Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Formulation and Evaluation of Anti-Emetic Microspheres for Nasal Drug Delivery System

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ARTICLE DETAILS

Article history:
Received on 13 February 2017
Modified on 23 March 2017
Accepted on 26 March 2017

Keywords:
Ondansetron,
Microspheres,
Optimized Formulation,
Mucoadhesive Drug Delivery

ABSTRACT

The microsphere with natural biodegradable polymer creates immense potential for various pharmaceutical applications like mucoadhesive drug delivery via nasal route. Microspheres formulation helps in sustaining the release may be suitable for long term therapy is controlled alleviation of clinical manifestation. The purpose of this research work was to develop optimized and systematically evaluate performances of microspheres of antiemetic drug ondansetron. Alginate microspheres coated with polymer pectin, starch corn were prepared by ionotropic-gelation technique utilizing various cross linking agents. The microspheres obtained were discrete, spherical and free flowing. Alginate microsphere loaded with Ondansetron by using Ionic-gelation technique for control prolonged release of drug. Ondansetron microspheres were formulated by using drug with sodium alginate, pectin and starch in 9 formulations wereF_1, F_2, F_3, F_4, F_5, F_6, F_7, F_8 and F_9. All the formulation were investigation for various evaluation parameters like particle size (360 - 280nm), bulk density (0.55 - 0.46 gm/ml),flow behavior, entrapment efficiency (72 - 85%), percentage yield (55 -78 %), and In-vitro drug release. All the formulation showed good flow behavior. SEM study revealed that the microspheres were almost spherical in shape with smooth surface. In-vitro drug release study showed that by increasing the polymer concentration, decreased drug concentration among all formulations and the optimized formulation (F_3) was able to sustain the drug release for 12 h. So, it was concluded that alginate microspheres loaded with Ondansetron can be prepared by ionic-gelation technique and used for sustaining the drug release for prolong period of time.

INTRODUCTION

Microsphere

Microspheres are solid spherical particles ranging in size 1 to 1000 mm. and are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. Solid biodegradable involves microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products [1]. Nasal drug delivery may be used for either local or systemic effects. Low molecular weight drugs which are rapidly absorbed through nasal mucosa.

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The main reasons for this are the high permeability, fairly wide absorption area, porous and thin endothelial basement membrane of the nasal epithelium [2].

Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body[3]. Anti-emetics are used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery.

Ondansetronhydrochloride (OND), a highly selective 5-HT3 receptor antagonist, is used as an anti-emetic and under goes extensive first pass metabolism [4, 5]. ONDis (±) 1, 2, 3, 9-tetrahydro-

9-methyl-3-[(2-methyl-1Himidazol-1-yl) methyl]-4H-carbazol-4-one (molecular formula $C_{18}H_{19}N_3O.HCl.2H_2O$, molecular weight: 293.4 g/mol, melting point: 230-232 °C, biological half-life: 5-7 h and log P value: 2.35) well absorbed and undergoes first-pass metabolism. Oral bioavailability of OND is almost 59% and peak plasma about 0.03–0.04μg/ml is obtained after 1.5 to 2 h of administration [6]. As administering drug by buccal route avoids hepatic first-pass metabolism and involves the administration of the drug through the buccal mucosal membrane lining of the oral cavity [7].

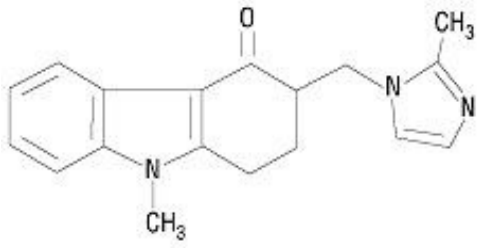

Figure 1: Chemical structure of Ondansetron

Preformulation Study [8-11]

It is one of the important steps for determination of physical and chemical properties of the drug before incorporating it in formulation development. The nature of the drug highly affects the processing parameters like method of preparation, selection of solvents, compatibility and pharmacokinetic response of the formulation.

Identification of pure Odansetron

Identification by FTIR study of pure drug and polymer

FTIR study of pure drug sample was carried out. This identification was done by measuring the wave number of particular functional group to characterize the pure drug. FTIR(Fourier Transform Infra-red Spectroscopy) spectrum of pure Ondansetron (Fig 2) showed the characteristic peak at 1734.27cm-1 which can be assigned to the C=O stretching in the aromatic ring and a peak at 1637.07 27cm-1 which can be assigned to the C=N in the aromatic ring, a peak at 1529.82 27cm-1 which can be assigned to the N-H stretching and a peak at 1279.87 27cm-1 which can be assigned to the stretching of C-C in the aromatic ring.

UV Spectroscopy

As a part of preformulation studies, the UV-VIS λ-max of Ondansetron was determined using UV-VIS spectrophotometer (Shimadzu, Mumbai) and the calibration curve of Ondansetron was designed by measuring absorbance at 200-400 nm in PBS (phosphate buffer saline) 6.8 making dilutions to yield concentration of 1,2,3,4,5 mcg/ml.

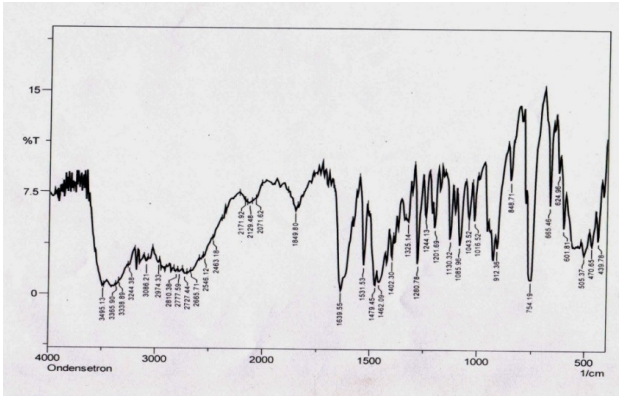

Figure 2: IR spectrum of pure drug Ondansetron

Determination of λmax

10 mg drug was dissolved in 10 ml of pH 6.8 buffer. Then 1ml of the above solution was further diluted to 100 ml with phosphate buffer (pH 6.8) to get a stock solution of 10 μg/ml solution. UV scanning was done for solution from 200–400 nm using 6.8pH phosphate buffer saline as a blank by Shimadzu, UV 1800 spectrophotometer.

The λmax was found to be at 248 nm.

Organoleptic properties

This includes recording of color, odour and taste of the drug using descriptive terminology:

- Color- stability problems, improve appearance by including dye in body or coating.
- Taste- palatability problems, flavor and excipients may be added.
- Odor- degradation products, stable form of drug to be used, flavors and excipients may be used.

Melting point

- Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase. It was determined by using the digital melting point instrument.
- Melting point of Odansetron- 218°C.

Solubility Study

The solubility test is an important parameter before formulation development. The solubility of solute means the maximum quantity of solute that can be dissolved in certain quantity of

solvent or quantity of solution at a specified temperature.

Solubility is usually determined in variety of commonly used solvents. The solubility of material is usually determined by the equilibrium solubility method.

Table1: Identification test of Ondansetron

Test	Ondansetron	
	Specification	**Observation**
Physical appearance	white to off-white powder	white powder
Taste	Tasteless	Tasteless
Odour	Nil	Nil
Melting point	216-219°C	218 °C
Infra-red spectra	Sample IR spectrum should comply with standard IR Spectrum	Sample IR spectrum complies with standard IR spectrum.

Table 2: Solubility of drug in different solvents

S. No.	SOLVENT	SOLUBILITY
1	water	soluble
2	methanol	free soluble
3	chloroform	slightly soluble
4	dichloromethane	sparingly soluble
5	methylene chloride	slightly soluble

Ondansetron is soluble in water and methanol (1:1), and sparingly soluble in dichloromethane, slightly soluble in methylene chloride.

Table 3: Interpretation of IR spectra

Functional group	Pure drug (cm^{-1})	Pure drug + Sodium alginate (cm^{-1})
C-H aromatic ring bending	1456.81	764
-NH stretching	1529.82	3404
C=0 group	1734.27	1640
C=H group	1637.07	1591
C=C group	1655.98	1082

Calibration curve of Odansetron

Calibration curve in pH- 6.8

The calibration curve of ondansetron was prepared in Phosphate buffer saline.100 mg of drug was dissolved in 100 ml of phosphate buffer pH-6.8. The second stock solution was prepared by withdrawn 2ml of solution from first stock solution and volume was made up to 100ml with phosphate buffer.

Drug excipient interaction studies

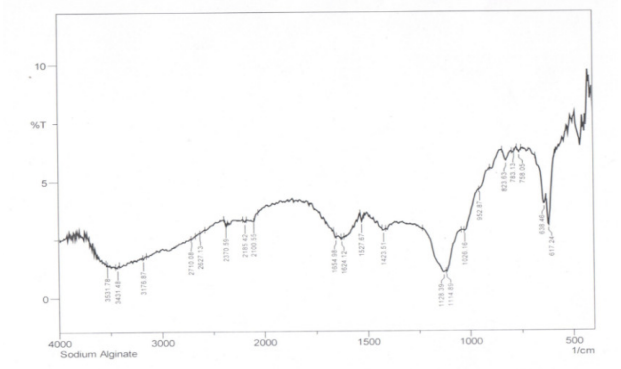

Figure 2a: IR spectrum of physical mixture (Ondansetron + sodium alginate)

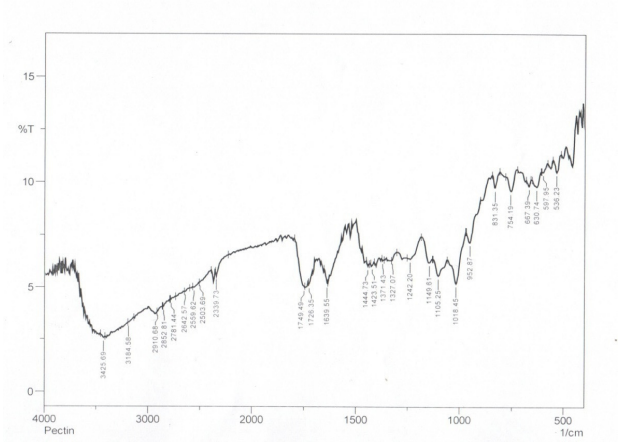

Figure 2b: IR spectrum of polymer pectin + OND

Table 4: Absorbance of ondansetron using pH 6.8 PBS

S. No.	Concentration (µg/ml)	Absorbance (nm)
1	2	0.085
2	4	0.149
3	6	0.231
4	8	0.285
5	10	0.367
6	12	0.424
7	14	0.496
8	16	0.577
9	18	0.626
10	20	0.717

Then the serial dilutions were done by withdrawn 1-10 ml solution from second stock solution and prepared concentration range from 2-20µg/ml .Then absorbance was noted using UV-spectrophotometer at 248 nm and plotted graph between absorbance and concentration.

Formulation Design

Table 5: Composition of ondansetron microspheres

Formulation code	Drug : polymer	drug (mg)	alginate	pectin	starch	% electrolyte	vesicle shape
F1	1: 1	50	50	-	-	5	X
F2	1 : 2	50	100	-	-	5	√
F3	1 : 3	50	150	-	-	5	√
F4	1:1:1	50	50	50	-	5	√
F5	1:1:2	50	50	100	-	5	√
F6	1:1:3	50	50	150	-	5	√
F7	1:1:1	50	50	-	50	5	X
F8	1:1:2	50	50	-	100	5	X
F9	1:1:3	50	50	-	150	5	√

Table 9: *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	15.16	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

Formulation Design

Method of microspheres preparation

Alginate microsphere coated with polymer pectin, starch corn was prepared by ionotropic-gelation technique utilizing various cross linking agent by using Ionotropic gelation method.

Polyelectrolyte solution
[Sodium Alginate (-)/ Gellan gum (-)/CMC (-)/ Pectin (-)/ Chitosan (+) + Drug]
↓
Added drop wise under magnetic stirring by needle
↓
Counter ion solution
[Calcium chloride solution (+)/Sodium tripolyphosphate (-)]
↓
Microspheres

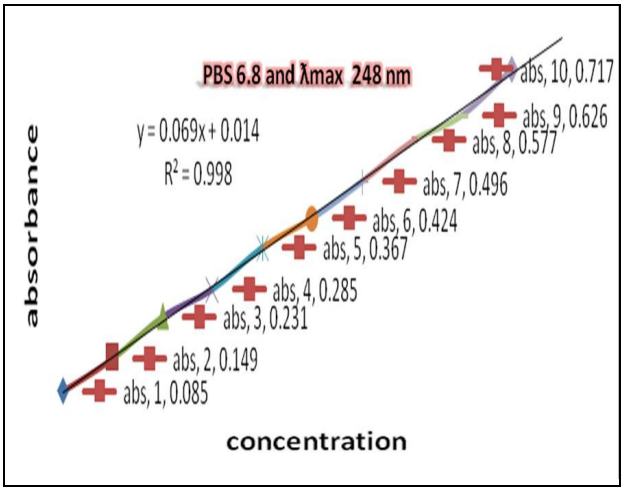

Figure 3: Calibration curve of Ondansetron using pH 6.8 PBS

Evaluation of Microspheres

Assay of ondansetron hydrochloride

To determine the total drug content of the microspheres 100mg of microspheres was ground to a fine powder and dissolved in 5ml (water and methanol) and diluted with phosphate buffer pH 6.8 to 100ml. the drug content was determined spectrophotometrically at 248 nm. Three determination of the microspheres content from the same batch for each ratio and method was performed.

Morphology Imaging

Microspheres vesicles can be visualized by microscopy, scanning electron microscopy (SEM). The stability of vesicle can be determined by assessing the size and structure of vesicles over time.

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# meshes 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.

Micromeritics Properties

Angle of repose

Angle of repose of different formulations was measured according to the fixed funnel standing cone method and was given by:

The angle of repose is designated by θ and given by equation

$$\tan \theta = h / r$$

Where, h = height of pile

r = radius of the base of the pile

Bulk Density and Tapped Density

The density was measured by tapping method. The bulk density, and tapped density were calculated using the following formula

$$\text{Bulk density, } \rho b = \frac{\text{Weight of the powder}}{\text{Bulk volume of the powder}}$$

$$\text{Tapped density, } \rho t = \frac{\text{Weight of the powder}}{\text{Volume of liquid it displaces the powder}}$$

Compressibility index (Carr's index): Carr's index calculated as per given formula

$$\text{C. I (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner Ratio=Tapped density / Bulk Density

Encapsulation efficiency (EE)

Drug entrapment efficiency of the formed microspheres was evaluated by taking by using cooling ultracentrifuge (Remi) at 4000 rpm in 3 subsequent rounds. The clear supernatant separated the un-entrapped drug and the absorbance taken at λmax at 248 nm using UV spectrophotometer (Shimadzu UV 1800).

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

Fourier transforms infrared spectroscopy

% entrapment = Amount in supernatant-amount in sediment/amount in supernatant ×100

(FTIR)

The FTIR spectra acquired were taken from dried samples. FTIR (Thermo Nicolet 670) spectrometer was used for the analysis in the frequency range between 4000cm^{-1} and 400 cm^{-1}.

***In vitro* Drug Release Studies**

In vitro dissolution studies were performed using (USP type II dissolution apparatus). The rotating basket method specified in USPXXI at 50 rpm. The microspheres were weighed and tied in the muslin bag and placed in the basket. The dissolution medium (900ml) consisted of 0.1M hydrochloric acid for the first 2 h and then changed to phosphate buffer pH 6.8 from the 3 h onwards.

The temperature was maintained at 37°C. An aliquot of (5ml) sample was withdrawn at specified time interval and replaced with an equivalent volume of dissolution fluid. Drug content was determined by UV-spectrophotometer (Schimazdu UV 1700 E 23) at

248 nm. The release studies were conducted in triplicate.

Kinetic Treatment of Release Data

The obtained dissolution data were fitted to zero order [12], first order [13], Higuchi [14], Korsmeyer-Peppas models to determine the mechanism of CAP release from the prepared microspheres.

Stability Studies

The success of an effective formulation was evaluated only through the stability studies. The purpose of stability testing was to obtain a stable product which assures its safety and efficacy up to the end of shelf life. In this study, stability study was done for at conditions like room temperature. (RT), 30ºC & 60 % RH, 40ºC & 75% RH. The samples were assayed for drug content at regular intervals for two weeks.

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.

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.

RESULT AND DISCUSSION

The objective of present research work was to formulate the microspheres system. Microspheres are vesicular system has ultra-deformable property, can easily penetrate and regain size inside the nasal. So the aim was to deliver the drug at the site of action more efficiently and enhance pharmacological action. Also overcome the problem related with the oral administration of drug. Different formulation of microspheres dispersion drug and polymer ratio (1:1, 1: 2, 1:3) were prepared and evaluated. The present study was taken to formulate and evaluate sustained release microspheres of ondansetron by Ionic cross linking technique.

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 6: 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

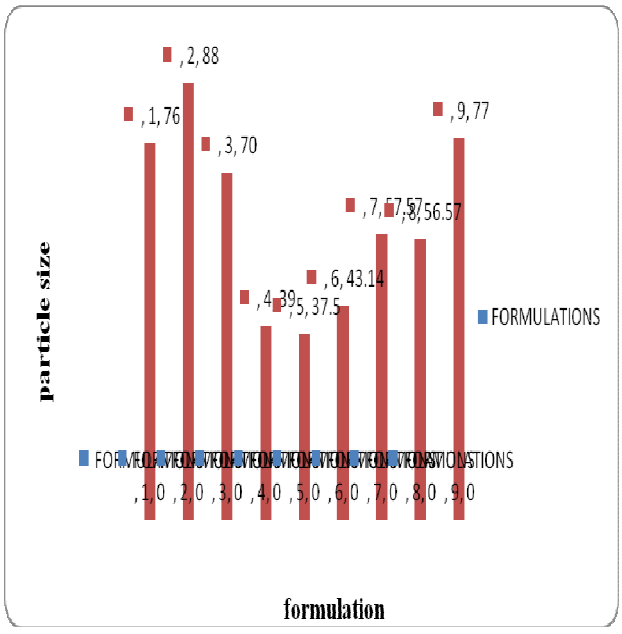

Figure 4: Graph of mean particle size of microsphere batches

Micromeritic properties of the microspheres

Angle of repose of microspheres was in the range of 28º12′. It shown excellent flow ability as represented in term of angle of repose (<40°).

Table 7: The angle repose values of microspheres

S.No	Formulation code	Angle of repose	Comments
1	**F1**	20°.56	Good flow
2	**F2**	28°.44'	Good flow
3	**F3**	28°.61'	Good flow
4	**F4**	24°.57'	Good flow
5	**F5**	26°.41'	Good flow
6	**F6**	26°.58'	Good flow
7	**F7**	28°.44'	Good flow
8	**F8**	28°.61'	Good flow
9	**F9**	24°.57'	Good flow

Bulk density values ranged from 0.312 to 0.365 gm/cm^{3}tapped density was determined by the tapping method. The tapped density values of the microspheres ranged from 0.357to0.400 gm/cm^{3}Carr's index values of microspheres was found to be 12.60 %.

Encapsulation efficiency (EE) and % drug content, % 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 Eq (1) (2) (3).

% Product Yield = total wt of the microspheres/total wt of the drug polymer x 100 ..... (1)

% Drug content = calculated amt of drug / total wt of microparticles x 100 ..... (2)

Encapsulation efficiency = Actual drug content/Theoretical drug content x 100 ..... (3)

Table 8: % drug content, % product yield and % entrapment efficiency

Formulation code	% drug content	% product yield	% drug entrapped
F1	50	76	40.92
F2	47	78	50
F3	53.33	88	56
F4	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

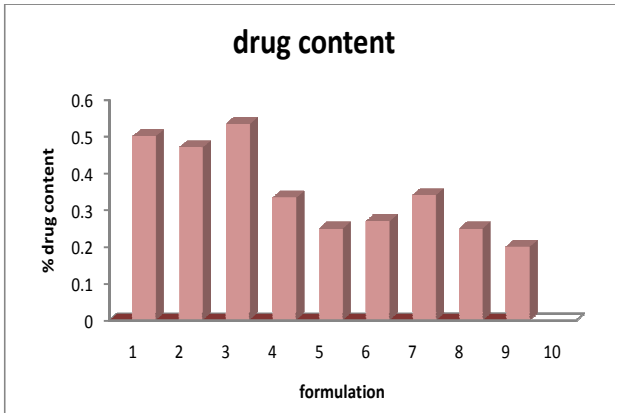

Figure 5: Graph of % drug content

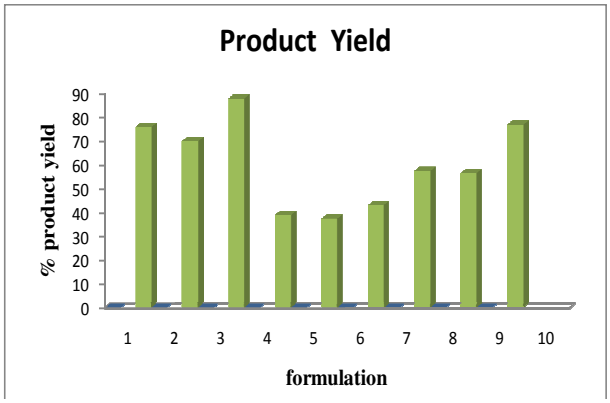

Figure 6: Graph of % product yield (nm)

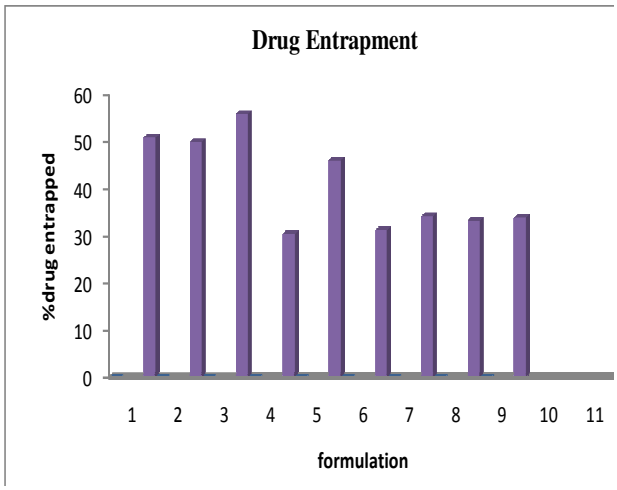

Figure 7: Graph of % entrapment efficiency

FTIR study

In this spectrum the peak at wavelength 3404 cm^{-1} indicated the presence of –NH Stretching, 1083 cm^{-1} peak indicated the presence of S=O group, 1646 cm^{-1} peak indicated the presence of C=0 group, 1588 cm^{-1} peak indicated the presence of NH group in secondary amide and 788 cm^{-1} peak indicated the presence of C-H bending with aromatic structure.

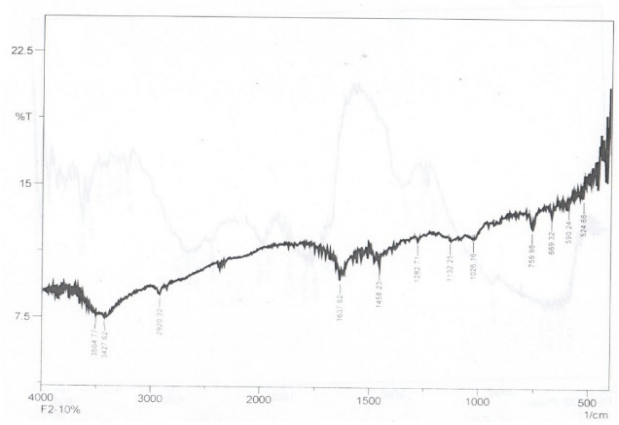

Figure 8a: IR spectrum of F_2

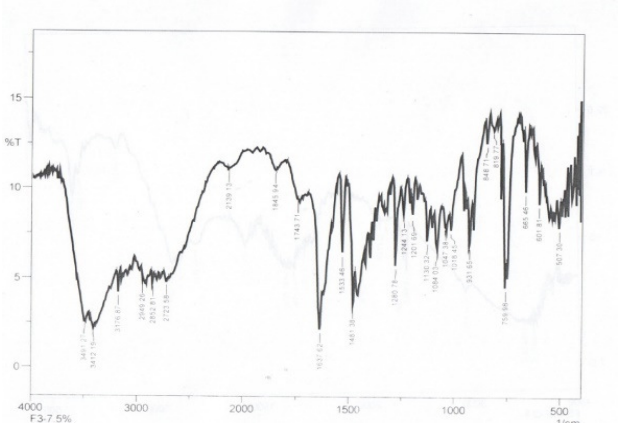

Figure 8b: IR spectrum of F_3

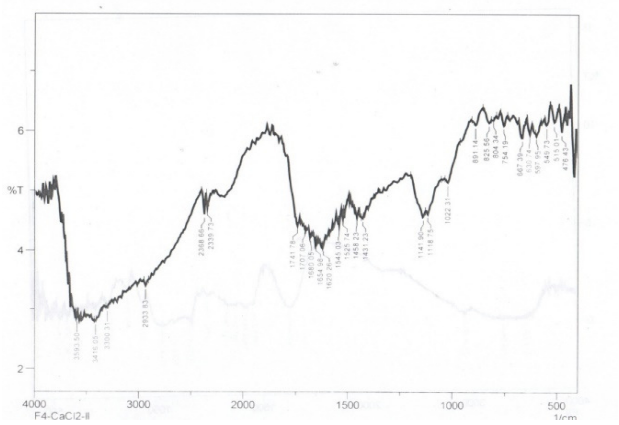

Figure 8c: IR spectrum of F_4

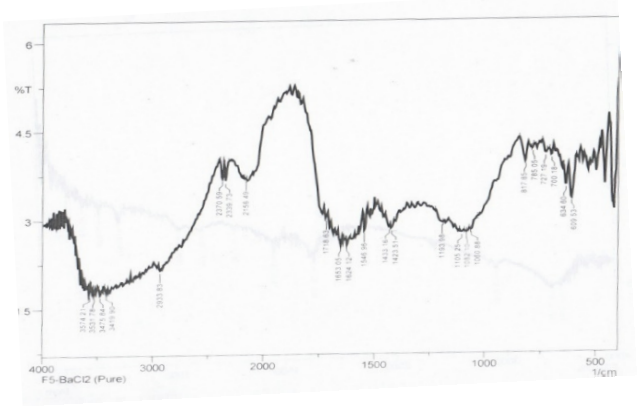

Figure 8d: IR spectrum of F_5

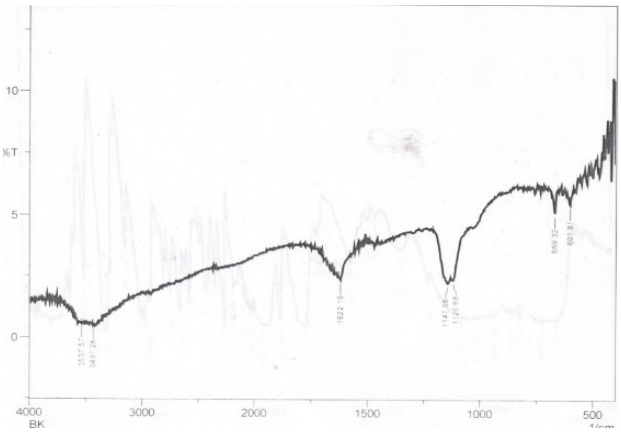

Figure 8f: IR spectrum of F_6

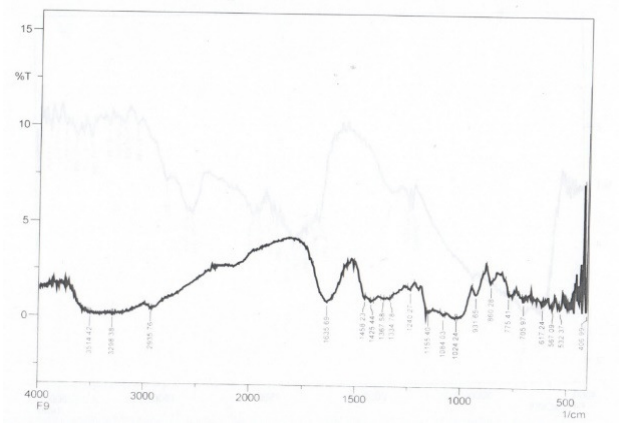

Figure 8g: IR spectrum of F_9

The FT-IR spectra of API and polymer mixture were compared with the FT-IR of pure drug, which indicates no interaction between drug and polymer, so drug was compatible with the polymer.

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 h. The % CDR of different formulation was found to be in range. The result indicates that F3 is the best 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 10: Stability of prepared vesicles during storage at room temperature for one month

Formulation code	vesicle size (nm)	
	Initial	Afterone month
F2	347	389
F3	952	978
F6	683	716

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. The SEM of the formulation is given in following figure.

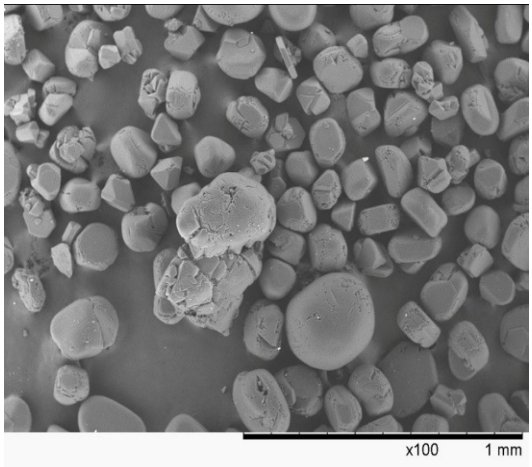

Figure 9: SEM image of microspheres

CONCLUSION

The principal object of present research work is to make ondansetron loaded microshpheres for nasal delivery which remove the gastrointestinal disorders by overcome the first pass metabolism and also help in reducing dose related side effect, increasing bioavailability, increasing residence time of the drug and better patient compliance.

Ondansetron is used for the nausea and vomiting management. It is generally given by oral route. However, it has poor bioavailability by oral route which makes oral treatment unsatisfactory. Nasal route may be a viable alternative for self-application where the limitations of oral route could be overcome.

Conventional dosage forms may be unsatisfactory due to their permeability through nasal route. It could be employed to increase the permeability of drug to enhance the bioavailability.

The Ondansetron loaded microspheres was prepared by ionic-gelation technique, which was hand shaking method. The prepared microspheres were characterized for their entrapment efficiency percentage, in-vitro drug release and compatibility study by FTIR spectroscopy and all the formulation showed good flow behavior.

SEM Study revealed that the spheres were almost spherical in shape with smooth surface. In–vitro drug release study showed that by increasing the polymer concentration the drug release of all the formulation were gradually decreased and the optimized formulation (f_3) was able to sustain the drug release for 12 h.

So, It was Concluded that Alginate Microspheres loaded with Ondansetron can be prepared by Ionic-gelation technique and used for sustaining the drug release for prolong period of time.

The present research work concluded that ultra-deformable vesicles can provide the novel solution for the transport related problems. They are free from the rigid nature of conventional vesicles and can transport even the large molecules. They work on number of mechanisms working together to provide an excellent carrier system for the drug transport. All above discussed properties of this technology strongly advocate its good future in nasal drug delivery.

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