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Formulation and Evaluation of Mesoporous Silica Nanoparticles to Treat Cancer Induced Emesis

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Abstract: ***The present work is aimed to formulate and characterize the Palonosetron HCl loaded mesoporous silica nanoparticles to treat chemotherapy induced emesis. This Palanosetron loaded MSNs were prepared by using solvent - based method (solvent immersion & DiSuplo method) at different weight ratios, speed (rpm), and time (h). The preliminary tests such as identification & solubility of drug studied by using UV & FTIR, various physicochemical characterization of mesoporous silica particles and Palanosetron loaded MCM - 41 MSNs (Mesoporous nanoparticles) F1 - F6 were evaluated by using Particle size, SEM & BET analysis. In vitro drug release studied from optimized (DOE) formulations using dissolution medium hydrochloric acid solution (pH 1.2) and phosphate buffer (pH 6.8). MCM - 41 - Palanosetron (F1) were determined to have the highest drug loading efficiency, 97.0±2.19%. The BET surface area of MCM - 41 were found to have 999.438 to 1472.227 m^2/g, pore volumes of 1.073 to 1.141 cc/g, and average pore sizes of 2.495 to 4.827 nm. SEM results of F1 revealed that, particle morphology as a uniform spherical like structure of size ≤ 450 nm to ≤ 570 nm at 4.00KX & 3.00KX magnification. The drug loaded MSNs were stable at 40±2°C/75±5% RH, throughout one month period. The optimized formulations revealed that palanosetron loaded MCM - 41 mesoporous particles are best suited for emetic therapy in case of Chemotherapy.***

Keywords: Mesoporous silica nanoparticles (MSNs), Emesis, MCM - 41, Palanosetron

1. Introduction

About 80% of cancer patients will have nausea and vomiting during Chemotherapy Induced Nausea & Vomiting (CINV) treatment. This is one of the most frequent side effects of chemotherapy drugs used to treat cancer [1]. One of the three main types of CINV is acute emesis, which begins within 1 - 2 h. Anticipatory emesis develops prior to chemotherapy and delayed emesis 24 h later due to a condition reaction to prior chemotherapy experiences. The most noticeable and frequent adverse effect of chemotherapy is nausea and vomiting (CINV). The majority of cancer chemotherapy treatments are cytotoxic in nature and have excruciatingly unpleasant side effects. CINV, which is also the most serious side effect, has the biggest detrimental impact on a patient's quality of life as well as their capacity to tolerate and adhere treatment [2]. If CINV is not successfully controlled, it may cause serious issues such as weakness, weight loss, nutritional deficiencies, electrolyte imbalances, dehydration, and physical and mental disturbances can happen as a result of CINV if it is not properly managed. It might also result in patient non - compliance and rejection of the cancer chemotherapy [3, 4].

Silica nanoparticles are mesoporous were categorized as silica - containing substances with nanometer - sized particles. Mesopores are defined as those with a diameter between 2 to 50 nm; and macropores are defined as those with a diameter greater than 50 nm. The International Union of Pure and Applied Chemistry specifies that pore diameters should range from 2 to 50 nm. The first ordered MSNs were created by the Mobil Corporation in 1992 as Mobil Composition of Matter or Mobil Crystalline Materials (MCM) [5, 6, 7]. Additionally, the MSNs' textural characteristics affect how well these nanosystems function as drug delivery systems [8, 9, 10]. Mesoporous carriers MCM - 41, MCM - 48, SBA - 12, SBA - 15, and SBA - 16, all have unique morphologies, pore sizes, and structures. In recent years, drug delivery systems such as SBA systems, MCM systems, TUD systems, and KIT systems have been developed. MSNs with various morphologies and structures can be produced utilizing various structure - directingagents [11, 12, 13, 14, 15].

Drug loading into MSNs

It is feasible for numerous medications to function, because of the regulated pore size and surface chemistry that may be effectively loaded within the pores of MSNs. These interactions between drugs and the walls of the pores may be caused by covalent bonds, hydrogen bonds, vanderwaals interactions, or even electrostatic binding. Over the past ten years, numerous approaches to drug loading into MSNs, such as melt techniques, supercritical fluid (SCF) processes, and various organic solvent procedures, have been developed [16, 17, 18, 19]. There are numerous methods for introducing medicines into the mesoporous silica's pores. These approaches can be divided into two main categories: solvent - free methods and solvent - based methods (so - called wet methods). A literature review revealed that methods to encapsulate different types of pharmaceuticals using solvents, such as adsorption, solvent evaporation, and incipient wetness impregnation, are frequently used. Melting and co - milling are two of the most recommended solvent - free techniques for getting the medicine inside MSN's pores. The drug's physicochemical characteristics, dispersion in silica, and degree of loading are all impacted by the method of drug loading that is used [20, 21, 22].

2. Materials and Methods

2.1 Materials

MCM - 41 and Palanosetron hydrochloride drug was purchased from Sigma Aldrich (Mumbai, India). All other chemicals and reagents used in the research were of Fine Chemicals (Bengaluru, Karnataka).

2.2 Preformulation studies:

Preliminary Solubility Study: The drug Palanosetron hydrochloride was dissolved in suitable solvents like water, ethanol, methanol, propylene glycol, 0.1N HCl, and phosphate buffer pH 6.8, the solubility was observed and categorized accordingly as per the descriptive term used in the Indian Pharmacopoeia.

UV Spectroscopy Analysis: The absorption maxima of Palanosetron hydrochloride in ethanol were found to be 265 nm. As per Beer's law, the concentration range was made from 7.5 to 25 µg/ml, and the regression coefficient was calculated.

Fourier Transform Infrared (FT - IR) Analysis: The molecular compound's structure is precisely described by infrared spectroscopy. To check the purity, characteristics, and compatibility between the drug and excipients, and to determine the potential interactions between Palanosetron hydrochloride and MSNs, FTIR studies were carried out on pure Palanosetron hydrochloride and physical mixtures of the drug with MCM - 41 were studied. These experiments were carried out using a Bruker FTIR instrument (APLHA - II, Germany). The samples were scanned at wave lengths ranging from 400 to 4000 cm^{-1}.

2.3 Preparation of drug loading into MSNs

Software called Design Expert 13 was used to construct the formulation chart [Table 01]. Mesoporous nanoparticles were loaded with Palonosetron using solvent immersion or DiSuplo methods [23]. In order to improve the drug loading process, which involved dispersing the MSNs in distilled water (250 ml) and stirring each formulation for 2 to 5 h at various speeds (rpm) in a beaker for different formulations at (37ºC). In the middle of the process for each formulation a weighed ratio of Palanosetronhydrochloride (100 mg) was dissolved inabout 50 ml ofwater and added into the MSNs slurry to be loaded with Palanosetron hydrochloride. At first, a weighed ratio of F1, 1: 4 (API/MCM - 41) slurry was prepared by using 100 ml of distilled water in a beaker using a mechanical stirrer set to 1200 rpm for 3 h at room temperature. In our present research work, all the above methods from the original developed methods are used for drug loading into the pores of MSNs. The reference standard method developed by Potrzebowski MJ*et al.*, 2020 [24]. The drug loaded MSNs are then recovered by filtration using Whatman filter paper, and the drug loaded MSNs were dried in a hot air oven at 45°C for 1 h before being kept in a clean sealed, sachet container for further processing.

Table 1: Formulation chart of Mesoporous nanoparticles

Run	Time (h)	Speed (rpm)	Drug (mg)	MCM - 41 (mg)
F1	2	1200	100	400
F2	2	800	100	100
F3	5	800	100	400
F4	5	1000	100	300
F5	3	1000	100	100
F6	5	1200	100	100

2.4 Evaluation of prepared drug loaded MSNs formulations

2.4.1 Particle size, PDI, Zeta potential analysis: TheMALVERN scientific (Nano Particle ZS - 90) nanoparticle analyzer was used to measure the mean particle size, PDI, and Zeta potential (mV) of pure Palanosetron. HCl and the physical mixtures of drug - loaded sample formulations of MCM - 4, using the Dynamic Light Scattering (DLS) method [25, 26].

2.4.2 Nitrogen adsorption - desorption Analysis: Under continuous adsorption circumstances, nitrogen adsorption/ desorption isotherms were measured using a surface area and porosity analyzer (Micromeritics ASAP 2020 V4.01, USA). The pure MSNs samples (MCM - 41) were degassed at 300ºC for 4 h. At relative pressures between 0.01 and 0.30, Brunauer, Emmett, and Teller (BET) analysis was used to determine the BET surface area, and Barrett, Joyner, and Halenda (BJH) analysis was used to determine the pore size and pore volume generated by the instrument from the desorption branches of the Isotherm [27].

2.4.3 Scanning electron microscopy: Using a scanning electron microscope (SEM, Hitachi S - 3400, Japan) the surface morphology of the particles was captured for the prepared drug loaded sample F1 (MCM - 41 - Palanosetron) formulations at various magnifications at room temperature, Using SEM micrographs, morphological characteristics were examined [28].

2.4.4 Drug Content: Mesoporous particles were loaded using batch process. The drug loaded MSNs were recovered by filtration using Whatman filter paper, and from the filtrate, taken 1 ml was further diluted using distilled water against a blank. The solutions were analyzed using a UV - Visible spectrophotometer at 265 nm.

2.4.5*In vitro* drug dissolution studies: Forformulation F1 - F6 MCM - 41 - Palanosetron hydrochloride. *In vitro* drug release studies were conducted. The right capsules (0) size capsules werechoosedto fill the drug loaded mesoporous nanoparticles, using the USP type II dissolution test apparatus, LABINDIA DS 8000, India. *In vitro* drug release studies conducted with pH 1.2 hydrochloric acid solution (0.1N HCl) at 37±0.5°C till 30 min. at 50 rpm in 900 ml of dissolution medium, and with the same condition by changing the pH of the medium used phosphate buffer (pH 6.8) dissolution was carried out till 60 min. To keep the sink condition, a 1 ml sample was taken out at regular intervals and replaced with new dissolution medium. The volume was increased to 10 ml by using a volumetric flask, and the withdrawn sample was filtered by using membrane filter,

and the absorbance was periodically measured using a UV spectrophotometer at a wavelength of 265 nm.

2.4.6 Short term stability studies as per ICH guidelines

The optimized formulations were filled into 0 size capsuleswrapped in aluminium foil, and kept in a stability chamber (Thermo lab, Scientific equipment's Ltd) maintained an accelerated stability condition at temperature 40±2°C/75±5% RH for one month [29]. The sample was examined for critical quality attributes such as drug content and drug dissolution studies, which would affect the efficacy of the product.

3. Results & Discussion

3.1 Preformulation studies

Palonosetron hydrochloride is freely soluble in water, soluble in ethanol, DMSO and Dimethyl formamide. Palonosetron in water is quantitatively determined using a UV - Visible spectroscopy method. The λ_{max} was found to be 265 nm for palonosetron hydrochloride in water and ethanol. It ensures that the procured drug is in pure state. It obeys beer's law in the concentration range of 7.5 to 25 µg/ml and regression coefficient was found to be 0.998.

A comparison is made between the position of the peak in the FTIR spectra of pure Palonosetron Hydrochloride and the FTIR spectra of MCM - 41 as well as with drug loaded MSNs. FTIR spectrums Palonosetron Hydrochloride bands were observed in the spectrum, 2874 cm^{-1} due to C - H stretching, 1710 cm^{-1} due to C=O stretching, 1660 cm^{-1} due to heterocyclic C=C stretching and 1189 cm^{-1} due to C - N stretching, these are the characteristic peaks of Palanosetron hydrochloride, physical mixture of MCM - 41 and palanosetron hydrochloride spectrum shows almost same characteristic peaks without much deviation, which indicates that there is no interaction between palanosetron hydrochloride and mesoporous nanoparticles as shown in Figures 01 to 03.

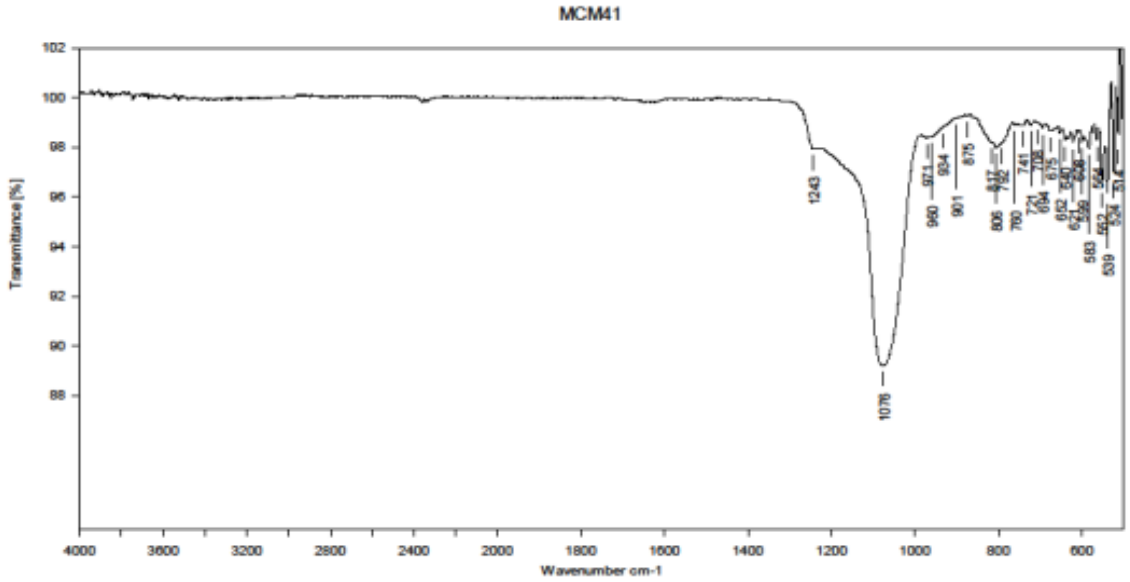


Figure 1: FTIR spectrum of MSNs (MCM - 41)

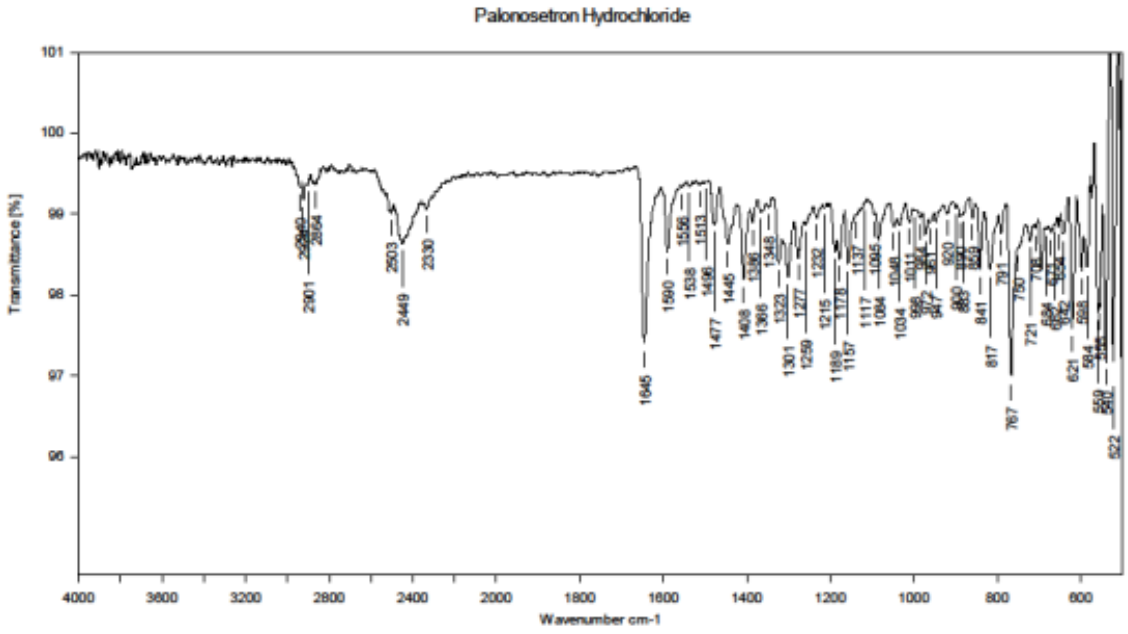


Figure 2: FTIR spectrum of Palanosetron Hydrochloride

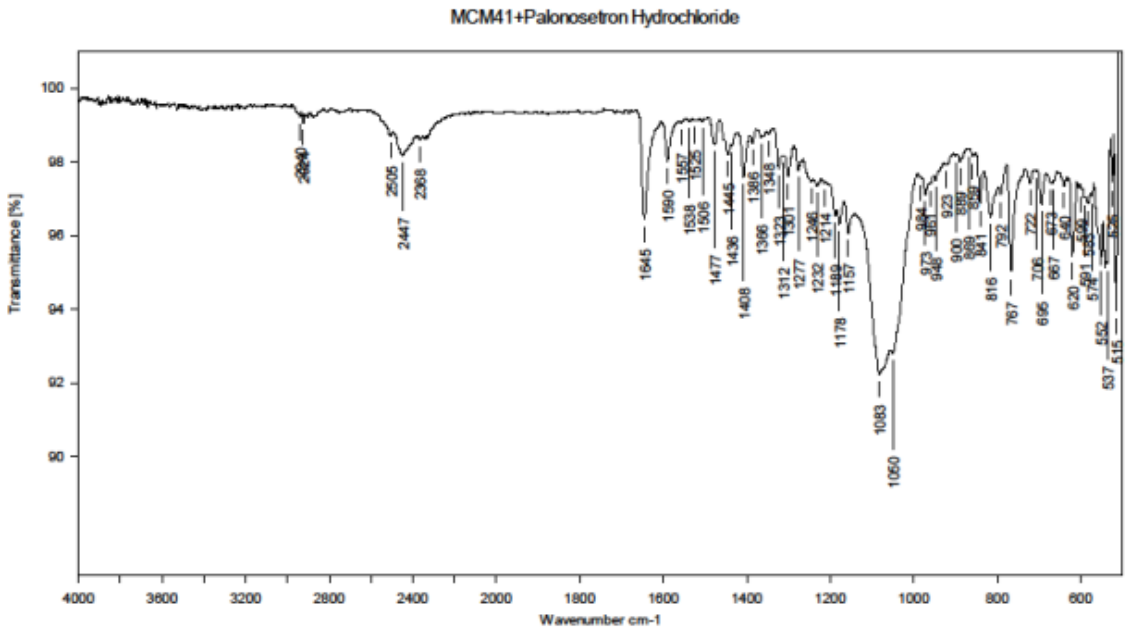


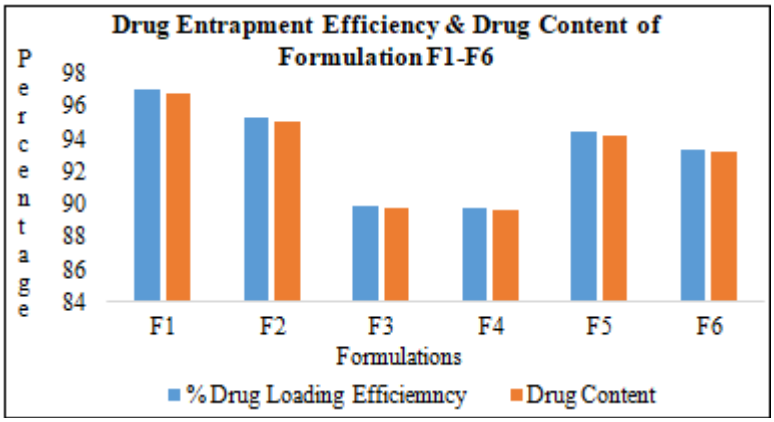
Figure 3: FTIR spectrum of drug loaded MSNs F1 (MCM - 41 - Palanosetron Hydrochloride)

3.2 Determination of Drug Loading Efficiency (%DLE) of drug loaded MSNs

The amount of drug that is effectively loaded into the nanoparticles, which is expressed in percentage. A crucial criterion that must be optimized in the delivery system is the percentage of drug loading efficiency. One of the most desirable characteristics of Mesoporous Silica Nanoparticles is the capacity to entrap a sufficient amount of drug. The percentage drug loading efficiency of drug loaded MSN formulations was found to be in the range of 95.71±2.14% to 97.0±2.68% as shown in the Figure 04. The highest drug loading was observed from F1 complex (MCM - 41 - Palonosetron HCl).

3.3 Drug content Estimation

According to the study, the formulation's drug content and the effectiveness of the drug loading were directly correlated. As a result, the drug content for 10 mg of each formulation was calculated using accepted practices. The results for formulation F1 (MCM - 41 - Palanosetron HCl) were as shown highest drug content as shown in the Figure 04. Drug content for all the formulation batches was found to be uniform and within the range of94.7±1.09% to 96.0±2.83%.



* (mean ± S. D, n=3)

Figure 4: Percent Drug loading efficiency of optimized formulations F1 - F6 (MCM - 41 - Palanosetron HCl).

3.4 Material characterization

3.4.1 Particle size, PDI, Z - average and Zeta potential of drug loaded MSNs

The results revealed that, the drug loaded MSNs F1 (MCM - 41 - Palonosetron hydro chloride) showed a mean particle size ranging from 225.6 to 353.7 nm, Z - average value between 855.6 to 1100 nm, PDI value between 0.920 to 1.000 and zeta potential values were in the range of - 0.283 to - 0.707. The graphical representation of the mean particle size distribution and mean zeta potential of drug loaded MSNs F1 formulations (MCM - 41 - Palonosetron hydrochloride) was as shown in the Figures 05 & 06.

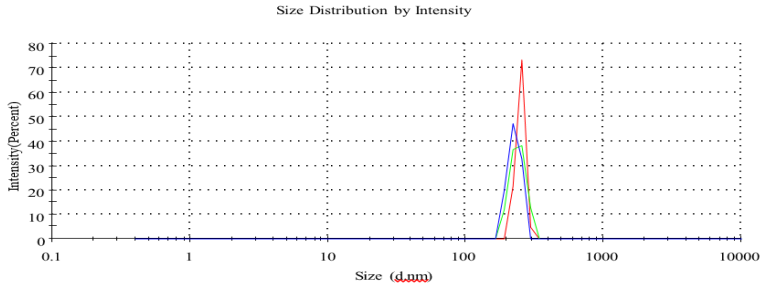


Figure 5: Graphical representation of mean particle size (nm) of MSNs (MCM - 41)

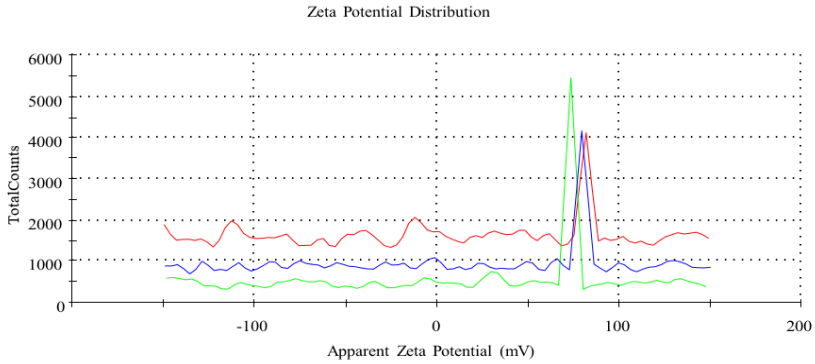


Figure 6: Graphical representation of mean zeta potential (mV) ofPalanosetron HCl drug loaded MSNs

3.4.2 Nitrogen adsorption - desorption analysis

Using the Brunauer - Emmett - Teller (BET) method, the specific surface areas were determined, and using BJH methods, the pore size diameters were determined from the desorption branches of the isotherms. The specific surface areas, average pore size diameter, and pore volume of pure MSNs were calculated using the Brunauer - Emmett - Teller (BET) method. The BET surface area (SA) of MSNs (MCM - 41) was found to be999.438 - 1472.227 m^2/g, the pore volume was 1.073 - 1.141 cc/g and the average pore size was about 2.495 - 4.827 nm, as shown in Table 02.

Table 2: BET and desorption data of Mesoporous nanoparticles

Sl. No.	Material	S_{BET} (m_2/g)	Pore Volume (cc/g)	Pore Diameter (nm)
1	MSNs (MCM - 41)	999.438 - 1472.227	1.073 - 1.141	2.495 - 4.827

3.4.3 Scanning electron microscopy (SEM) analysis

Both the drug - loaded sample F1 (MCM - 41 - Palanosetron hydrochloride formulation's surface morphology were recorded. Images produced by scanning electron microscopes have been used to analyse the surface morphology and form of materials that have been loaded with drugs. Using a scanning electron microscope (SEM, Hitachi S - 3400, Japan) at room temperature, SEM pictures of material F1 (MCM - 41 - Palanosetron HCl) were captured at magnifications of 4.00KX and 3.00KX), as shown in Figures 07&08. A consistent crystalline structure, consisting of clusters of hollow, spherical discrete particles smaller than 450 nm, was observed in the images.

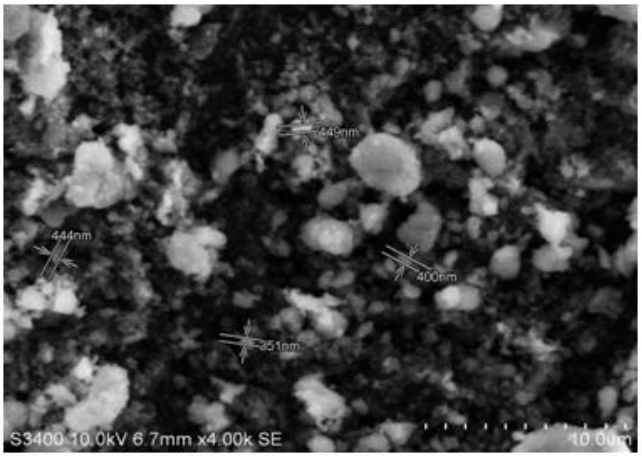


Figure 7: SEM image of F1 MCM - 41 - Palonosetron HCl at 4.00KX

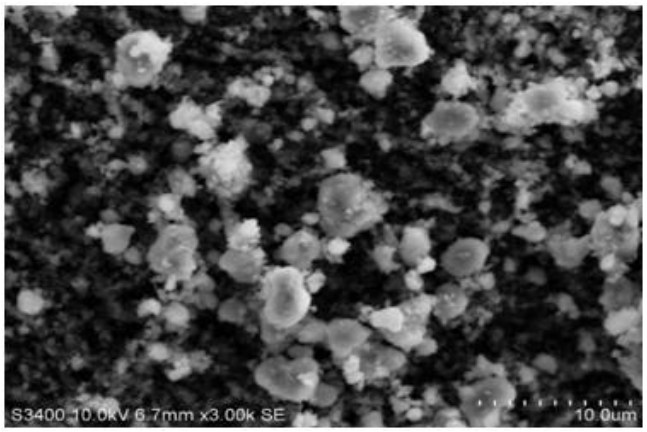


Figure 8: SEM image of F1 MCM - 41 - Palonosetron HCl at 3.00KX

3.4.4 Drug release: A study on the *in vitro* drug release of drug loaded MSNs F1 - F6 formulations was conducted. With the use of 0.1N hydrochloric acid at the end of 30 min, drug release ranges from 57.4±0.28 to 85.7±0.66%. The percentage of drug was released from phosphate buffer (pH 6.8) at the end of 60 min, a range of 83.9±1.40 to 94.9±0.71%. The results of*in vitro* drug release were found to be lowest 32.7±3.93% in F2 formulation (MCM - 41 - Palanosetron) by using phosphate buffer (pH 6.8) as shown in the Figures 09&10. The lowest 19.7±0.62% drug was released in F3 formulation by using a pH 1.2 hydrochloric acid solution (0.1N HCl). Overall, the formulations produced the best results.

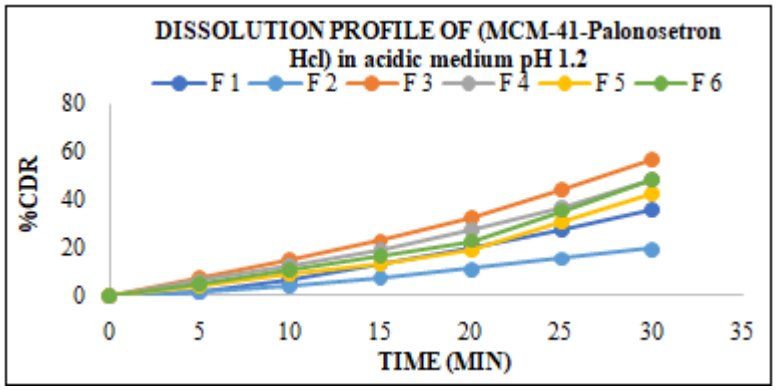


Figure 9: *In vitro* dissolution profiles of F1 - F6 formulations by using pH 1.2 buffer.

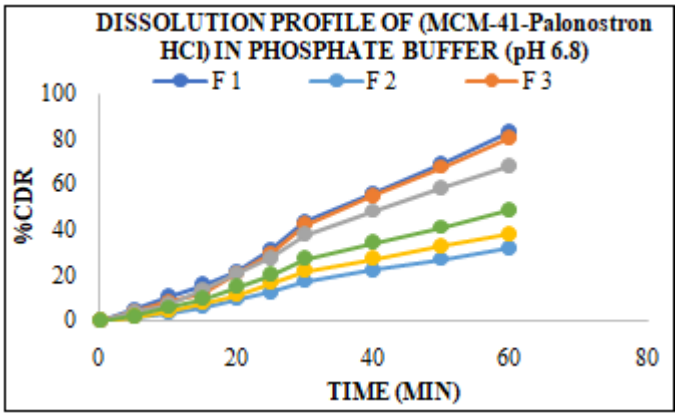


Figure 10: *In vitro* dissolution profile of F1 - F6 formulations by using phosphate buffer pH 6.8.

3.4.5 Stability studies of the most satisfactory formulation

The optimized formulation F1 is the most satisfactory formulation, was subjected to stability studies. The samples were filled in "0" size capsules, was packed in aluminium foil, and kept in stability chamber (Thermo Lab, Scientific, Mumbai) maintained at 40±2°C/75±5% RH for one month. After one month, no significant changes in drug content or drug release pattern were observed.

4. Conclusion

The present research was carried out to formulate, characterize, and assess the drug loaded mesoporous silica nanoparticles for the treatment Chemotherapy Induced nausea and vomiting were successfully developed. With the drug loaded MSNs developed by using solvent - based methods, and alternative routes of drug administration like the nasal route, dose reduction may be possible. This formulation will be best suited for chemotherapy induced emesis.

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