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Research Article

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Development and Characterization of Ondansetron Hydrochloride Intranasal Mucoadhesive Microspheres

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ABSTRACT

Aim: This study aimed to design, develop, and evaluate polymeric mucoadhesive microspheres loaded with ondansetron hydrochloride for intranasal delivery. The objective was to bypass first-pass metabolism in the liver, enhance bioavailability, and extend the residence time of the drug.

Methodology: Microspheres were formulated using the solvent evaporation technique with carbopol 940 and HPMC K15M as mucoadhesive polymers, alongside ethyl cellulose as a film-forming polymer. The study evaluated the impact of formulation variables, such as polymer-to-polymer ratio and stirring rate, on the microsphere characteristics. Comprehensive characterization included assessments of drug-polymer interactions, entrapment efficiency, drug loading, swelling properties, particle size analysis, thermal behavior, morphology, in-vitro mucoadhesion, ex-vivo drug permeation, *in-vitro* drug release, histopathology, and release kinetics.

Results: The microspheres demonstrated favorable characteristics, including satisfactory entrapment efficiency, controlled drug release, and excellent mucoadhesive properties. Particle size analysis confirmed uniformity, while morphological studies revealed a spherical structure. In-vitro and ex-vivo evaluations indicated effective drug permeation and sustained release. The histopathological findings confirmed the safety of the formulation, and release kinetics followed a controlled release profile.

Conclusion: The results establish that ondansetron hydrochloride-loaded mucoadhesive microspheres, prepared using the solvent evaporation method, offer a promising approach for intranasal drug delivery. This formulation strategy effectively enhances bioavailability, provides sustained drug release, and has the potential for future advancements in nasal drug delivery systems.

Keywords: Ondansetron hydrochloride, Mucoadhesive Microspheres, Intranasal Delivery, Solvent Evaporation Technique, Sustained Drug Release, Bioavailability Enhancement

INTRODUCTION

Ondansetron hydrochloride is a novel and specific antagonist of the 5-HT3 receptor used in the management of chemotherapeutic induced and post-operative nausea and vomiting. Its relative bioavailability is about 60% due to first pass metabolism and its plasma half-life is about 3–4 h.[1] The shorter biological half-life and frequent dosing in chemotherapy-induced nausea and vomiting make it as an ideal candidate for sustained release drug delivery system.[2] Microencapsulation is the technique to sustain the release rate of the drug.[3] Nasal drug delivery is a promising drug delivery option where common drug administrations (e.g. intravenous, intramuscular, or oral) are inapplicable. Recently, it has been shown that many drugs have better bioavailability by nasal route than by oral route.[4] This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic firstpass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. It is a promising route which offers noninvasive systemic delivery of numerous

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therapies and drug delivery route to the brain. However, nasal delivery has limitation which has restricted its use due to rapid clearance of the formulation from nasal cavity due to mucociliary clearance mechanism.[5] Different delivery systems based on mucoadhesive polymers have been developed which are able to enhance the residence time of formulation at site of absorption of drug. The mucoadhesive system as microspheres not only protects the drug from enzymatic degradation but also remains in close contact with the absorption tissue. The mucous membrane releases drug at the site of action which leads to enhanced bioavailability.[6]

The aim of the study "Development and Characterization of Ondansetron Hydrochloride Intranasal Mucoadhesive Microspheres" is to design, develop, and evaluate ondansetron-loaded polymeric mucoadhesive microspheres for intranasal delivery to enhance the bioavailability of ondansetron, bypass the first-pass metabolism, prolong its residence time in the nasal cavity, and provide sustained drug release for effective management of nausea and vomiting.

MATERIALS AND METHODS

Chemicals

Various materials from standard suppliers have been procured and used. All modern instrumentation was part of the study. Various chemicals used along with the company name are listed in **Table 1**.

Table 1: List of chemicals.

S. No.	Chemical used	Company
	Ondensetron	Alkan Pharma
	Chitosan	Lobachemie
	Acetic Acid	Central drug house
	Liquid paraffin	Lobachemie
	Heavy Liquid paraffin	Pure chemicals co. Chennai India
	Span 80	Lobachemie
	Light Liquid paraffin	Sigma- Aldrich

Instruments

Various instruments used along with their manufacturers and model number are listed in **Table 2**. All other chemicals used in the study were of analytical grades. Solution of drugs and chemicals were freshly prepared before use.

Table 2: List of instruments.

S. No.	Instrument	Model No.	Manufacturer
1.	Digital weighing balance	Ab265 -s/ fact	Mettler Toledo, Switzerland
2.	Digital weighing balance	Shc-126	Shimadzu, Japan
3.	Magnetic stirrer	Rq-122	Remi work, India
4.	Purified water system	Milli-Q	Millipore, USA
5.	Mechanical stirrer	IKA RW20	Cole-parmer
6.	UV-Vis Spectrophotometer	UV-1700	Shimadzu, Japan
7.	FT-IR Spectrophotometer	RX1	Perkin Elmer
8.	Dissolution apparatus	DS-800	Labindia
9.	Hot air oven	NA	Perfit India
10.	Scanningelectron microscope	Durene SV4	Equip. Durene India
11.	Optical microscopy	NA	Daihan Labtech
12.	Differential scanning calorimetry	DSC 60	Shimadzu, Japan

Pre-formulation Studies

Pre-formulation studies are an important tool for the determination of purity, identity, physical and chemical properties of the drug substances or excipients before incorporating them in formulation development. The nature of the drug highly affects the processing parameters like the method of preparation, entrapment efficiency, compatibility, and the pharmacokinetic response of the formulation. Pre-formulation studies are an indispensable protocol for the development of a safe, effective, and stable dosage form.[7]

Purity and Identification studies of Ondensetron

To check the purity and identification of the drug various studies have been performed.[8]

Physical Appearance

The physical appearance of the drug was checked by visual observation, dispersing the drug on clean butter paper.[9]

Determination of absorption maxima (λmax)

To obtain structural information regarding of the Ondensetron, UV spectrophotometric method was used. The stock solution of 1000µg/ml of the drug was freshly prepared in water and it was further diluted to obtain the concentration of 100µg/ml with acetic acid. Spectra were recorded in the range of 200-800 nm to determine the absorption maxima of Ondensetron.[10]

Melting point

A capillary melting point apparatus was used to determine the melting point of the drug. A small amount (1.3 mg) of the drug was filled into the capillary previously sealed on one side and the melting point was analyzed on the melting point apparatus to observe the melting point range.[11]

Solubility Study

A 30 mg of Ondensetron was placed in 10 ml of distilled water and phosphate buffer at pH 6.8. The samples were then stirred for 2 hours in magnetic stirrer at room temperature. The solutions were then passed through a whatmann filter paper and the amount of the drug dissolve was analyzed in UV spectrophotometer (UV Shimadzu 1700, Japan) at 310 nm.[12]

Method

Spray-Drying Technique

Chitosan (CH) and Eudragit L 100 (EU) microspheres were prepared by spray-drying technique (**Table 3**). The chitosan solution (1% w/v) was prepared in aqueous glacial acetic acid by continuous stirring using a sharp blade mechanical stirrer, this solution was filtered through 0.45 µm Millipore filter paper then the drug was dispersed in the polymeric solution and stirred. Sufficient amount of 25% (v/v) aqueous glutaraldehyde (cross-linking agent) was added slowly with continuous stirring. In the case of Eudragit L 100 microspheres required quantity of Eudragit L 100 was dissolve in methanol by continuous stirring with the help of sharp blade mechanical stirrer then the drug was added to the polymeric solution and stirred continuously. Drug-loaded microspheres were obtained by spraying the feed solution with a spray dryer using astandard 0.7 mm nozzle. The solution was fed to the nozzle with a peristaltic pump, atomized by the force of compressed air and blown together with heated air to the chamber where the solvent in the droplets was evaporated. The dried microparticles were harvested from the apparatus collector and kept in a desiccator. The process parameters of the spray-drying technique includes inlet temperature of 80-85°C, outlet temperature 60-65°C, aspirator speed 40–50%, and feed pump speed 8-10 ml min^{-1}.[13]

Table 3: Composition of intranasal mucoadhesive microspheres.

Types of polymer	Formulation Batch	Drug : Polymer ratio	Drug (mg)	Polymer (mg)
Chitosan	CH-B	-	-	2000
	CH-1	1: 2	1000	2000
	CH-2	1: 3	1000	3000
	CH-3	1: 4	1000	4000
Eudragit L 100	EU-B	-	-	2000
	EU-1	1: 2	1000	2000
	EU-2	1: 3	1000	3000
	EU-3	1: 4	1000	4000

Evaluation of the Microspheres Percentage entrapment efficiency

A total of 25 mg microspheres were crushed and dispersed in 100 ml phosphate buffer pH 6.8 and sonicated for 20 min. Dispersion was stirred on magnetic stirrer for 6 h. The dispersion was filtered and drug content was analyzed spectrophotometrically at 262 nm.[14] The percentage drug entrapment efficiency was calculated using following equation:

% Entrapment Efficiency = Theoretical drug content × 100

Practical drug content

Particle size analysis

Particle size analysis of drug-loaded chitosan microspheres was performed by optical microscopy using a compound microscope. A small amount of dry microspheres was suspended in purified water (10 ml). The suspension was ultrasonicated for 5 s. A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing chitosan microspheres was mounted on the stage of the microscope and diameter of atleast 300 particles was measured using a calibrated ocular micrometer.[15]

In vitro drug release

A total of 20 mg Ondensetron equivalent microspheres were weighed and filled in the empty capsule shells. Dissolution tests were performed in a USP Dissolution Tester Apparatus I (Basket method) at 37 ± 0.5°C. The baskets were rotated at a speed of 50 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 h and the phosphate buffer pH 6.8 for 3-12 h (900 ml). Aliquots of 5 ml were withdrawn at different time intervals, filtered through Whatmann filter paper and the content of were Ondensetron determined spectrophotometrically at a wavelength of 262 nm using ultraviolet (UV) spectrophotometer.[16]

Surface morphology Morphological characterization of the microspheres was carried out by using scanning electron microscopy (SEM) under higher and lower resolution.[17]

Partition coefficient

To calculate the partition coefficient of drugs, n-octanol and water will be utilised in equal parts in a separating funnel. A drug solution will be prepared, and 1 ml will be added to a 50/50 mixture of octanol and stimulated tear solution (pH 7.4) in a separating funnel. The mixture will then be stirred

for 10 minutes, let to stand for an hour, and then continued for another 24 hours. Following this, the aqueous and octanol phases will be centrifuged for 10 minutes at 2000 rpm to separate them. Using a UV-Vis Spectrophotometer, the aqueous and octanol phases will be measured at their respective maximums before and after partition in order to estimate the partition coefficient.[18]

Drug-polymer interaction study (Fourier transform-infrared (FT-IR) spectroscopy)

In order to assess the Drug-polymer interaction study, Fourier transform-infrared (FT- IR) spectroscopy will be employed. The pellets will be scanned in 128 scans with a resolution of 4cm^{-1} and a 1 cm^{-1} interval over a wave number range of 4000-400 cm^{-1} in an inert atmosphere.Each spectrum's background will be taken away.[19]

Scanning Electron Microscopy (SEM)

For SEM, one drop of Microspheres were mounted on the stab covered with clean glass and coated with gold and were observed under the scanning electron microscope at an accelerating voltage of 20KV and photomicrographs of suitable magnification was obtained.[20]

Physical Stability Studies

Physical stability tests of the prepared vesicles were carried out to investigate the aggregation of vesicles and leakage of drug from them during storage. The prepared drug vesicles were stored in transparent vials covered with plastic cap at room temperature for one month. The physical stability was evaluated by vesicle size, EE% and over a one month period. Samples from each vesicle were withdrawn after a month and the particle size, EE% were measured.[21]

RESULTS AND DISCUSSION

Pre-formulation studies

Various pre-formulation parameters such as physical appearance solubility, and melting point, were evaluated. FT-IR and UV-Visible spectroscopy were performed. Pre-formulation studies suggested that Ondensetron was pure and free from impurities.

Purity and Identification studies of Ondensetron

Physical appearance

Ondensetron was visually observed and was found to be white to off white powder, practically odorless as mentioned in Indian Pharmacopoeia (I.P.-2018) shown in **Figure 1**.

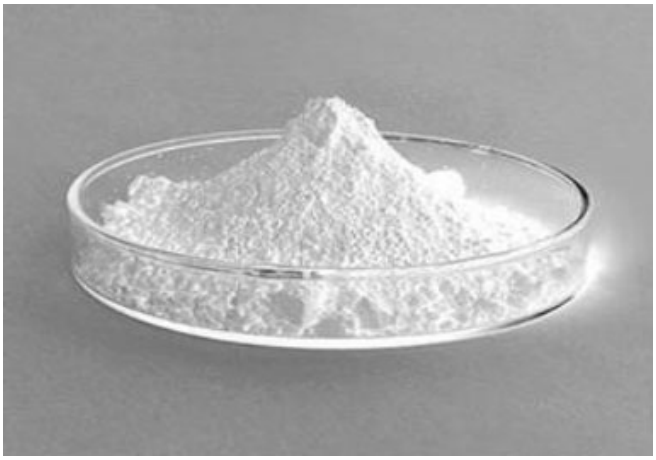

Figure 1: Ondensetron white powder.

Melting point

The melting point determination was performed to check the purity of the drug. The melting point of the Ondansetron was found to the range between 154-176°C which complies with the standard; *i.e.*, 158-179°C. The drug melts completely over a narrow temperature range indicating the crystalline pattern of the drug.

Solubility studies

The solubility of drugs will be tested in distilled water, a number of buffer solutions (pH 4.0, pH 7.4, and pH 8.0), and methanol. Three identical readings will be used to calculate the average.

Table 3: Solubility of drug in different solvents.

S. No.	Solvent	Solubility
1	Water	Soluble
2	Methanol	free soluble
3	Chloroform	free soluble
4	Dichloromethane	Sparingly soluble
5	Methylene chloride	Slightly soluble

Absorption maxima of Ondensetron

The UV-Visible spectrum of fluconazole showed absorption maxima at 310 nm in ethanol which is comparable with the reference spectrum of the drug 311 nm. The UV-Visible spectrum of fluconazole has been shown in **Figure 2**.

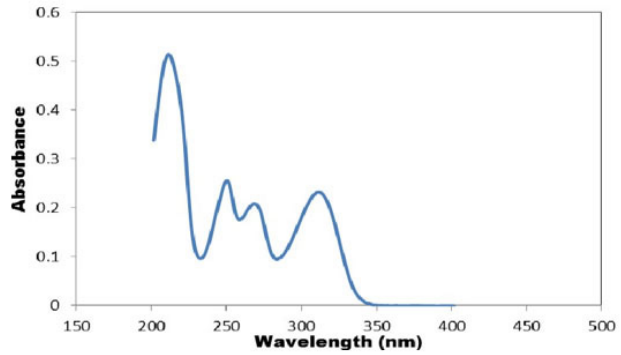

Figure 2: Determination of λmax of ondensetron.

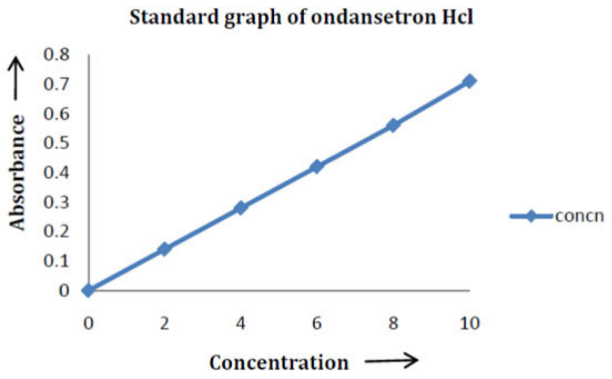

Figure 3: Standard curve of ondensetron.

Standard curve of ondensetron

The absorbance was measured, and a graph was plotted between concentration (X-axis) and absorbance (Y-axis). The line equation and correlation coefficient were calculated for the calibration curve of equation (y = mx + c), y is absorbance, m is slope, x is concentration and c are intercept. The curve was found to be linear on the basis of R^2 value which was found 0.07 as per ICH guideline.

Partition coefficient

To calculate the partition coefficient of drugs, n-octanol and water will be utilised in equal parts in a separating funnel. A drug solution will be prepared, and 1 ml will be added to a 50/50 mixture of octanol and stimulated tear solution (pH 7.4) in a separating funnel. The mixture will then be stirred for 10 minutes, let to stand for an hour, and then continued for another 24 hours. Following this, the aqueous and octanol phases will be centrifuged for 10 minutes at 2000 rpm to separate them. Using a UV-Vis Spectrophotometer, the aqueous and octanol phases will be measured at their respective maximums before and after partition in order to estimate the partition coefficient.

FT-IR spectroscopy

Fourier-Transform Infrared (FT-IR) spectroscopy is a powerful analytical technique used to study the vibrational modes of molecules. It provides valuable information about the chemical structure and functional groups present in a compound. In the case of Ondansetron, a well-known antiemetic drug, FT-IR spectroscopy is employed to characterize its molecular composition.

***Molecular Structure of Ondansetron*:** Ondansetron, chemically known as (RS)- 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4- one, belongs to the class of serotonin 5-HT3 receptor antagonists. Its molecular structure contains various functional groups, including a carbonyl group, imidazole ring, and a tertiary amine.

***Carbonyl Stretching (C=O)*:** Ondansetron exhibits a characteristic peak in the region around 1700-1650 cm^{-1}, corresponding to the stretching vibration of the carbonyl group (C=O) in the carbazone ring. This peak provides insights into the carbonyl functional group's involvement in the molecule.

***Aromatic Ring Stretching*:** The FT-IR spectrum of Ondansetron typically shows peaks in the range of 1600-1500 cm^{-1}, corresponding to the stretching vibrations of the aromatic rings in the molecule. This region aids in confirming the presence of aromatic structures within Ondansetron.

***N-H Stretching of Imidazole Ring*:** Ondansetron contains an imidazole ring, and the N-H stretching vibrations of this ring are usually observed in the FT-IR spectrum. A peak around 3300-3200 cm^{-1} signifies the presence of N-H bonds in the imidazole moiety.

***C-H Stretching*:** The aliphatic and aromatic C-H stretching vibrations contribute to peaks in the fingerprint region (below 1500 cm^{-1}). These bands offer additional information about the structure and symmetry of the molecule.

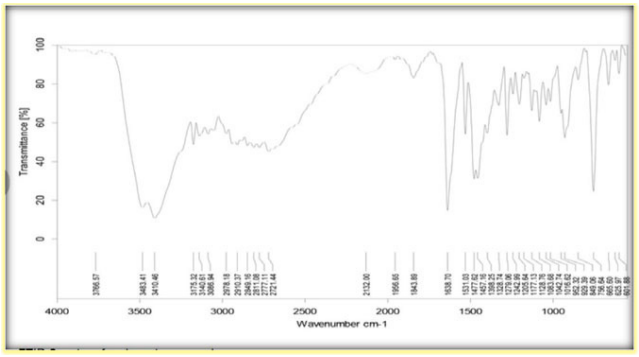

Figure 4: FTIR spectrum of ondensetron.

Drug loaded microspheres

Encapsulation efficiency (EE), % Drug Content, and % Product Yield

Drug loaded microspheres were weighed and dissolved in phosphate buffer pH 6.8 and mixture was filtered. The percent entrapment was calculated using the following equations:

% Product Yield = total wt of the microspheres/total wt of the drug polymer × 100

% Drug content = calculated amt of drug / total wt of microparticles × 100

Encapsulation efficiency = Actual drug content/ Theoretical drug content × 100

Table 4: % Drug Content, % Product Yield, and % Entrapment efficiency.

Formulation	% Drug Content	%Product Yield	% Entrapment efficiency
F1	50	76	40.92
F2	47	78	50
F3	53.33	88	56
4F	33.33	39	30.46
F5	25	37.5	46.14
F6	27	43.14	31.23
F7	34	57.57	34.25
F8	25	56.57	33.27
F9	20	77	33.98

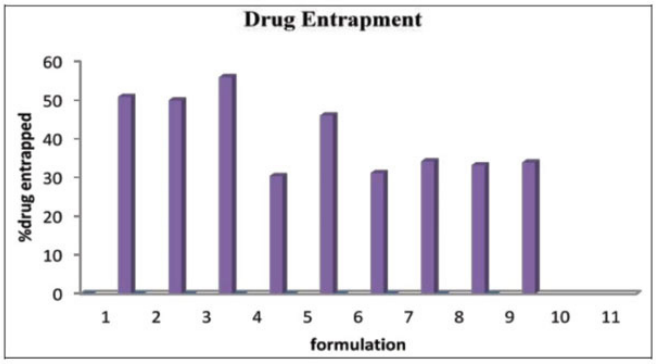

Figure 5: % Entrapment efficiency

Particle Size analysis

All the batches prepared were analyzed for particle size. Microspheres were placed on the set of standard sieves ranging from sieve No. 16# – 60#. The sieves were arranged in such a way that in descending order of the mesh size 16# on the top and 60# mesh in the bottom. The microsphere passed through the set of sieves and the amount retained on each sieve was weighed and the average mean diameter was determined.

Table 5: Particle Size determination of microspheres batches.

S.No.	Formulation code	Mean particle size (nm)
1.	F1	334
2.	F2	396
3.	F3	387
4.	F4	323
5.	F5	346
6.	F6	384
7.	F7	334
8.	F8	336
9.	F9	330

In vitro drug release

In vitro drug release carried out of different formulation through egg membrane and graph was plotted. The drug release was performed for 5 hr. The % CDR of different formulation was found to be in range. The result indicates that F3 is the best formulation.

Table 6: *In vitro* drug release.

S. No.	Time (min.)	F1	F2	F3	F4	F5	F6	F9
1	0	-	-	-	-	-	-	-
2	5	-	16	33.38	2.055	13.33	4.722	9.44
3	15	-	35.83	47.22	8.45	14.55	5.056	9.944
4	30	-	46.50	51.16	5.22	15.12	7.56	10.23
5	60	-	46.83	51.38	5.77	15.83	9.27	10.50
6	120	-	49.5	51.66	6.33	17.55	10.95	10.68
7	180	-	51.77	52.22	6.88	19.78	11.67	11.16
8	240	-	53	52.38	7.44	21.67	12.45	12.18
9	300	-	53	52.77	10.77	23.25	0.239	13.50
10	360	-	53.22	53	11.33	29.28	13.28	16.83
11	420	-	53.45	53.33	12.24	32.56	18.17	18.55
12	480	-	53.54	64	12.78	36.23	20.28	19.34
13	540	-	53.72	70	13.45	36.57	25.48	19.68
14	600	-	54.33	72	14.16	43.61	32.5	20.28
15	660	-	56.66	76	15.88	45.73	37.56	20.66
16	720	-	64.45	78	16.45	49.12	38.73	25.56

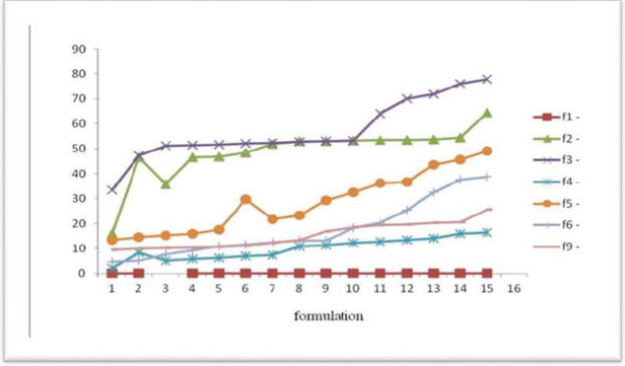

Figure 6: ***In vitro*** drug release.

Scanning Electron Microscopy (SEM)

For SEM, one drop of Microspheres were mounted on the stab covered with clean glass and coated with gold and were observed under the scanning electron microscope at an accelerating voltage of 20KV and photomicrographs of suitable magnification was obtained.

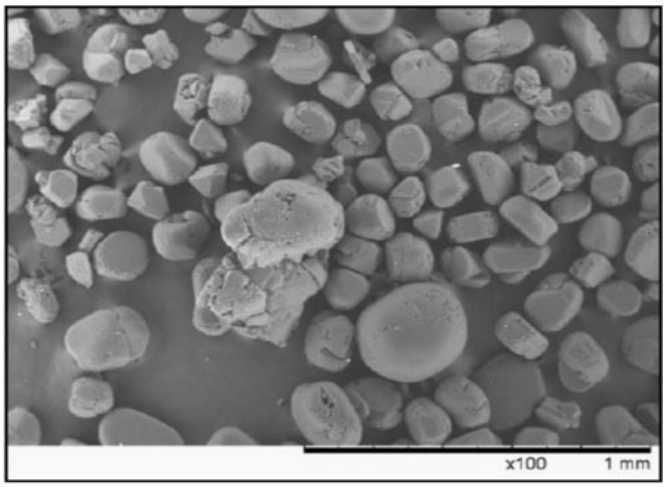

Figure 7: SEM image of microspheres.

FTIR Spectra

The FTIR spectra of ondansetron and optimized formulation were shown in **Figure 8**. The results obtained with IR studies showed that there was no interaction between the drug and other excipients used in the formulation. The FTIR of ondansetron has shown intense band at 3483.41 cm^{-1}, 2910.11cm^{-1}, and 1638.7 cm^{-1} corresponding to the presence of functional groups such as NH group, C-C-Aromatic group and C-C-Aliphatic group. The FT-IR of optimized formulation has shown intense bands at 3483.93 cm^{-1}, 2925.03 cm^{-1}, and 1637.96 cm^{-1} which indicate no change in the functional groups such as NH group, C-C-Aromatic group, C- C-Aliphatic and confirmed undisturbed structure of ondansetron, which indicates no drug- excipient interaction.

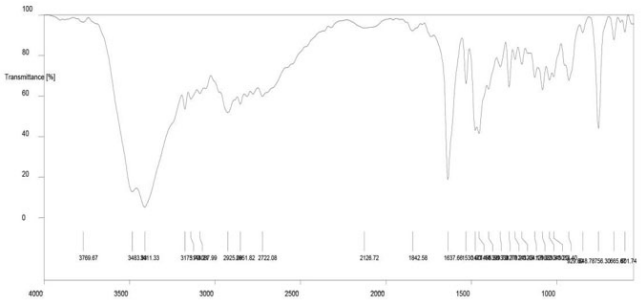

Figure 8: FTIR Spectra of ondansetron optimized formulation.

Physical stability studies

Physical stability study was performed at room temperature for one month. Stability of the prepared vesicles showed that drug leakage after one month. Vesicles also were found to be reasonably stable in terms of aggregation and fusion. In accordance with the results, it can be concluded that at room temperature, there were slightly but insignificantly increase in the particle size. Results suggest that keeping the vesicular product at room temperature minimizes the stability of vesicles, but vesicular product may be stable in refrigerated condition.

Table 7: Stability of prepared vesicles during storage at room temperature for one month.

Formulation code	Vesicle size (nm)	
	Initial	After one month
F2	347	389
F3	952	978
F6	683	716

CONCLUSION

The primary objective of this research was to develop ondansetron-loaded microspheres for nasal delivery to address gastrointestinal side effects by bypassing first-pass metabolism. This strategy aimed to minimize dose-related adverse effects, enhance bioavailability, increase drug residence time, and improve patient compliance. Ondansetron, commonly used to manage nausea and vomiting, has limited effectiveness when administered orally due to its low bioavailability, making oral therapy less satisfactory. The nasal route offers a promising alternative for self-administration, effectively overcoming the limitations of oral delivery. Ondansetron-loaded microspheres were prepared using the ionic-gelation technique through a hand-shaking method. The microspheres were thoroughly characterized for parameters such as entrapment efficiency, *in-vitro* drug release, and compatibility using FTIR spectroscopy. The surface morphology and shape of the microspheres were assessed using SEM. The results indicated that the microspheres had satisfactory flow properties, a spherical

shape, and a smooth surface. The in-vitro drug release studies revealed that an increase in polymer concentration led to a gradual decrease in drug release. Among the formulations, the optimized batch (F3) successfully sustained drug release for up to 12 hours. In conclusion, alginate-based microspheres loaded with ondansetron were effectively prepared via the ionic-gelation method, providing a prolonged and sustained drug release profile. This research highlights the potential of ultra-deformable vesicles, which overcome the rigidity of conventional vesicles, as a promising carrier system capable of transporting even large molecules. The unique properties of this delivery system underscore its potential to address transport-related challenges and establish itself as a valuable advancement in nasal drug delivery technologies.

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CONFLICT OF INTEREST

No Conflict of interest declared.

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AUTHORS' CONTRIBUTION

Bhaskar Kumar Gupta: Analysis, Plagiarism correction, Revision

Eisha Ganju: Concept, Checking, Editing, Grammar correction

Shubham Prajapati: Literature Review, Formatting, Writing manuscript

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