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Original Article

IN VITRO SOLUBILITY ENHANCEMENT OF ONDANSETRON HCL BY PREPARATION OF ONDANSETRON-POROUS SILICA COMPOSITES

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ABSTRACT

Objective: To enhance the solubility of Ondansetron (OND), a wet impregnation approach utilizing porous silica was explored to produce OND-Porous silica composite, and then UV spectrophotometric protocols were employed to evaluate the equilibrium solubility and the loading capacity of the obtained preparation.

Methods: Ondansetron and porous silica composites were synthesized via the wet impregnation method and subsequently subjected to evaluation. for their surface morphology and roughness of was carried out using Scanning Electron Microscope (SEM) and Atomic Force Microscopy (AFM), along with X-Ray defrractometry (XRD), Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and nitrogen adsorption and desorption experiments.

Results: The solubility profile of OND was maximized through the development of OS3 composite formula which was 3-4 times higher than the former. Furthermore, the TGA and UV evaluation tests of the enhanced OS3 formula revealed an improvement in the loading capacity of the drug (45-48%).

To confirm the successful introduction of OND within the porous of silica structure, XRD analysis exploited, showing a significant alteration in OND amorphousness. The XRD data confirmed a notable reduction in silica surface area (from 68.239 m2/g to 26.226 m2/g), pore width (from 46.13 nm to 1.21 nm), and porous volume (from 1.2229 cm3/g to 0.178 cm3/g) following the loading of drug on silica.

Conclusion: It was concluded that this approach was able to introduce a promised method for enhancing the solubility of OND to produce a powder with physical properties, enable to establish further processing steps like tablet compression or even transdermal patch fabrication.

Keywords: OND, Porous silica, OS3, Composites, CINV

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INTRODUCTION

In the treatment of cancer patients, avoiding and controlling Chemotherapy-Induced Nausea and Vomiting (CINV) is essential. The most serious, distressing, and reciprocal side effect of cancer management is CINV. It affected life quality significantly and occurred in around 80% of populations populations [1]. Numerous serotonin receptors inhibitors has been tested to alleviate CINV [2] A potent antiemetic drug prescribed for the management of CINV, ondansetron HCl (OND) is a 5HT3 antagonist. Due to 1ST pass metabolism, it only has an oral bioavailability of 60–70% and a very short half-life of 3-5 h [2]. Owing to its reduced water solubility and increased permeability, OND is classified as a BCS II medication in the Biopharmaceutical Categorization System (BCS) [3]. Ondansetron has been effectively administered transdermally trans dermally via a transfersomal gel formulation [4].

The bioavailability of this class of medications has been added to the use of numerous strategies, including particle size reduction, salt creation, solubilization, fatty-based drug delivery systems, and Solid Dispersion (SD) [5]. Enhancing the bioavailability of drugs by formulating a topical drug delivery has been experienced [6]. Another way is tantamount to inject low water-soluble API into a porous carrier, which aids API diffusion when the carrier disintegrates. Numerous substances, including metallic oxides and porous silica, have been used for this purpose. Owing to its capacity to enhance GIT absorption and dissolution, medication assimilation into porous silica is a common strategy in drug delivery systems [7]. Since assimilation of medicines into porous silica can increase GIT absorption and dissolution, it is a joint strategy in drug delivery systems [8]. Additionally, the loading of medicines into porous composite was used only for the stabilization and oral delivery of drugs in amorphous form [9]. Porous composite has increased unambiguous surface areas, which results in an elevated surface free energy (SFE). As a result, the system can advance with a lower free energy level thanks to the pharmaceuticals' surface absorption on the porous composite [10]. This form of stability resulted from a decreased value of the device's Gibbs free energy due to the adsorption and size limitation effects of silica on the drug molecule's crystallization property [11]. Therefore, we envisioned that loading OND on porous silica could lead to an improvement of drug PK and its bioavailability. This study aimed to introduce a composite of OND-Porous silica with enhanced water solubility characteristics.

MATERIALS AND METHODS

Materials

Porous silica 20–30 nm, and OND HCL were acquired from Merck Specialties in India, while methanol was acquired from Dr. Reddy's Laboratories in India. The study utilized double-distilled water (DDW). All the substances and components mentioned in this study were analytical-graded chemicals.

Fabrication of OND-charged porous silica composites

The OND loading into porous silicate composite was performed using wet impregnation method and as described in literature [12].

Briefly, the OND was dissolved in 50 ml methanol in 100 ml burets and added gradually to a beaker of porous silica in water in ratios of 1:1, 2:1, 3:1, and 4:1, respectively, while being stirred in a magnetic stirrer at 250 rpm for six hours. These mixtures are centrifuged for ten minutes at 3000 rpm to obtain OND-encumbered composites, which are then desiccated for the entire night at room temperature to remove any liquid remnants.

Drug loading capacity

In order to calculate the OND load of charged composites, 5 mg of the sample was dissolved in 5 ml of methanol, vortexes for 30 min, and then centrifuged at 3000 rpm for up to 15 min to separate the Si traces. The percentages of OND were calculated in triplicate by using

UV spectroscopy to examine the unsinkable component at 310 nm after the appropriate methanol attenuations. The following method was utilized to achieve the Drug Loading Capacity (DLC) [13].

$$\% \text{ Drug loading } = \text{Amount of drug in formulation} \div \text{Amount of formulation taken } \times 100$$

Saturation solubility test

Phosphate buffer solutions with a pH of 6.8 used to test the saturation solubility of OND and loaded composite. In triplicate, additional sample amounts added to a 25 ml conical flask containing 5 ml of buffer solution. These mixtures were then reserved for 24 h of trembling in an orbital shaker. They then centrifuged for 10 min at 4000 rpm. U. V. Visible spectroscopy at 310 nm used to determine the amount of OND in the supernatant filtrate after appropriate attenuations with buffer solutions.

Morphological characterization

AFM used to study the external morphological characteristics of pure OND, porous silica, and the optimized formula. An SPM-9600 (SHIMADZU, Kyoto, Japan) and a PPP-SEIHR-20 (NANOSENSORS, Neuchatel, Switzerland) cantilever with a length of 225 m, a force constant of 5-37 N m-1, and a resonance frequency of 130 kHz were used to conduct the AFM observations. Utilizing % (MERA3 TESCAN Czech Republic) for OND, porous silica, and OS3, FESEM study was carried out to look at the shape and distribution of the drug in the composites.

X-ray diffraction study (XRD)

The incidence of crystallinity and the amorphous environment of the trials identified using the X. R. D. test. Using an X-ray diffractometer (XPERT, PAN alytical; Netherlands) equipped with a Cu K object, X-ray diffractograms of OND, porous silica, loaded composites, and the physical mixture of OND and porous silica taken. Data were collected with a step size of 0.013° and a dwell time of 23.97 s per step in the range of 3 to 50° (angle 2).

Differential scanning calorimetry (DSC)

With the help of differential scanning calorimetry (DSC 25, TA, USA), the sample's thermal analysis was conducted. An empty aluminum pan and indium employed to calibrate the instrument. An aluminum zero pan that was the subject with a special cover and crimped shut held precisely balanced doses of 5–10 mg of OND, porous silica-loaded composites (optimized OS3 Composites), and a physical mixture of OND and porous silica. Then, with a nitrogen pressure of 50 ml/min, heat the model from 25 to 250 °C at a rate of 10 °C/min.

Thermogravimetric analysis (TGA)

The thermal performance of composites containing OND, porous silica, a sensible mixture of OND and porous silica, and OND-loaded composites evaluated using TGA. By using the T. G. A/D. S. C device (Toledo, USA), the temperature maintained at a rate of 10 °C/min and the nitrogen pressure maintained at 40 ml/min.

At 196 °C, the nitrogen adsorption-desorption isotherm was used to examine the pore characteristics of porous silica and an optimized OND-charged composite by analyzing the surface area and pore size (Autosorb-1, Quantachrome, Japan). Before analysis, the weighed samples were degassed to remove contaminants and moisture. Porous silica and an improved composite exposed for 24 h to 150 degrees Celsius. Using the Brunauer-Emmett-Teller (BET) equation and the Barrett-Joyner-Halenda (BJH) technique from the adsorption divisions of the isotherms, the surface area and the pore size were calculated.

Statistical analysis

The mean and SEM were utilized to express each result. Excel's one-way ANOVA used to examine the data from all groups. The threshold for statistical significance in all tests was $p \geq 0.05$.

RESULTS AND DISCUSSION

Drug loading capacity

Table 1 displays the results of a UV-visible spectrophotometer calculation of the amount of OND loading in composites.

The main objective of this experiment was to ensure a high loading charge of OND in composites, as was demonstrated. In a 2:1 drug: silica ratio, the highest DLC, or 45.34% w/w observed. It was noted that practical drug loading increases with drug concentration up until percentages of 3:1 and 4:1, where there is a plateau caused by the pores becoming saturated with drug molecules.

Table 1: OND: SILICA loading capacity for prepared composites

Code	Drug-silca ratio	DLC%*
OS	1:1	20.54±1.02
OS1	1:2	17.53±0.22
OS2	1:3	19.72±2.1
OS3	2:1	45.34±0.76
OS4	3:1	23.94±1.1
OS5	4:1	24.42±0.65

n=3, all data were represented as mean±SD

Saturation solubility test

When drugs are added to porous silica, the surface area increases, potentially increasing saturation solubility [14]. When compared to the saturation solubility of pure OND, there was a highly significant increase (p 0.01) in the saturation solubility of various formulations (fig. 1). According to the Ostwald-Friendlich equation, the saturation solubility was discovered to increase inversely with particle size.

$$\text{Log CsC} = 2sV/2.303RT\ r_1r$$

where

*C*s = solubility, *C* = solubility of the solid consisting of large particles, s = interfacial tension substance, *V* = molar volume of the particle material, *R* = gas constant, *T* = absolute temperature, r_1 = density of the solid, and *r* = radius

Morphology study

AFM study

The various surface images for OND (a), porous silica (b), and optimized composite OS3 (c) and (d) are shown in fig. 2. For precise resolution of the sample surfaces, only images with the smallest cross-sectional dimensions (1.99 mm to 4.92 mm) chosen. Image (b) clearly demonstrates the porous silica pores that had vanished in the images of the optimized formula OS3 (c and d), indicating that these pores had been filled with drug molecules and demonstrating the loading of OND to composites.

SEM study

Fig. 4 shows various images at various magnifications that were used to highlight the homogeneity in the disposition of OND particles and the porous surface of the silica. Image (a) of fig. 3 represents OND particles in a field of 10 m, showing a variety of sizes, shapes, and crystallinity.

The porous and traditional hexagonal misconstruction silica is shown in image (b), and image (c) is a cross sectional view inside the branched and multichannel pore. It has been found that these two types of silica have distinct long channels next to the pore surface.

In addition, images (d, e, and f) are all photomicrographs of OND-loaded composites that clearly show how their microstructure changed in response to the booming drug loading that was observed as a result clusters on the pore's orifice and inside its channels.

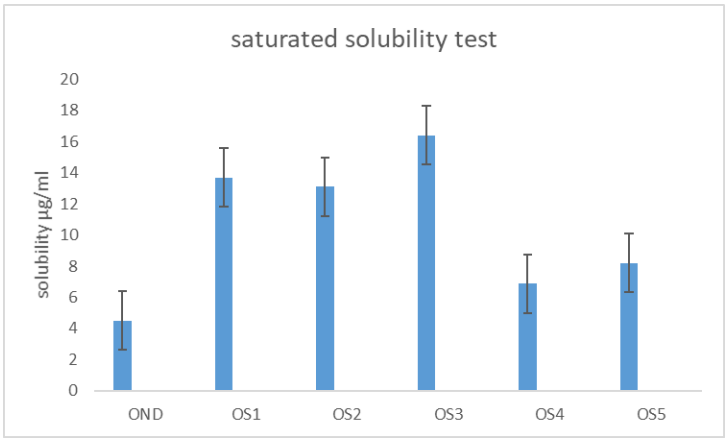


Fig. 1: Saturated solubility test of different composites and pure OND, n=3, All data were represented as mean±SD (Adapted by mind the graph https://mindthegraph.com/)

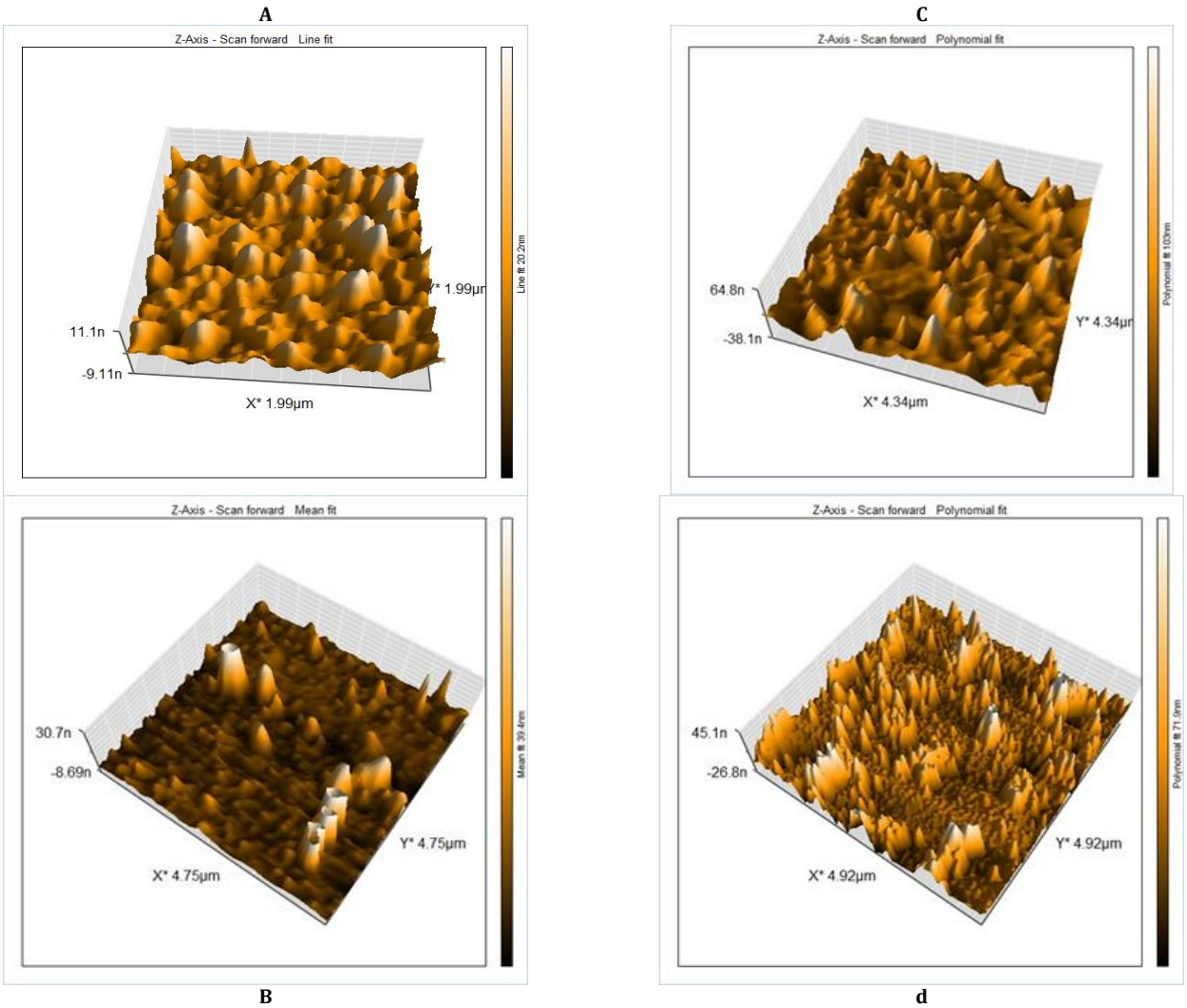


Fig. 2: AFM images for the surface of (a) OND, (b) Porous silica, (c and d) OS3-optimized composite

Powder X-ray differaction (XRD)

Fig. 4 shows in the XRD diffraction images of OND, porous silica powder, a physical amalgam of OND and porous silica, and OND-loaded composites (OS3).

The OND's X-ray diffraction pattern (fig. 4a) revealed a few distinct peaks at 24° and 31° as well as numerous minor peaks that indicated the material's crystallinity. Additionally, it agreed with the findings of earlier research [15].

The powder mixture of OND and porous silica (fig. 4d) also displays crystal peaks in the diffractogram because of the crystalline nature of OND. The amorphous nature of loaded OND is evidenced by the fact that while the porous silica (fig. 4c) showed a distinct peak at almost 25°, the loaded composite OS3 (fig. 4b) did not. Therefore, an

XRD analysis revealed that after being in charge into silica pores in the composite structure, the crystalline OND changed into an amorphous form.

Celecoxib [16] and telmisartan [17] showed similar results in the amorphous formation of a drug after integration into mesoporous silica pores. However, in all of the denoted cases, the sharpness of the peaks in the XRD diffractogram of the drug-charged mesoporous carriers had vanished that was explained by the decrease in OND's crystallinity following its adsorption on the mesoporous materials.

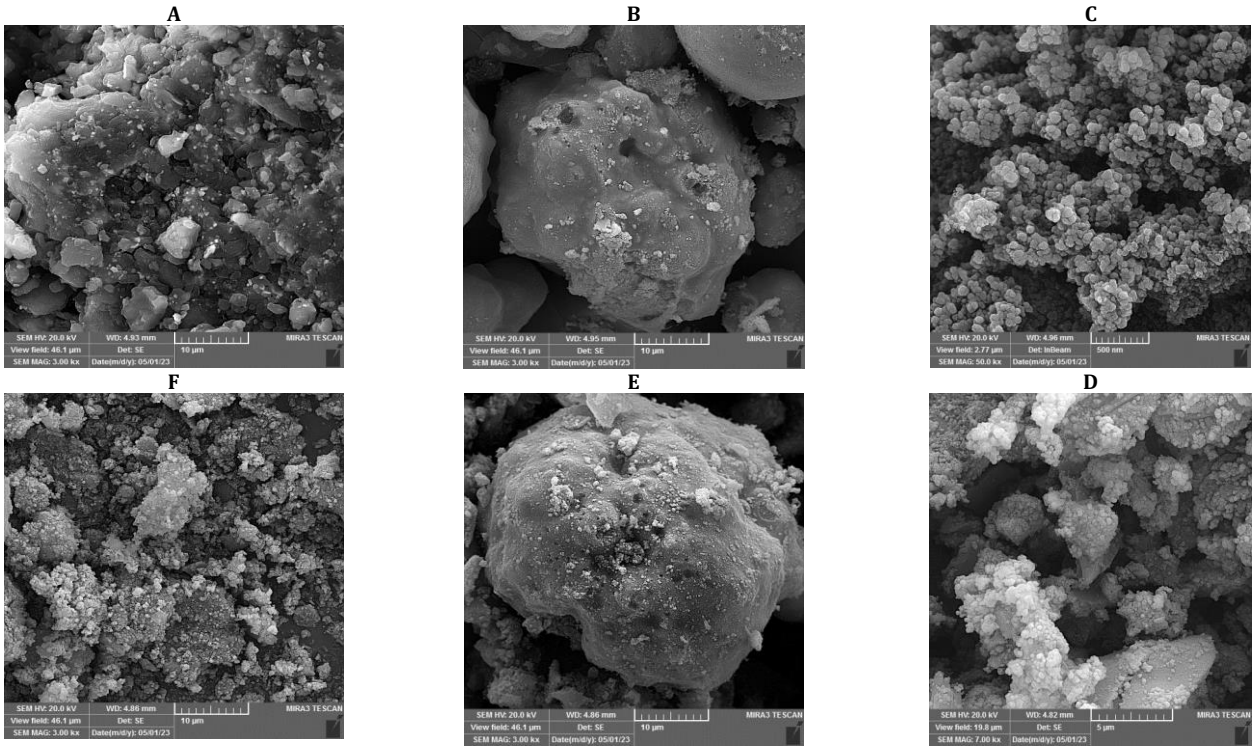


Fig. 3: SEM photographs As taken by MIRA3 TESCAN. (a) OND, (band c) porous silica microstructure, (d, e and f) OND loaded composites in 5, 10 µm magnification field

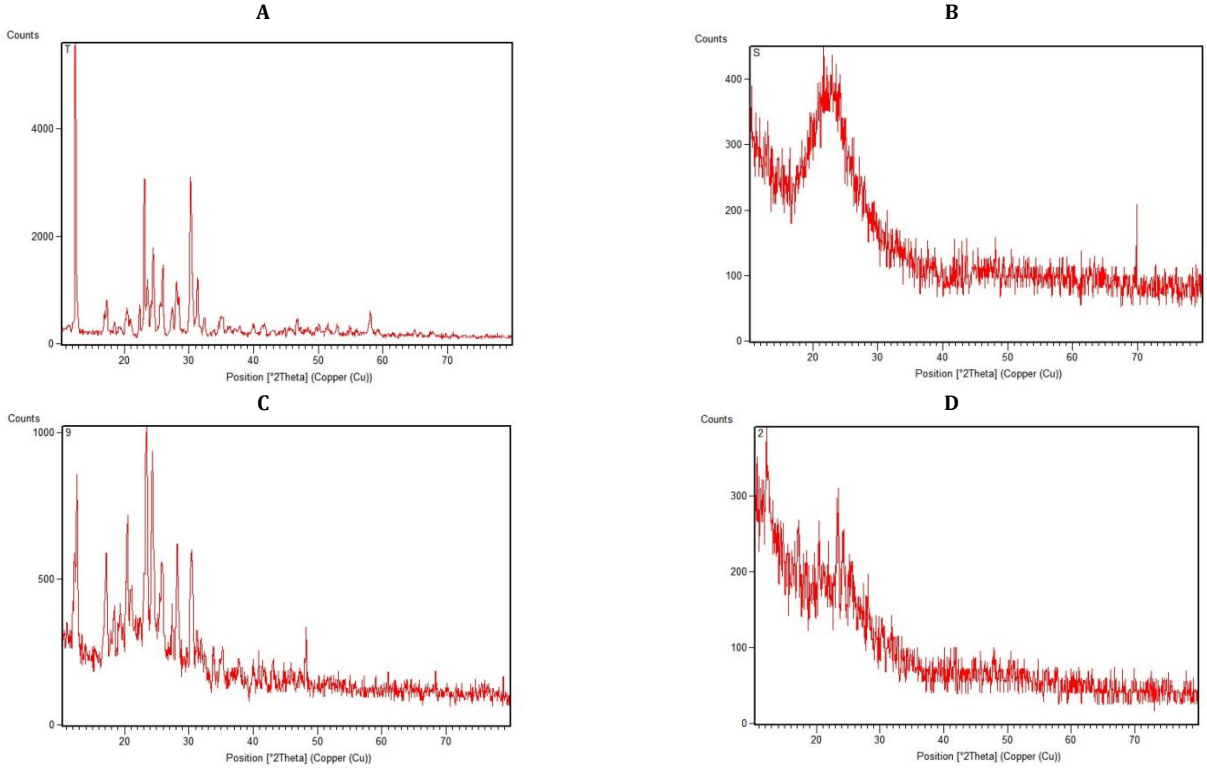


Fig. 4: XRD defractograms of (a) Pure OND, (b) Porous silica, (c) Physical mixture of OND and porous silica, (d) OND loaded composites OS[3]

Differential scanning calorimetry (DSC)

Fig. 5 displays the DSC thermograms of pure OND, porous silica, a physical blend of OND and porous silica, and OND-loaded composites OS3. Investigating the crystalline and amorphization forms is made easier by these thermograms.

The distinct endothermic melting peak of OND was observed at 178 °C, which is similar to the melting point of OND, as shown in (fig. 5a). Because OND was integrated into the pores of silica in a non-crystalline state, a very low-intensity endothermic peak was also seen at 180 °C in OND loaded composites in fig. 5d.

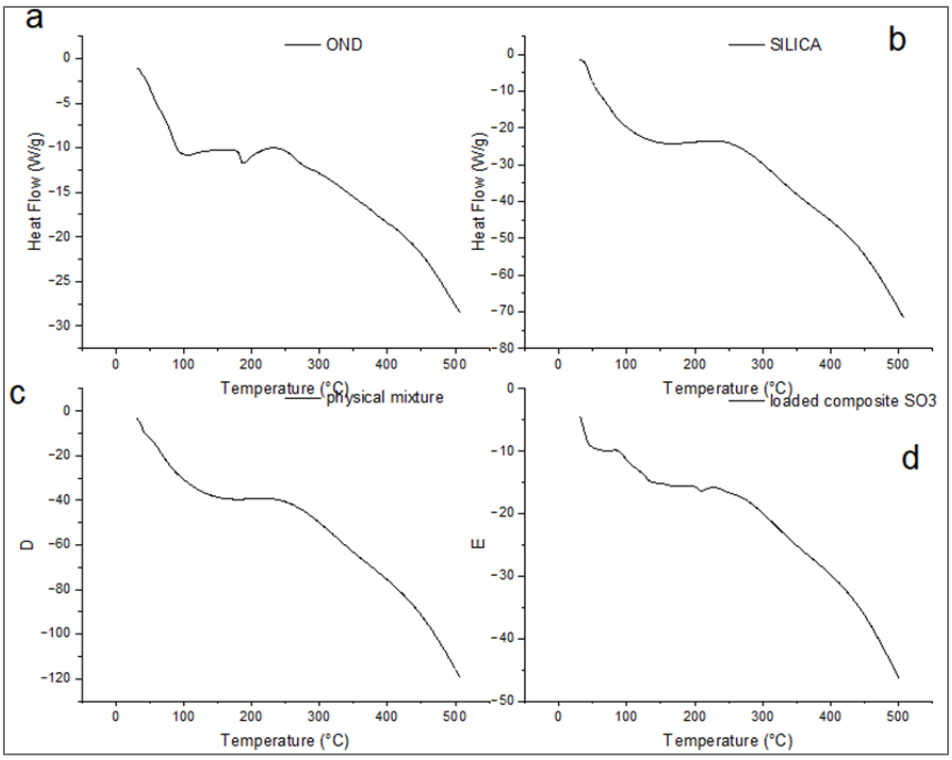


Fig. 5: DSC Thermogram of A OND, B Silica, C OND –silica physical mixture, and OND loaded composites OS3 (Adapted by mind the graph https://mindthegraph.com/)

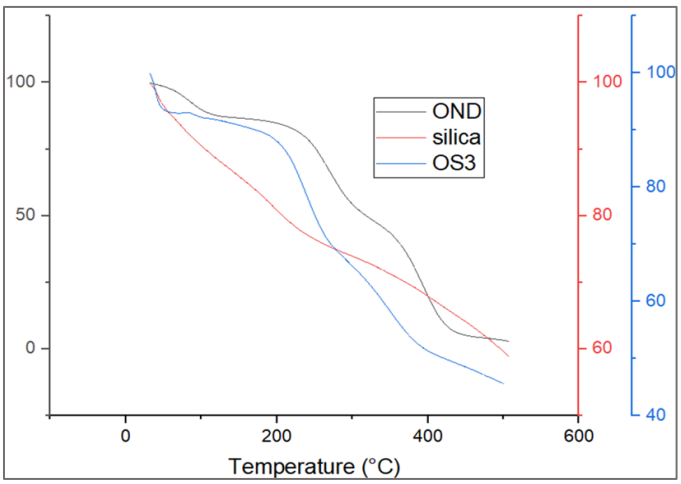


Fig. 6: TGA Of OND (black line), Porous Silica (red line), and OND Loaded Composites OS3 (blue line) (Adapted by mind the graph https://mindthegraph.com/)

Thermagravemetric analysis (TGA)

As seen in fig. 6, the TGA thermograms of OND, porous silica, a physical blend of OND and porous silica, and OND-loaded composites OS3 are all displayed. TGA can be used to identify how much OND is loaded overall into the porous silica.

A temperature-dependent weight loss can be seen noticed as a result because of API desorbed and then decomposed during the TGA measurement [18].

More variables must be taken into consideration than just the drug's total content in the sample when measuring the mesopore-loaded drug portion in porous ingredients [19].

As shown in fig. 6, the percentage of OND loading in porous silica was calculated from the weight loss between 100 and 500 °C to the total weight at the beginning.

Additionally, all samples below showed a 10–20% weight loss below 100 °C, which could be attributed to the pores' evaporation of moisture

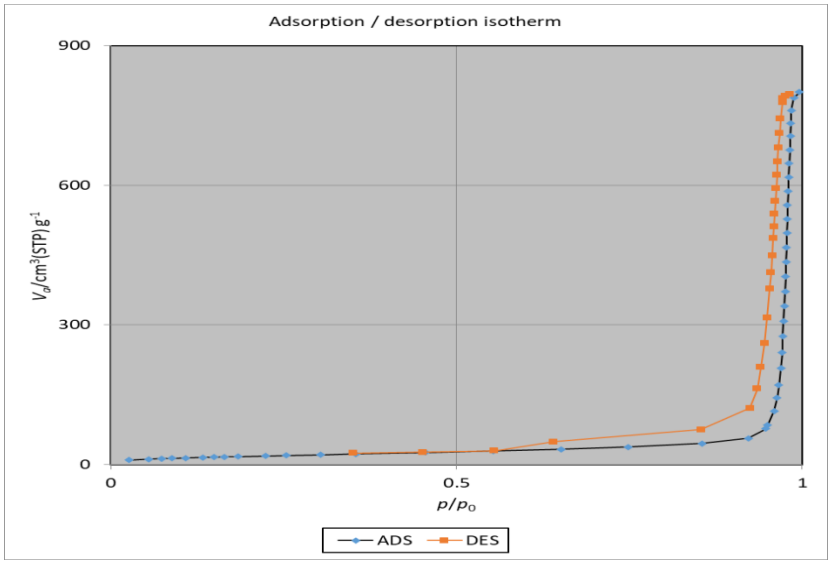
once the temperature reaches 100 °C in agreement with a previous work [20]. Nearly more of the drug was degraded at about 400 °C, where a sudden weight reduction of OND was observed. The weight loss of the OND-loaded composites OS3 was found to be 48% w/w, which is noticeably in agreement with the UV spectroscopy-determined DLC of 45.34% w/w. A similar tendency for dramatic weight loss in TGA was noted for MSN that contained ketoprofen [21].

Nitrogen adsorption isotherm

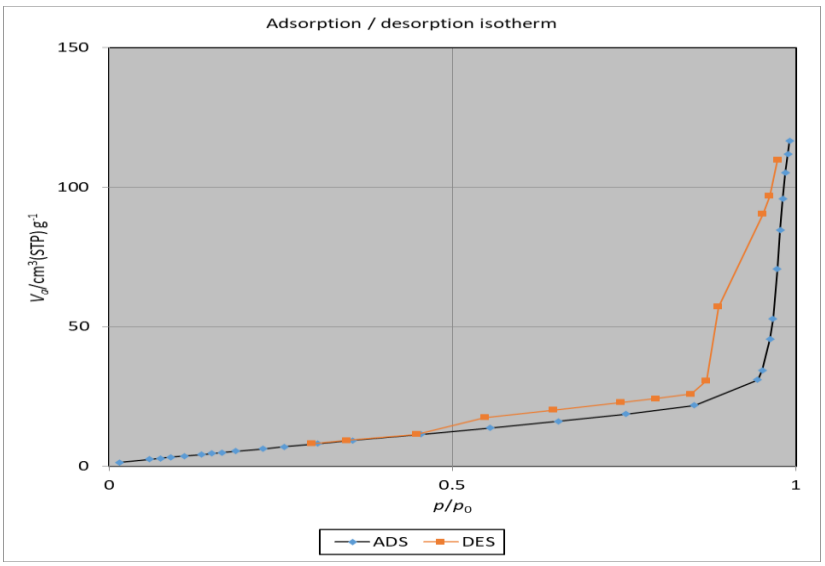
Fig. 7 displays the porous silica and loaded composite OS3 nitrogen adsorption isotherms. According to IUPAC classification [22], the nitrogen adsorption/desorption isotherms of porous silica and OS3 (fig. 7A, B) showed a typical type III isotherm.

Table 2 displays the values for the BET-specific surface area (SBET), the total pore volume (Vt), and the peak (Area) of the BJH pore diameter (rp). Higher values for porous silica indicated that more drug molecules could be loaded onto it as a host, which complied with previous study [23].

Additionally, table 2 values showed that SBET, Vt, and rp, peak (Area) for porous silica were reduced in the OS3 composites after OND loading compared with porous silica before loading the drug; such decline may have been brought on by the charging of OND within the silica pores is in agreement with outcomes of a reduction in SBET, Vt, and rp, peak (Area) were previously reported for felodipine-loaded MSN [24].



A



B

Fig. 7: Nitrogen adsorption/desorption isotherm of (A) Porous silica and (B) Loaded composites OS[3]

Table 2: Characterization of porous silica before and after OND loading

Sample name	As, BET [m2 g-1]	Total pore volume Vt [cm3 g-1]	$r_{p,peak}$(*Area*) nm
Porous silica	68.239±0.003	1.2229±0.052	46.13±1.02
OS3 composite	26.226±0.02	0.1783±0.003	1.21±0.07

n=3, All data were represented as mean±SD

CONCLUSION

It can concluded that incorporation of OND to porous silica composite using a wet impregnation method leading to enhance its *in vitro* solubility by integration of OND into the porous architecture of silica in the amorphous state.

That can be proved by the over mentioned decrease in pore surface area, pore volume, and pore diameter of the porous silica before and after loading of OND, which indicate that OND has been incorporated inside the pores of silica particles which renders the drug's solubility increased by more than three to four times in the selected optimized formula OS3.

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AUTHORS CONTRIBUTIONS

Qasim Allawi Bader is the principle investigator, conducted experiments, measurements, writing, and funding the project, Wedad K. Ali conceived the concept supervised the project through their academic advisory., Fouad A. A. AL-Saady contribute through revision and academic corrections

CONFLICTS OF INTERESTS

The authors declare that they have no competing interests.

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