

A Novel Approach of Nanosponges Capsules of an Antiemetic Drug

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ABSTRACT

The goal of this study was to create a Nanosponges formulation of Domperidone for oral capsule solubility and bioavailability enhancement of the drug. They have an established spherical colloidal nature, and their inclusion and non-inclusion behaviours show that they have a very high BCS class II drug solubilization capability. The physicochemical characterization for a pure drug such as organoleptic properties, spectral analysis UV spectroscopic studies, ATR-FTIR and DSC were investigated and confirmed. Preformulation studies such as solubility studies, angle of repose, tapped density, cars index, bulk density and Hausner ratio are performed for blend powder showing micromeritic characteristics are within the pharmacopeial specifications. The emulsion solvent diffusion method is used to formulate drug-loaded Nanosponges, and the capsule filling process is used to make the capsules. The drug-loaded nanosponges prepared were evaluated for surface morphology analysis (SEM), percent yield and entrapment efficiency show the nanosponges have a spherical form and a smooth surface morphology at 200nm. Then the prepared capsules were subjected to evaluation tests including dissolution studies that lasted up to 12 hr The stability studies were conducted for the optimized formulation (period of three-month) stability assessment at accelerated and room temperature. Based on the results of various studies, it is concluded that the Domperidone loaded nanosponge capsules formulation provide an effective modified formulation for the oral route of administration.

Keywords: Core, Smooth surface, Dissolution study, ICH guidelines, Modified formulation.

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INTRODUCTION

Some people experience vomiting while travelling and it is also used in the treatment of chemotherapy-induced nausea and vomiting. Few medications, such as Domperidone, operate as antiemetic and anti-motion sickness pharmaceuticals with promising results. It is efficiently used for vomiting and motion sickness. Dysphagia affects paediatric, geriatric, and immobile patients, resulting in a high rate of unsuccessful therapy

and widespread vomiting. Nanosponges have the potential to deliver drugs in a predictable and regulated manner. Nanosponges may transport hydrophobic molecules in the hydrophobic cavity and hydrophilic molecules in the spaces between the hydrophobic moieties because they are amphiphilic. Hydrophobic drugs can be inserted into the nanosponge structure to increase their solubility. Nanosponges can be tagged with specific linkers to target sick cells, improving efficacy while reducing side effects, decreasing dose and dosing frequency, and increasing patient compliance. Nanosponges are minute mesh-like tightly cross-linked polymer-based colloidal structures with a variety of therapeutic compounds at their centre. They have a demonstrated spherical colloidal nature, and their inclusion and non-inclusion behaviour implies that they have a strong BCS class II solubilization capability

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(poorly soluble pharmaceuticals). They've just lately been produced and proposed as a medicine delivery system. It has the capacity to solubilise poorly water-soluble medicines, allowing for longer release and increased bioavailability. Because of their interior hydrophobic chambers and exterior hydrophilic branching, nanosponges may carry both hydrophilic and hydrophobic medicinal molecules, providing versatility. An ideal drug therapy maintains effective drug concentration at the target site for a set period of time while minimising both general and local side effects. To obtain the intended therapeutic response, the correct amount of medication should be transported and delivered to the site of action, and the drug input rate should then be managed. As a result, it appears that drug transport to other tissues is unnecessary, inefficient, and maybe hazardous. Targeted drug delivery refers to the administration of a medicine to a receptor, organ, or another part of the body to which the drug is to be administered exclusively. Medical experts have worked for years to figure out how to transfer drugs to the proper area in the body while simultaneously managing drug release.^[1-4]

MATERIALS AND METHODS

Domperidone was received as a gifted sample from Lohitha life sciences Pvt. Ltd, Hyderabad, India and Ethyl Cellulose, Polyvinyl Alcohol, Ethanol, Dichloromethane were purchased from Mercury scientific lab in Salem, Tamilnadu, India. The rest of the chemicals and reagents utilised in this experiment were of analytical grade.

Methods

Physicochemical Characterization and Drug Identification^[5]

To characterise API, researchers looked at its organoleptic characteristics. Prior to beginning the trial, it was critical to validate the identification of the medicine obtained.

Spectroscopic Studies (UV spectral analysis)^[6]

The UV-Vis spectra (UV-Vis) were acquired in the 200–400 nm range using a Shimadzu spectrophotometer; a phosphate buffer solution with pH 6.8 was produced for this analysis.

Preparation of Stock Solution

The standard stock solution of domperidone was made by precisely weighing 10 mg of domperidone raw material into a 100 ml volumetric flask. The drug was dissolved in a few ml of ethanol and the volume was

raised to 100 ml using ethanol to form a stock solution of 100 g/ml. The result was given in Figure 1,2.

Solid characterization (DSC- Differential scanning calorimetry)^[7]

DSC was used to study the drug's solid form. A weighed amount of nanosponges was deposited in a crucible, which was immediately placed into the apparatus. For DSC analysis, a sample (3–5 g) was heated from 0–25°C in a nitrogen atmosphere at a scanning speed of 100 C/min. The result was given in Figure 3.

ATR-FTIR Spectra analysis^[8]

The spectrum was captured between the wavelengths of 4000 to 400cm⁻¹. An IR spectrum was acquired using an ATR-FTIR spectrophotometer after a homogenous mixture of the drug, polymer, physical mixture was

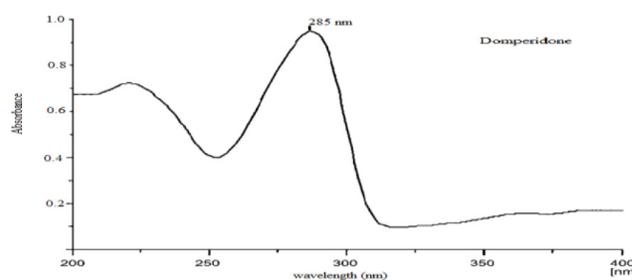


Figure 1: Maximum absorbance of Domperidone.

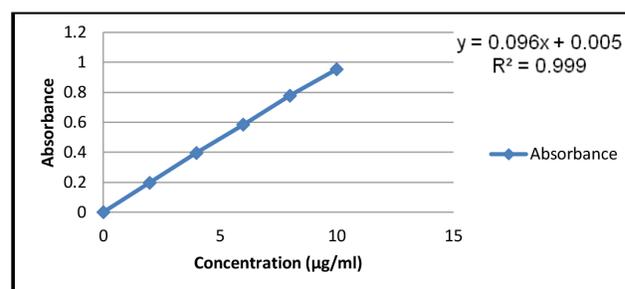


Figure 2: UV absorbance for Domperidone using pH 6.8 phosphate buffer.

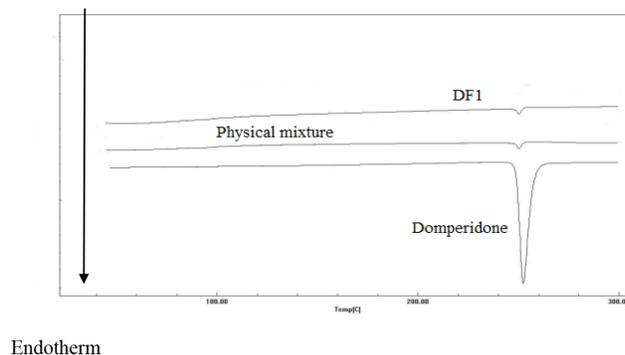


Figure 3: Differential scanning calorimetry (DSC) of Domperidone, Physical mixture and DF1.

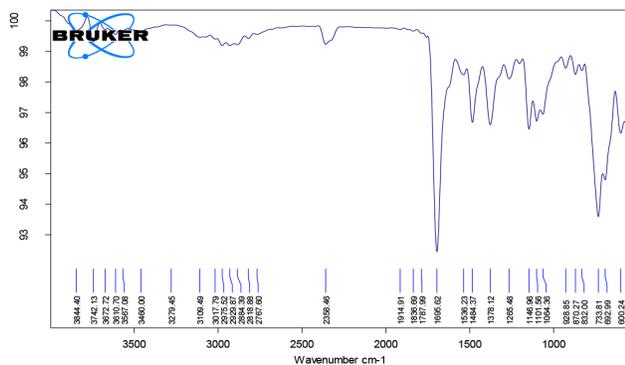


Figure 4: ATR-FTIR spectrum of Domperidone.

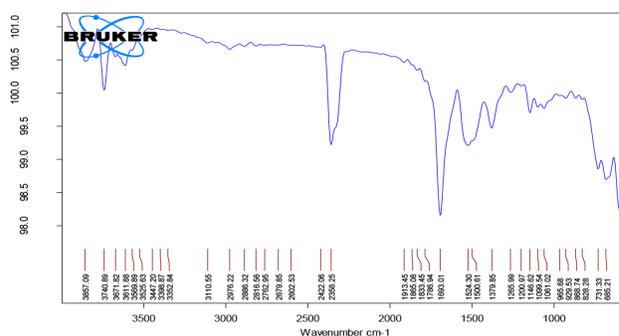


Figure 5: ATR-FTIR Spectroscopy of Domperidone Nanosponges Formulation.

Table 1: Preparation of Domperidone Loaded Nanosponges.

SI.No	Ingredients	DF1	DF2	DF3	DF4	DF5
1	Dispersed Phase					
	Domperidone(mg)	10	10	10	10	10
2	Ethyl cellulose(mg)	5	10	15	20	30
3	Ethanol(ml)	10	10	10	10	10
4	Dichloromethane(ml)	20	20	20	20	20
5	Aqueous Phase					
	PVA(mg)	2	2	2	2	2
6	Water(ml)	100	100	100	100	100

loaded into the sample holder. The result was given in Figure 4,5.

Nanosponges are Formulated by using an Emulsion Solvent Diffusion Process^[9]

Nanosponges can be made in various concentrations of ethyl cellulose and polyvinyl alcohol. The dispersed phase, which included ethyl cellulose, was dissolved in 20 mL dichloromethane, and the drug was dissolved in (10 mL) ethanol, and the two solutions were mixed together before being slowly added to a known quantity of polyvinyl alcohol in 100 mL of the aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for 2 hr in a magnetic stirrer. The nanosponges were collected via filtration and then dried in a 40°C oven for 24 hr. The dried nanosponges were maintained in vacuum desiccators to ensure that any leftover solvents were removed. The formulation detail is shown in Table 1.

Filling of Hard Gelatin Capsules^[10]

The empty capsules are put in a loading tray located above the bed. By opening the handle on the loading tray, the capsule bodies are fastened and the caps are separated, and the handle is then released by moving the lever. The powder tray, which is already in position over the bed, is filled with the weighed amount of medicine to be poured into the capsules. Distribute the powder uniformly in the capsule bodies using a powder

spreader. Collect any excess powder on the platform of the powder tray. Lower the pin plate and slide it down to press the powder into the bodies. Remove the powder tray and place the caps holding the tray in their place. Press the caps with the help of the plate with the rubber top and operate the lever to free the cap and body of the capsules. Place the filled capsules in a separate container after removing the loading tray.

Evaluation Studies for Nanosponges

Determination of Percentage Yield and Entrapment Efficiency^[11]

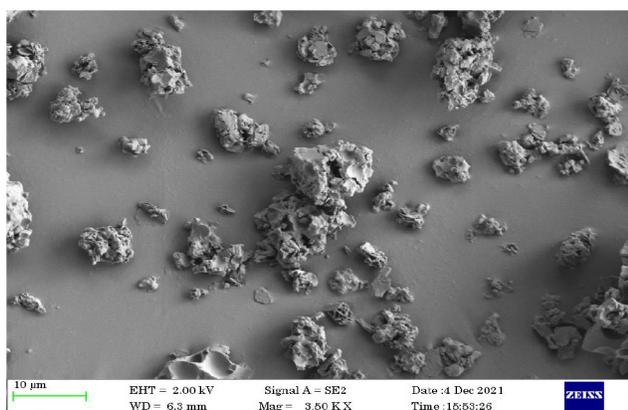
The domperidone-loaded nanosponges were weighed after drying. By sonicating 10 ml of phosphate buffer at pH 6.8 in a bath sonicator and filtering the solution, the yield was calculated as a percentage and the entrapment efficacy of nanosponges was evaluated. 1 mL of filtrate was generated in phosphate buffer up to 10 mL and spectrophotometrically measured at 285 nm (UV visible spectrophotometer, model UV-1601 PC, Shimadzu). The result was given in Table 2. The equation was used to compute the quantity of drug entrapped.

$$\text{Percentage yield} = \left(\frac{\text{Practical yield}}{\text{Theoretical yield}} \right) \times 100$$

$$\text{Entrapment efficiency} = \left(\frac{\text{Practical drug content}}{\text{Theoretical drug content}} \right) \times 100$$

Table 2: Percentage yield and Entrapment efficiency.

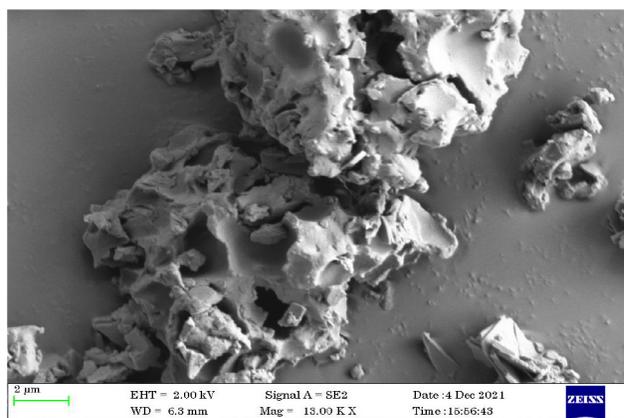
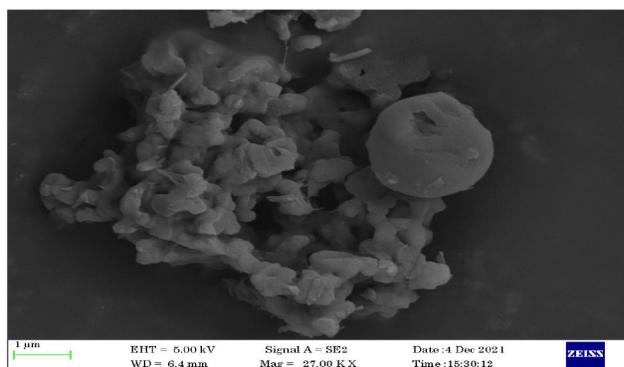
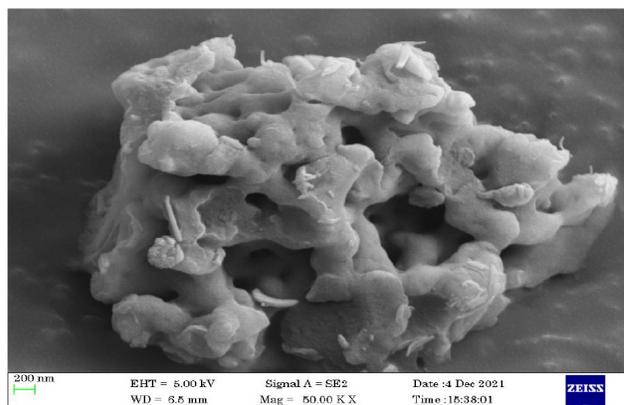
Formulation code	Percentage yield (%)	Entrapment Efficiency (%)
DF1	69.78	93.3
DF2	73.42	91.6
DF3	77.13	84.8
DF4	81.25	86.1
DF5	84.36	84.6

**Figure 6: The nanosponges view under 3.50 K X magnification (10 μm).****Scanning Electron Microscopy (SEM)^[12]**

After the nanosponges were created and dried correctly to decrease moisture content, the microscopic properties (shape and morphology) of the generated domperidone nanosponges were assessed by SEM analysis at various magnifications. Samples were coated with a thin gold coating using a sputter coater and apparatus running at 15kv acceleration voltage after becoming vacuum-sealed on a glass slide. The result was given in Figures 6, 7, 8, and 9.

In-vitro Release Studies^[13]

The USP XXII dissolution apparatus type II was used to determine the release of drugs from the formulated formulations in the gastrointestinal tract environment (basket type). At 37°C and 100 rpm, capsules containing the NS formulation are placed in a beaker containing 900 ml of dissolving medium. For cumulative release studies, a pH 6.8 phosphate buffer solution was used as the dissolving medium for twelve hours. Every hour, 10 ml aliquot samples were obtained and replaced with the same quantity of fresh media. Correction factors were used to compute the release profile for each aliquot. With the use of a UV spectrophotometer (Shimadzu UV 1601). The sample's absorbance was measured at 285 nm against a blank after appropriate dilution. To calculate the concentration of the drug, standard

**Figure 7: The nanosponges view under 13.00 K X magnification (2 μm).****Figure 8: The nanosponges view under 27.00 K X magnification (1 μm).****Figure 9: The nanosponges view under 50.00 K X magnification (200 nm).**

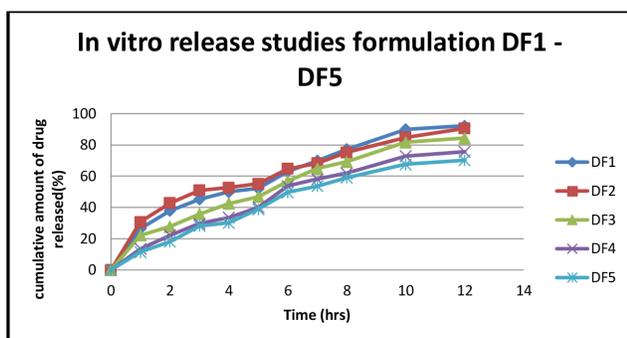
plots of the drug in buffer were used to estimate the percentage of drug release at each sample time. The result was given in Table 3, Figure 10.

Stability studies^[14]

The Domperidone-loaded Nanosponges capsule was tested for stability according to ICH guidelines, A three-

Table 3: In vitro drug release profile of Domperidone nanosponges.

Si. No	Time (hrs)	Cumulative percentage drug release (%)				
		DF1	DF2	DF3	DF4	DF5
1	0	0	0	0	0	0
2	1	26.53	30.69	22.24	13.58	11.45
3	2	37.94	42.73	27.71	22.19	18.16
4	3	45.18	50.96	35.68	29.71	28.18
5	4	50.42	52.74	42.46	33.53	30.13
6	5	52.14	55.16	46.89	40.55	38.91
7	6	63.17	64.73	56.86	53.83	49.75
8	7	69.87	68.33	64.92	58.12	53.67
9	8	77.18	75.24	69.17	61.92	59.11
10	10	89.96	84.79	81.75	72.86	67.56
11	12	92.28	90.56	84.37	75.64	70.19

**Figure 10: In vitro drug release profile of Domperidone nanosponges (DF1-DF5).**

month stability study was conducted for the optimised formulation at Accelerated temperature at 40°C and Room temperature at 25°C in this study. The result was given in Table 4.

RESULTS AND DISCUSSION

The goal of this study was to produce Nanosponges formulations of Domperidone in order to improve solubility and bioavailability. The importance of synthesising stable drug-loaded Nanosponges-based capsules, as well as studying the pre-formulation and evaluation factors, were investigated for this technique, and the findings are detailed below.

Organoleptic Properties

The organoleptic characteristics of the drug sample were investigated and the results are white in colour, bitter in taste and characteristic in odour since they are one of the initial criteria for compound identification and show conclusions that are comparable with literature review standards.

Table 4: Entrapment efficiency and in vitro release study of the optimized formulation.

Time	40°C±2°C/75% RH±5%RH Accelerated stability study	Room Temperature stability study	40°C±2°C/75% RH±5%RH Accelerated stability study	Room Temperature stability study
	Entrapment Efficiency (%)		In vitro release studies (%)	
Initial	93.3	93.3	95.52	95.52
15 days	92.8	93.3	95.35	95.51
30 days	92.5	93.3	94.89	95.46
45 days	92.2	93.1	94.65	95.38
60 days	91.8	92.9	94.36	95.24
90 days	91.6	92.7	94.11	95.17

UV-Visible Spectrophotometer

Using a double beam UV Spectrophotometer, the stock solution with a concentration of 100 g/mL was shown in the range between 200-400nm for λ_{max} .

ATR-FTIR (drug interaction studies)

The drug interaction studies were analysed using ATR-FTIR, and these excipients were combined in varied ratios with domperidone depending on the functional category. The peaks obtained in the spectra in DOM-NS1 formulation are compared with the peaks of the Domperidone spectrum. This denotes that the drug is compatible with the formulation components.

Stability Studies

A three-month stability study was conducted for the optimised formulation at Accelerated temperature at 40°C and Room temperature at 25°C. The results revealed that the entrapment efficiency and in vitro release tests had a mildly significant difference.

DISCUSSION^[15-17]

Organoleptic Properties

The preformulation studies were carried out and the results were found to be satisfactory. The micrometric characteristics are within the pharmacopeial specifications.

UV-Visible Spectrophotometer

It was determined that the drug passed the preliminary identification test on the basis of the preliminary identification test. It was also determined that the drug had a maximum wavelength of 285 nm after scanning it in phosphate buffer pH 6.8 dissolving medium. The

drug obeys Beer-Lamberts law in the concentration range of 2,4,6,8, and 10 g/ml for pH 6.8 buffer in the media, according to the standard calibration curve of Domperidone in phosphate buffer pH 6.8 dissolving medium. Here, UV spectroscopic studies show the maximum peak observed at 285nm range and good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Solid characterization (DSC-Differential scanning calorimetry)

Differential scanning calorimetry was used to evaluate the drug and excipient compatibility in the NS formulation (DSC). The pure drug, DF1, and physical combinations of polymers and drugs were examined using DSC thermograms. DOM's DSC thermogram exhibits a prominent endothermic peak at 248–252°C, which corresponds to its melting temperature.

ATR-FTIR (drug interaction studies)

The drug interaction studies were analysed using ATR-FTIR, and these excipients were combined in varied ratios with domperidone depending on the functional category. The peaks obtained in the spectra in DOM-NS1 formulation are compared with the peaks of Domperidone spectrum. This denotes that the drug is compatible with the formulation components.

Evaluations for Prepared Nanosponge Capsules

Determination of Percentage Yield and Entrapment efficiency

The nanosponges formulations contain a different ratio of polymer (DF1 to DF5) that shows an entrapment efficiency and percentage yield ranging from 84.6 to 93.3% and 69.78% to 84.36% respectively. From this study formulation, DF1 showed percentage yield and entrapment efficiency values of 69.78% and 93.3% respectively which shows an optimal range than other formulations.

Scanning Electron Microscopy

The drug-loaded nanosponges prepared were evaluated for percent yield (DF1- 69.78% - DF5-84.36%). Here SEM study for DF1 formulation, SEM images are visible in 3.50K X, 13.00 K X, 27.00 K X, 50.00 K X. The nanosponge was porous, with a smooth surface morphology and a spherical form, according to SEM images. The nanosponge shell was discovered to be smooth porous due to solvent evaporation, with a sparkling smooth outer surface and a porous interior surface. The above images demonstrate the nanosponges' spongy and porous character. The

existence of pores was caused by the impression of dichloromethane diffusion.

In-vitro Drug Release Studies

The Dissolution method was used to evaluate the *in-vitro* drug release of the prepared Domperidone nanosponges. The amount of drug released at various time intervals was measured. The *in-vitro* drug release studies of domperidone from nanosponges capsules were conducted using the dissolution method in a pH 6.8 phosphate buffer. *In vitro* release was determined to be conventional in pH 6.8 phosphate buffer based on the results. In a pH 6.8 phosphate buffer, drug release from DF1, DF2, DF3, DF4, and DF5 formulations was 95.52 %, 90.56 %, 84.37 %, 75.64 %, and 70.19 %, respectively, from formulations containing ethyl cellulose.

Stability Studies

A three-month stability study was conducted for the optimised formulation at Accelerated temperature at 40°C and Room temperature at 25°C . The results revealed that the entrapment efficiency and *in vitro* release tests had a mildly significant difference. The appearance of nanosponges formulation DF1 entrapment efficiency was found to be 91.6% at accelerated stability study and *in vitro* drug release studies DF1 nanosponges capsule was found to be 94.11% at accelerated stability study. As a result, was revealed to be the formulation, and all of the reports are within the accelerated stability studies specification ranges and follow it.

SUMMARY AND CONCLUSION

The current study used a dispersion phase and aqueous phase to manufacture and analyse Nanosponges formulations for Domperidone, and all nanosponges were put in empty hard gelatine capsules. It is insoluble in water and undergoes first-pass metabolism. This occurred as an attempt was made to create drug-loaded nanosponges in order to improve drug bioavailability while giving in controlled release. The goal of this study was to create a Nanosponges formulation of domperidone for oral capsule bioavailability enhancement. Based on the results of various studies, it is concluded that the Domperidone loaded nanosponge capsule formulation especially DF1 optimized formulation exhibited improvised release behaviour, which would help in minimizing the dose frequency, improvise the patient compliance, and promising effective formulation in the treatment of anticancer therapy and provide an effective modified formulation for administration.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATR-FTIR: Attenuated Total Reflectance- Fourier Transform Infrared; **DF:** Domperidone Formulation; **DSC:** Differential Scanning Calorimetry; **DOM:** Domperidone; **Hrs:** Hours; **Ml:** Milli Litter; **NS:** Nanosponges; **RH:** Relative humidity; **RPM:** Rotations Per Minute; **UV:** Ultra Violet.

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