depression and neuropathic pain.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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