Formulation And Evaluation Of Mucoadhesive Microspheres Of Anti-Emetic Agent For Nasal Delivery.

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Abstract:
The objective of research work was to develop and optimize mucoadhesive microspheres of anti-emetic agent (Metoclopramide HCL) for nasal delivery with the aim to enhance the residence time and improve therapeutic efficacy and at the same time increase the local absorption of drug and reducing systemic side effects and also to develop unique delivery system for patients suffering from nausea & vomiting. Mucoadhesive microspheres (Chitosan based) of Metoclopramide HCL were prepared by emulsification-crosslinking method in different ratios. Glutaraldehyde was used as crosslinking agent. The mean particle size was significantly increased when high concentration of chitosan was used. Aqueous to oil phase ratio, stirring rate and dioctyl sodium sulfosuccinate (DOSS) concentration also influenced the particle size distribution of the microspheres. Microspheres were evaluated with respect to the production yield, particle size, entrapment efficiency, swelling index, FTIR, in vitro mucoadhesion, cumulative percentage drug release, and stability studies. Formulation F3 was found to be optimized. The optimized formulation F3 was mucoadhesive in nature which adhere on the mucus membrane and increase the residence time within the nasal cavity. Utilizing a high concentration of chitosan resulted in a noticeably larger mean particle size. Particle size distribution of the microspheres was also affected by the concentration of dioctyl sodium sulfosuccinate (DOSS), stirring rate, and aqueous to oil phase ratio. In vitro mucoadhesion, cumulative percentage drug release, swelling index, FT-IR, manufacturing yield, particle size, entrapment efficiency, and stability studies were all taken into consideration when evaluating microspheres. There was an optimized discovered formulation F3. Since it adhered to mucus and lengthened its stay in the nasal cavity, the improved formulation F3 was mucoadhesive in nature.

Keywords: Metoclopramide HCL, Mucoadhesive Microspheres, Nasal Delivery, Antiemetic agent, Chitosan, Emulsion Cross-linking Technique.

INTRODUCTION:

Nasal administration has been used historically for both local and systemic conditions. Because of its quick absorption and potency, it is a desirable alternative to needle-based systemic drug delivery for immunizations. Furthermore, it has become well-known as a stable way to distribute drugs widely, which is particularly helpful for injectable drugs that are inefficient when taken orally because of digestive system breakdown [1-2].

Nasal Delivery and Overcoming Challenges: By avoiding liver metabolism, nasal administration helps to mitigate problems like sluggish absorption, low bioavailability, and drug degradation. Not for administering medication or vaccines, though; rather, it's important to remember that the nose tube serves mainly to protect the lungs from dangerous substances [3].

Perks of Drug Absorption through the Nasal Cavity: A well-vascularized epithelium, effective absorption, a porous endothelium, a large surface area, improved blood flow, and neutral pH mucus are benefits of medications absorbed through the nasal cavity. These advantages are obtained without undergoing early metabolism in the stomach or pancreas[2, 4 &5]

Nasal Drug Delivery Challenge: Mucociliary clearance (MCC), which indicates that medications have a brief window of time to be absorbed in the nasal cavity before being flushed out, is one disadvantage of nasal drug delivery. [2 & 6] Consequently, mucoadhesive microspheres have been created by scientists to lessen the effects of mucociliary clearance. By extending the medication's adhesion to the nasal membrane, these microspheres enhance absorption. There is one more technique that is called spray drying. Compared to other methods, this one produces nasal particles from mucoadhesive materials more quickly and affordably [7].

Metoclopramide hydrochloride is one example of a dopamine receptor antagonist that can help with nausea and vomiting brought on by radiation therapy, surgery, cancer treatment, and pregnancy. Nasal distribution of the drug is one possible substitute delivery technique for people who have trouble swallowing, especially those who are nauseous [8]. One strategy that has been investigated to improve drug absorption through the nasal route is the use of bio adhesive polymers. Bio adhesive polymers increase the absorption of nasal medications by extending the duration of the drug in the nasal cavity and promoting the formation of tight connections between epithelial cells. Mucoadhesive medication

administration technique, particularly for usage in the nose and other mucosal areas, are made of bio adhesive polymers known as carbomers [9-10]. Using absorption enhancers, such as cyclodextrins, fusidate derivatives, fatty acids, phospholipids, surfactants, and bile salts, is another technique [11-12].

Chitosan microspheres are becoming more and more well-liked as efficient nasal medication delivery devices. Biocompatible, non-toxic, and biodegradable, chitosan is a polymer that adheres well to biological surfaces. Because of its amino group, it has a positive charge and is created by deacetylating chitin. With the nasal epithelium's negatively charged mucus layer, chitosan's positive charge enables it to create robust connections [13].

Prolonging the duration of drug-nasal membrane interaction is the idea, which will provide the medication more time to enter the bloodstream before the mucocilliary clearance process removes it. Furthermore, through temporary opening of tight junctions, chitosan has been demonstrated to facilitate the passage of polar medicines through the gaps between epithelial cells. In this study, emulsification and crosslinking using glutaraldehyde as the crosslinking agents were used to generate chitosan microspheres intended to administer metoclopramide HCL via the nasal route [14-16].

A Study on Developing Mucoadhesive Microspheres for Metoclopramide HCL: With the goal of minimizing systemic adverse effects, enhancing local absorption, and extending the drug's presence in the nasal cavity, this study produced and assessed mucoadhesive microspheres containing metoclopramide HCL. Furthermore, the emulsion cross-linking method with chitosan was used to produce a tailored delivery strategy for allergy and rhinitis sufferers.

SUPPLIES & METHODS:

Substances, Equipment, and Chemicals:

Pantoli-based Vaikunth Chemicals Pvt Ltd sent me a gift of metoclopramide HCL. The supplier of chitosan was Sisco Research Laboratories Pvt Ltd. The remaining chemicals were analytical grade and used exactly as it is, no further purification was needed. The Shimadzu Pharma Spec 1700 double-beam UV spectrophotometer, located in Kyoto, Japan, was used for the spectrophotometric studies.

The Process of Creating Mucoadhesive Microspheres: [17-18]

Synthesis of Chitosan Microspheres: Chitosan microspheres were made using a simple water-in-oil (w/o) emulsification-crosslinking process, with a 1 to 1 ratio of liquid paraffin, heavy to light serving as the external phase [19]. In short, until a uniform solution was achieved, chitosan was constantly agitated to dissolve it in a 2% aqueous acetic acid solution (Table 1). By whisking the medication into the chitosan solution, a certain amount was evenly distributed. After isolating the solidified microspheres using vacuum filtration, they were repeatedly washed with hexane to remove any remaining oil. Finally, distilled water was used to wash the microspheres in order to remove any remaining glutaraldehyde (GLA). After a full day of drying, the microspheres were placed in vacuum desiccators to await their next use.

TABLE 1: DIFFERENT MICROSPHERES VARIABLES:

Formulation	PROCESS VARIABLES			CONSTANT PARAMETERS		
	Drug polymer Ratio	DOSS as Stabilizing Agent (ml)	GLA as Cross Linking Agent (ml)	Phase Ratio of Aqueous to Oil	Agitating Rate (rpm)	Cross Linking Period (hours)
F1	1:1	2	2	10:100	1500 – 1600	2
F2	1:2	2	2			
F3	1:3	2	2			
F4	1:1	3	4			
F5	1:2	3	4			
F6	1:3	3	4			

Mean ± Std. Deviation whereas n=3

Characteristion of Metoclopramide HCL Loaded Microspheres:

Particle Size:

A modified version of Magnus Pro 3.0 and Olympus Master were installed on an optical microscope (OLYMPUS CH 20i) in order to quantify the particle size of the microspheres. Images of a sample number of microspheres suspended in glycerine were taken using a camera. By using an optical microscope to measure more than 100 microspheres at random, the mean particle size was calculated.

Production Yield:

The weight of the finished product after drying was compared to the original combined weight of the medication and polymer employed in microsphere manufacture in order to calculate the production yield of microspheres from various formulations.

Determination of Entarpment Efficacy:
An ultrasonic stirrer was used to crush and dissolve an exact measurement equal to 5 mg of metoclopramide HCL microspheres in 100 ml of ethanol, which was then left overnight. Whatmann filter paper No. 41 was used to filter the final mixture. The appropriate dilutions (5, 10, 15, 20, & 25 mcg/ml) were made. By means of a UV spectrophotometer at 273 nm, the drug content of the samples was examined. The following equations (1) were used to calculate entrapment efficiency.

$$\textbf{Entrapment efficiency} = \frac{\textbf{Actual amount of drug in microspheres}}{\textbf{Theoretical amount of drug in microspheres}}$$

Eqn……1

Particle's Microscopic Evaluation Using SEM Technique:
Using scanning electron microscopy, the surface properties of the updated formulation (F3) were examined (JSM 6100, Jeol Ltd, Japan). Images were captured with a 100X magnification and an acceleration voltage of 10 kv.

Fourier Transform Infrared Spectroscopy (FTIR) Analysis for Investigating Potential Interactions between Metoclopramide HCL, Chitosan & Cross-Linking Agent:
An FTIR spectrophotometer (model – Spectrum Two, PerkinElmer, US) was used to analyse metoclopramide, chitosan, and the improved formulation (f3). The test sample was put into the device after being diluted with KBr until it reached a final dilution of 1:10. Measurements were made in transmittance mode against the pure KBr background spectrum, in the 400–4000 cm-1. The resolution of the instrument was set at 4 cm^{-1}, and every measurement was taken 50 times [20-21].

Differential Scanning Colorimetric Technique for Thermal Characteristics Assessment of Mucoadhesive Microspheres & Pure Medicament:
With the aid of a differential scanning calorimeter (DSC), the thermal properties of the pure medicine and the mucoadhesive microspheres loaded with the drug were evaluated. An empty pan was used as the reference pan, and samples weighing 3–5 mg were weighed using a Mettler M3 Microbalance and put in crimped sealed aluminium pans. Under static air conditions, the samples were heated at a rate of 10°C/min over a temperature range of 30 to 250°C. Hold at 30°C and 250°C for one minute, respectively [22-23].

UV Spectrophotometric Studies of Pure Metoclopramide HCL:
Using distilled water, ethanol, and phosphate buffer with a pH of 6.8, standard curves were created for values ranging from 5 to 25mcg/ml. Within a particular range of 273 nm, the absorbance was measured and recorded [24].

The Capacity of Mucoadhesive Microspheres to Swell:
The capacity of the microspheres to expand was assessed by allowing them to reach their stable state in a 6.8 pH phosphate buffer solution [25-26].

$$\text{Swelling index} = \frac{(D2 - D1)}{D1} \text{ X } 100$$

Eqn…..2

Where,
D_1 = Microspheres' Final Diameter after swelling.
D_2 = Microspheres' Initial Diameter before swelling.

Microscopic Testing by In-vitro Wash-off Method:
The wash-off method, an in vitro adhesion testing methodology, was used to evaluate the mucoadhesive characteristics of the microspheres. A freshly removed nasal mucosal membrane measuring 3×2 cm from a goat was used in this technique, and it was put using thread on the paddle of a USP dissolving test device. After that, each wet, washed tissue specimen received an equal distribution of microspheres. Following that, the assembly was moved right away to the arm of the USP dissolving test device for support washing. Use the USP dissolving test device in a pH 6.8 phosphate buffer solutions at 37°C ± 0.5°C, with the paddle moving at 25 rpm. After 30 and 60 minutes, as well as at hourly intervals for up to six hours after that, samples should be taken.

Drug Release Studies and Research Procedures in Vivo:
The drug release investigation was conducted using the USP XXIV basket apparatus, rotating the basket at 50 rpm and 37°C ± 0.5°C. 900 mL of phosphate buffer with a pH of 6.8 was utilized as the dissolve media in accordance with the USP XXVI dissolving standards. Microspheres containing metoclopramide HCL (5 mg) were utilized in the experiment. The sample solution was extracted in a quantity of 5ml at predetermined intervals, passed through a Whatmann filter paper, diluted appropriately, and then analyzed using spectrophotometry [22,23,27&28]. A new batch of

dissolving medium was quickly added in an equivalent volume after the test sample was removed. Based on absorbance measurements at 273 nm, the percentage of medication dissolved at different time periods was computed.

Examination of Drug Release Mechanism and Kinetics:
To investigate the drug release kinetics and mechanism, the cumulative release data were fitted to a variety of models, including zero order (Q vs t), first order (Log [Q0 Q] versus t), Higuchi's square root of time (Q versus t 1/2), and Korsemeyer Peppas double log plot (log Q versus log t). The cumulative percentage of drug remaining at time t is represented by (Q0-Q), while the cumulative proportion of drug discharged at time t is indicated by Q. In summary, the findings from the in vitro release studies were evaluated using four different kinetics models.

- Log cumulative percentage of drug retention V/S Time (first order rate kinetics)
- Cumulative percentage of drug release V/S Time (zero order rate kinetics)
- Higuchi's classical diffusion equation cumulative percentage of drug release V/S √T
- Record total percentage of drug release V/S Log Time (Korsmeyer Peppas equation)

Process:
The data were fitted to Zero order, first order, Higuchi, and Peppas models after kinetic analysis was performed. Values for the Peppas model's diffusion exponent (n) and regression coefficient (R) were included in the evaluation. Based on the dependability of fit, which is denoted by 'R' value that is closer to one, the best model was chosen. When drug release is concentration-dependent, the first-order model makes sense, but the zero-order model is not affected by drug concentration. The Peppas model is used when the release mechanism is unknown, and the matrix model is appropriate when a matrix polymer is used. Fickian' diffusion occurs when $n<0.5$, whereas non-Fickian' diffusion occurs when $n>0.5$[29-31].

Investigations into Stability:
Stability assessments were carried out using the refined formula F3. For each of the three formulation sample sets, three different temperatures were maintained: 4±1˚C, 25±2˚C with 60±5% RH, and 37±2˚C with 65±5% RH. The drug release of the selected formulation was assessed one to six months later using the previously described in vitro drug release technique. The percentage entrapment efficiency for the identical formulation was also computed.

RESULTS & DISCUSSIONS: [32-55]
Preparation of Mucoadhesive Microsphere:
This work showed that the emulsification-cross linking approach (described below) was a suitable and simple way for loading metoclopramide into chitosan microspheres. A polar organic solvent was used as the "aqueous phase" to produce water-in-oil (w/o) emulsion.

Characterisation of metoclopramide loaded Mucoadhesive microspheres:
Size of Particle:
Table 2 displays the average particle sizes of the formulas. The microspheres had mean particle sizes ranging from 10 to 22 µm. Mucoadhesive polymer concentration gradually affects the particle size, and stirring rate is the main factor influencing it. Regardless of polymer concentration levels, it is clear that increased stirring speeds lead to smaller particle sizes. On the other hand, there is an inverse link between particle size and mucoadhesive polymer concentration.
Production Yield:
The emulsion cross-linking approach produced microspheres with production yields ranging from 80.12% to 89.46% for metoclopramide HCL, as shown in Table 2. The study showed that the microspheres with a 1:3 (drug to polymer) ratio produced a higher production yield than the formulations with ratios of F1 (1:1) & F2 (1:2), in which the amounts of DOSS and Glutaraldehyde are the same at 2 ml each, as well as the formulations with ratios of F4 (1:1), F5 (1:2) & F6 (1:3), in which the amounts of DOSS and Glutaraldehyde are 3 ml respectively. The likely cause of this event might be attributed to the high viscosity of the chitosan solution, which ultimately led to decreased manufacturing yields of the microspheres by causing the drug-polymer solution to be wasted. A further possible contributing element could be the polymer's adherence and agglomeration to the beaker walls and stirrer blades during the microsphere-forming process.

Entrapment Efficacy:
The entrapment consistently exceeded 75%, high encapsulation values. It was noted that increased drug to polymer ratios were associated with higher entrapment efficiencies (79.48±0.46% to 88.47±0.87%).

TABLE 2: CHARACTERISATION OF METOCLOPRAMIDE HCL LOADED MICROSPHERES:

Sr. No.	Formulation code	Particle Size (µm)	Production yield (%)	Encapsulation Efficiency (%)	Mucoadhesion (%)	Swelling index (%)
1.	F1	22±2.87	80.12	79.48±0.46	64.87±0.287	0.71±0.005
2.	F2	18.43±3.56	84.46	80.56±0.32	75.87±0.390	0.86±0.021
3.	F3	10±1.20	89.46	88.47±0.87	87.52±0.570	1.16±0.081
4.	F4	21±2.32	83.62	82.45±0.51	66.71±0.329	0.76±0.049
5.	F5	19±2.97	86.98	85.37±0.67	79.45±0.497	0.91±0.074
6.	F6	10±1.73	87.23	84.62±0.77	86.25±0.540	1.09±0.036

Mean ± Std. Deviation whereas n=3

Scanning Electon Microscopy i.e SEM:

SEM was used to examine the optimized formulation, F3. Figure 1 shows the F3 SEM images. The optimized formulation, F3, produced spherical shaped microspheres with a smooth surface, according to SEM examination.

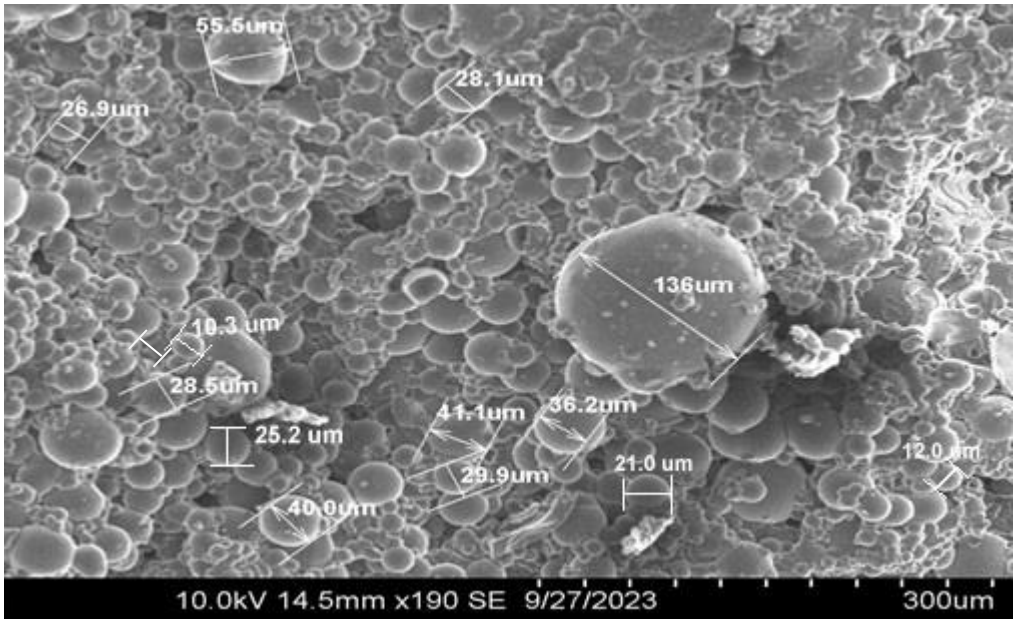

Fig. 1: Formulation F3's SEM

Infrared Fourier Transform Spectroscopy (FTIR):

With FTIR spectroscopy, potential interactions between the crosslinking agent, chitosan, and metoclopramide HCL were investigated. Chitosan and metoclopramide HCL both showed distinctive peaks in the 400–4000 cm–1 spectral range. The drug is preserved within the formulation and there is no drug-polymer interaction, the drug-loaded microspheres' spectrum indicated. Variations in peak intensity suggest that the drug-polymer interaction is not significant. The results of the FTIR for the F3 Formulation, Metoclopramide HCl and Chitosan are displayed below as Figures 2, 3, and 4 respectively.

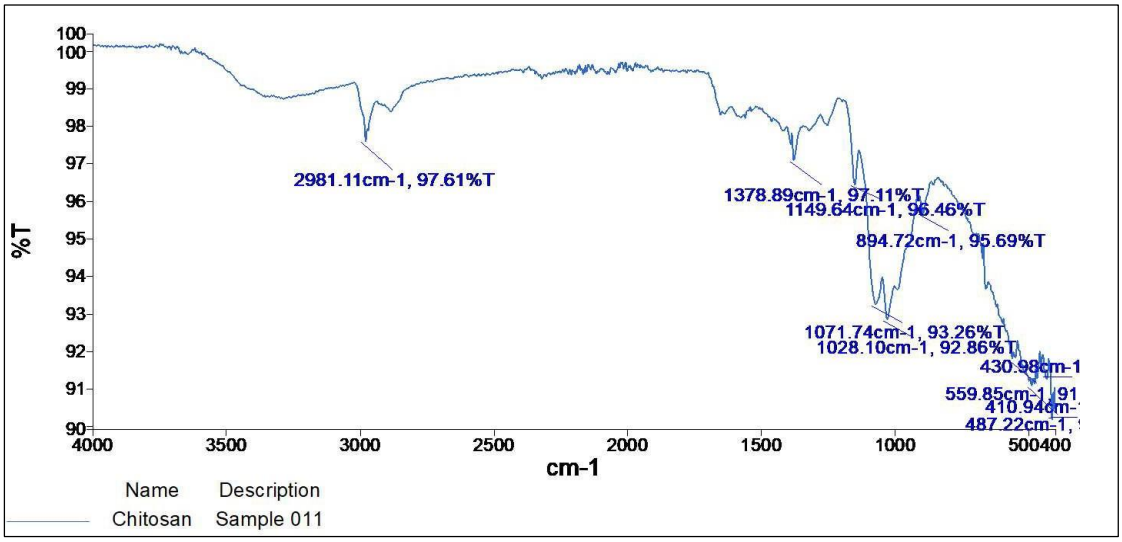

Fig. 2: FTIR of Chitosan

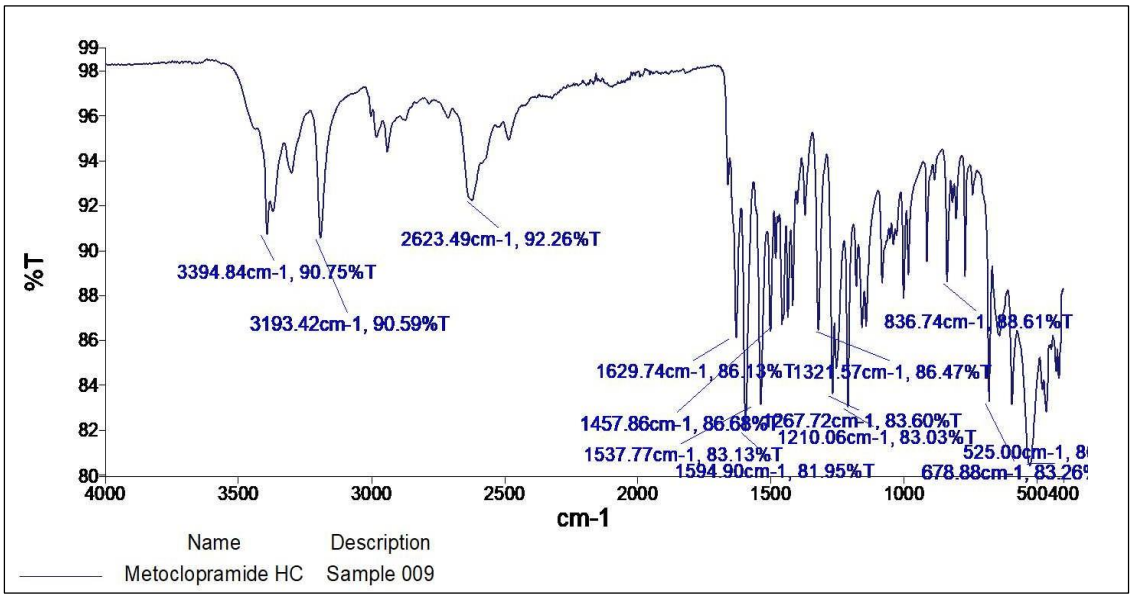

Fig. 3: Pure Drug Metoclopramide HCL's FTIR

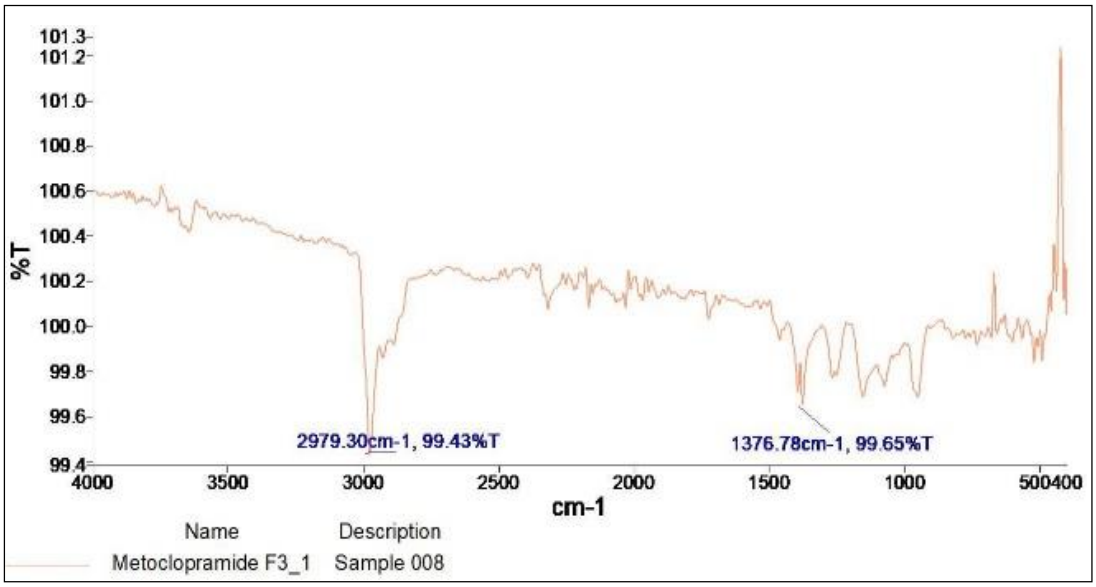

Fig. 4: F3 Formulation' FTIR

Differential Scanning Colourimetry:

As shown in figures 5, where pure metoclopramide hydrochloride, plain blank, F4 & F6 formulation batches & in figure 6, individual F3 Preparations were subjected to differential scanning calorimetry (DSC) investigations. It was observed that the distinctive endothermic peak, which signifies the melting of the drug and polymer, stayed mostly unaltered in both instances. The fact that there is no interaction between the medication and polymers is supported by the DSC thermo grams of the F3, F4 and F6 formulations displayed in Figures 5 and 6. Furthermore, there was no change in behaviour from endothermic to exothermic, and there was a decline in peak intensity without the formation of additional peaks. As a result, it was determined that the medicine and excipients did not interact.

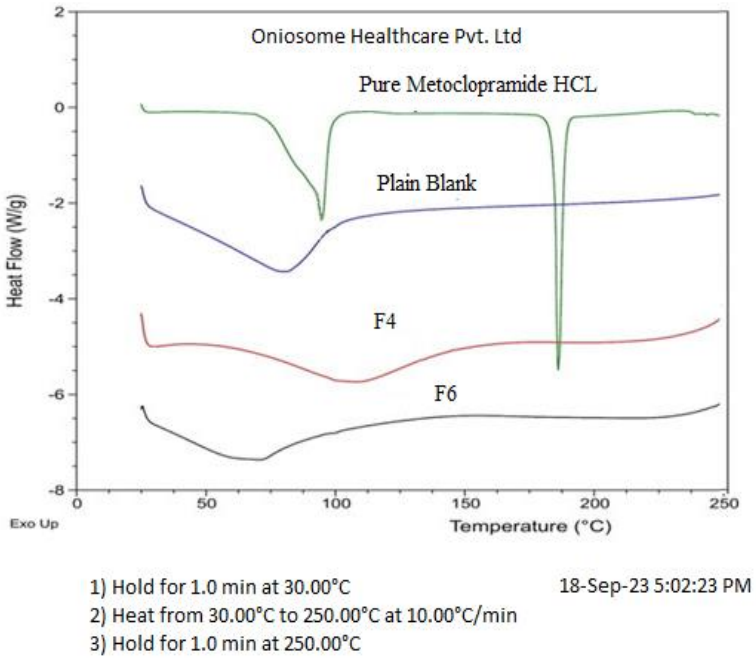

Fig. 5: DSC of Pure Drug & formulations (F4 & F6)

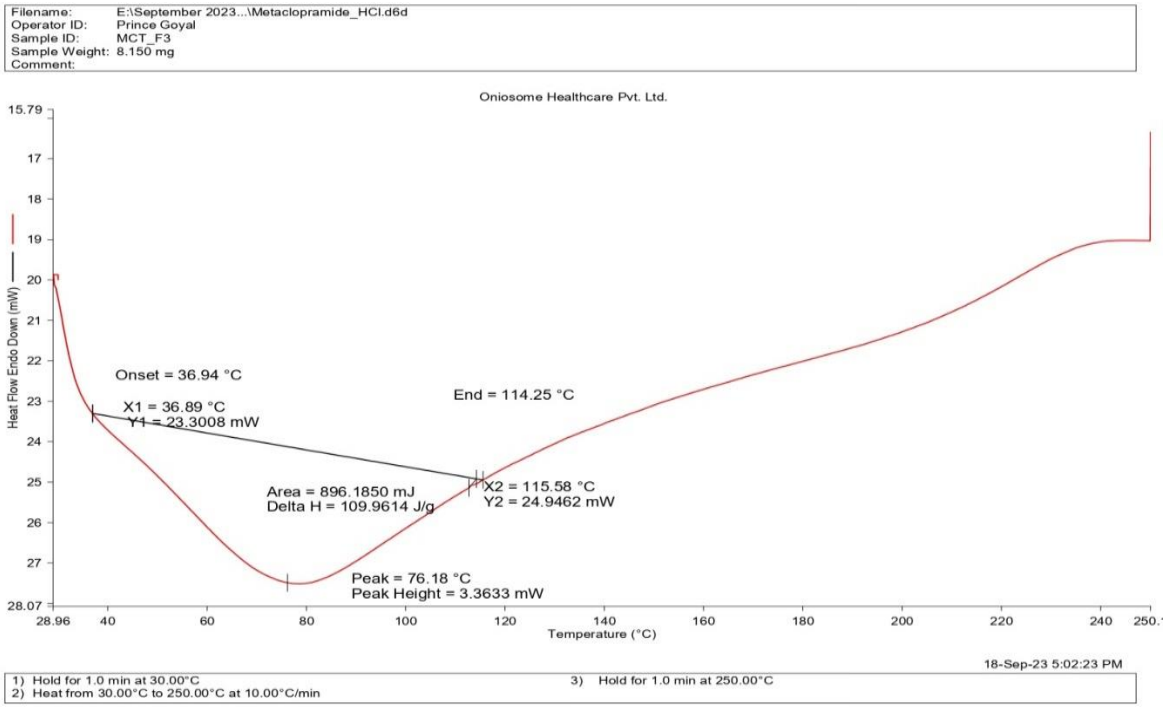

Fig. 6: DSC of Individual Formulation F3

Assessment of Pure Metoclopramide HCL by UV Spectrophotometric Method:
Following the application of Beer-Lambert's Law over the concentration range of 5–25 µg/ml and using three different solvents - distilled water, ethanol and phosphate buffer with a pH of 6.8 the absorbance at 273 nm was measured (table 3) and calibration curves were produced (figure 7).

TABLE 3: STANDARD CALIBRATION OF METOCLOPRAMIDE HCL:

Sr. No.	Concentration (µg/ml)	Absorbance		
		Distilled water	Ethanol	Phosphate Buffer (6.8 pH)
1.	5	0.373	0.617	0.811
2.	10	0.726	1.135	1.214
3.	15	1.056	1.605	1.704
4.	20	1.409	2.087	2.142
5.	25	1.768	2.591	2.635
R Value		0.9998	0.9999	0.9998

Mean ± Std. Deviation whereas n=3

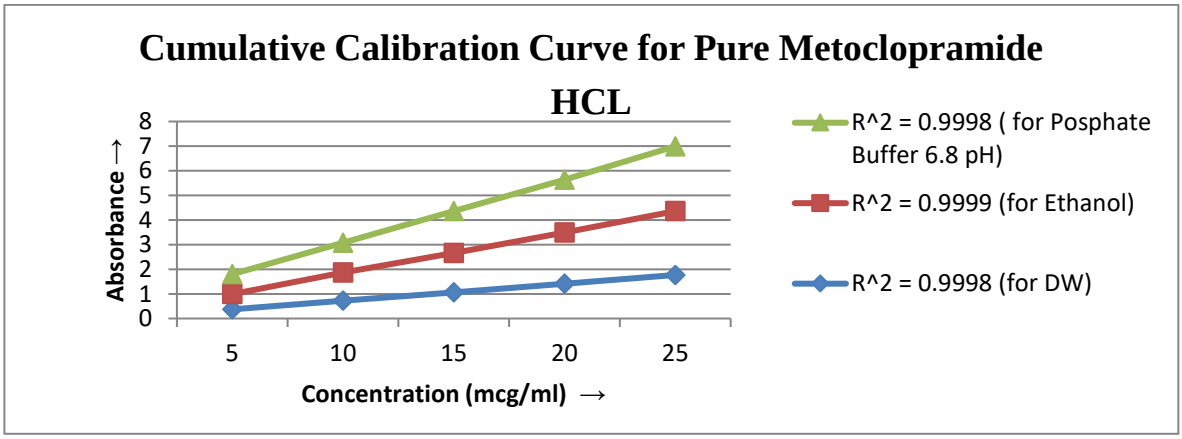

Fig. 7: Cumulative Calibration Curve for Pure Metoclopramide HCL in Different Solvents.

Swelling Ability of Microspheres Prepared:
Table 2 displays the swelling index for each formulation. The microspheres' degree of swelling varied amongst formulations, ranging from 0.71±0.005% to 1.16±0.081%. It is noted that as mucoadhesive polymer concentrations rise, the degree of swelling tends to significantly increase. Because those formulations have a higher amount of film-forming polymer (chitosan), which inhibits water absorption into the polymer matrix, there may be a little reduction in swelling at lower levels of mucoadhesive polymer. This shows that microspheres quickly inflate and absorb liquid from the mucus layer upon coming into contact with it. As a result, epithelial cells shrink and shed water, which makes it easier for epithelial tight junctions to open and improves drug absorption.

In-Vitro Mucoadhesion:
Based on polymer content, the mucoadhesion of nasal microspheres loaded with metoclopramide HCL varied from 64.87±0.287 % to 87.52±0.570 % (Table 2). Chitosan and mucin are attracted to each other electrostatically, which accounts for the exceptional mucoadhesion seen in chitosan microspheres. Furthermore, significant chain flexibility is made possible by the linear structure of chitosan molecules, which permits interpenetration and entanglement. The polymer's strong mucoadhesive property can be attributed to its polar functional groups and remarkable flexibility. Cross-linking of polymer molecules with cross-linking agents, however, reduces the flexibility of the polymer chain. By stopping cross-linked polymers from entering the mucin network, this reduced flexibility lowers the mucoadhesive strength.

In-Vitro Release Investigations:
Table 4 provided an overview of each formulation's in vitro release profiles. For formulations F1 through F6, after eight hours, the total drug release was discovered to be 84.6±0.879 %, 89.6±0.325 %, 98.7±1.607 %, 85.6±0.235 %, 89.1±0.107 % and 92.7±0.623 %, as shown in Table 4. Figure 8 shows the release characteristics of chitosan microspheres loaded with metoclopramide HCL. It became evident that the polymer concentration and stirring rate had a big influence on the drug's release. Drug release increased proportionately to an increase in mucoadhesive polymer concentration. The medication release was more affected by stirring rate than by mucoadhesive polymer concentration. In particular, drug release increased significantly as stirring rates increased, suggesting a substantial relationship between stirring rate levels and drug release.

This behaviour is probably explained by the smaller microsphere particles at greater stirring speeds, which increase the drug's accessible surface area for release and shorten its diffusion path length. The greater drug release from chitosan microspheres could be attributed to the higher degree of chitosan swelling, which creates hydrophilic pathways inside the microspheres and aids in drug diffusion. Water enters the microspheres more easily thanks to the chitosan's expanded hydrophilic pores, hastening the erosion of the expanding matrix. Consequently, drug release from the microspheres is facilitated by a mix of erosion and diffusion processes. The medication release graph displaying percentages showed that formulations F3 produced the best results.

TABLE 4: IN-VITRO DRUG RELEASE OF PURE METOCLOPRAMIDE HCL & FORMULATIONS OF MICROSPHERES LOADED WITH DRUG i.e. METOCLOPRAMIDE HCL:

Sr.No.	Time (hrs)	In-Vitro Drug Release in %						
		Pure Drug	Formulations					
			F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0	0
2.	1	10.4±0.384	14.6±0.526	18.7±0.289	19.1±0.975	16.7±0.317	17.4±0.721	18.9±0.375
3.	2	19.5±0.726	18.5±0.265	25.7±0.500	26.9±0.524	23.5±0.431	24.3±0.521	23.6±0.500
4.	3	31.8±0.327	27.8±0.608	31.7±0.564	40.8±0.679	29.5±0.500	33.7±0.763	39.9±0.234
5.	4	39.7±0.500	37.9±0.500	52.5±1.603	58.4±0.529	32.1±0.794	42.9±1.904	57.8±0.671
6.	5	46.8±0.671	52.0±0.570	59.2±0.500	70.4±0.376	55.4±0.265	63.0±0.246	65.6±1.509
7.	6	55.71±0.64	68.7±0.420	73.0±0.764	81.7±0.268	72.9±0.569	72.9±0.661	79.6±0.623
8.	7	62.5±0.564	76.4±0.794	83.9±0.500	91.7±0.500	79.1±0.451	82.9±0.971	89.8±0.928
9.	8	73.8±0.925	84.6±0.879	89.6±0.325	98.7±1.607	85.6±0.235	89.1±0.107	92.7±0.623
R^2 value		0.9956	0.9506	0.9714	0.9852	0.9667	0.9678	0.9689

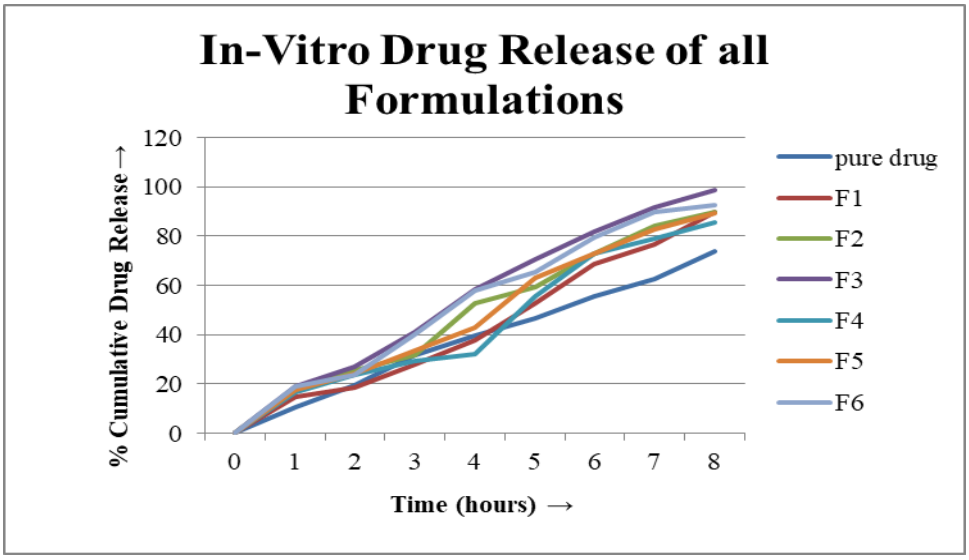

Fig. 8: In-Vitro Drug Release of All 6 Formulations

Drug Release Kinetic Studies in Vitro Using Different Models:

The Higuchi Equation, the Korsemeyer-Peppas model, the Zero-order, and the First-order models were used to analyze the in vitro drug release properties of each formulation. Table 5 displays the outcomes. For first-order kinetics, 'r^{2}' values for formulations F1 through F6 ranges from 0.949 to 0.980, whereas the value of 'r^{2}' for zero-order kinetics varied from 0.951 to 0.985. The regression coefficient (r^2) value for the zero-order equation was found to be greater than that of the first-order equation when compared between the two equations. Accordingly, the drug release follows zero order for all formulation F1 through F6, as seen by the zero order drug release values (Fig 9). Additionally, to better understand the drug release process, we evaluated the in-vitro data using the Higuchi diffusion model. For formulation F1 through F6, the Higuchi diffusion' 'r^{2}' values varied from 0.949 to 0.975, respectively. As a result, it verifies that the drug is released through the diffusion-controlled process described by the Higuchi diffusion mechanism. Furthermore, the diffusion exponent values (n) derived from the Korsemeyer-Peppas model varied from 0.971 to 0.987 across all formulations, indicating that a non-Fickian' diffusion mechanism underlies drug release, as illustrated in Table 5.

TABLE 5: THE DIFFUSION COEFFICIENT (N) VALUES OF THE PEPPAS EQUATION AND REGRESSION COEFFICIENT (r^2) VALUES, USED IN THE ANALYSIS OF MICROSPHERIC RELEASE DATA ACCORDING TO DIFFERENT KINETIC MODELS.

Sr. No.	formulation code	r^2 value for Zero Order	r^2 value for First Order	r^2 value for Higuchi Matrix	Peppas plot		best model fits
					r^2 value	'n' value	
1.	F1	0.951	0.949	0.949	0.971	0.801	Zero Order
2.	F2	0.971	0.968	0.969	0.974	0.793	Zero Order
3.	F3	0.985	0.980	0.975	0.987	0.843	Zero Order
4.	F4	0.966	0.959	0.971	0.983	0.753	Zero Order
5.	F5	0.968	0.969	0.972	0.986	0.739	Zero Order
6.	F6	0.968	0.973	0.974	0.986	0.722	Zero Order

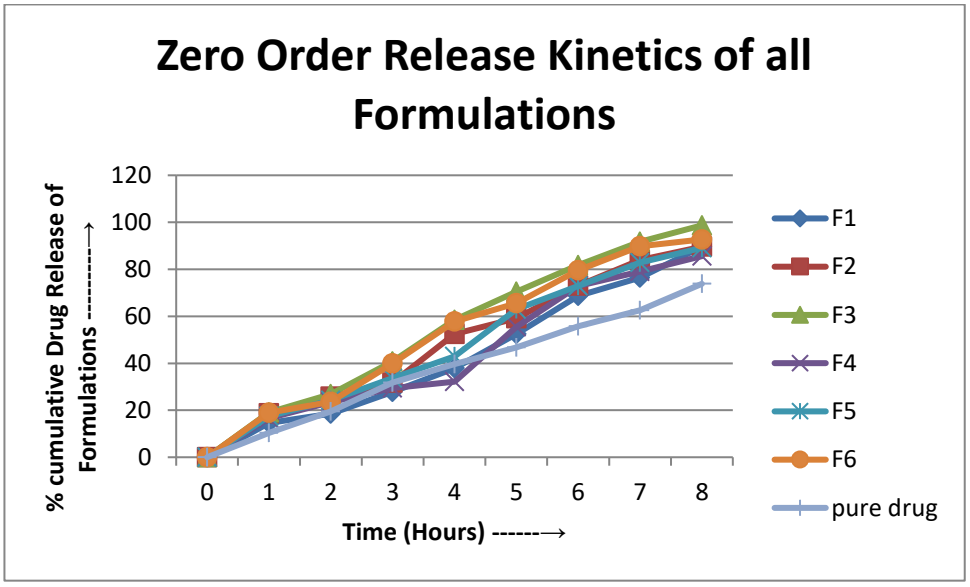

Fig. 9: Metoclopramide HCL Microsphere Formulations: Zero Order Release Kinetics.

Stability Assessment of Metoclopramide HCL Microspheres:

For the purpose of evaluating the stability of the formulated Metoclopramide HCL microspheres, the ideal formulation F3 was stored for six months under the following conditions: 4±1˚C, 25±2˚C with 60±5˚C RH, and 37 ± 2˚C with 65 ± 5% RH. Among the metrics that were evaluated were the percentage of cumulative drug release and the percentage of entrapment efficiency & the results after the six-month storage period are displayed in Table 6. The findings demonstrated a decline in the percentage cumulative drug release as well as trapping efficiency. It's interesting to note that formulations kept at 25±2˚C with 60±5˚% RH showed the highest percentage cumulative drug release and levels of entrapment, followed by formulations kept at 4±1˚C and 37±2˚C with 65±5% RH conditions. These findings may be explained by the facts that point to a partial erosion of the polymer matrix during storage.

TABLE 6: STABILITY STUDIES OF F3, THE OPTIMISED FORMULATION:

Sr. No.	Time in Months	4±1ºC		25±2ºC with 60±5% RH		37±2ºC with 65±5% RH	
		A	B	A	B	A	B
1	**1**	87.9	86	87.9	86.05	87.9	86.03
2	**2**	87.8	85.6	87.8	86.03	87.6	86.01
3	**3**	87.7	85.6	87.8	86	87.1	86
4	**4**	87.0	85.5	87.7	86	86.7	85.8
5	**5**	86.7	85.4	87.7	85.9	86.3	85.7

A= % Entrapment Efficacy & B= % Cumulative Drug Release

CONCLUSION:

It is clear from the ongoing studies that metoclopramide HCL microspheres, which are made with chitosan using emulsification cross-linking technique, have potential for use in nasal delivery. As a result, the created microsphere

becomes a potential candidate for an intranasal controlled medication delivery system, especially for symptoms related to nausea and vomiting.

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