NEW DRUG DELIVERY SYSTEM WITH CATECHIN LOADED IN MESOPOROUS SILICA NANOPARTICLES

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Catechin is a polyphenol found in high quantities in green tea and its properties make it have a high potential to be used in controlled release systems with important activity on the human body. Mesoporous systems loaded with catechin have the potential to be used in drug delivery systems with different biological applications imposed by the support itself (suitable for bone-related application) or by the nature and properties of the loaded biological active agents. In this study, catechin was loaded into mesoporous silica: MCM-41 and MCM-48. The obtained mesoporous systems were characterized from a morphological and structural point of view and the release of catechin from mesoporous silica in two simulated biological fluids was monitored.

Keywords: catechin, mesoporous silica, drug delivery system, release study, simulated gastric fluid, simulated intestinal fluid.

1. Introduction

Controlled delivery systems for natural substances or extracts, based on loaded nanoparticles like ZnO [1], Fe_3O_4 [2] or SiO_2 [3] are attracting a great interest due to their rich tailoring properties [4].

Catechins belong to the group of flavonoids, an important class of polyphenols known for their strong antioxidant [5], anti-inflammatory and chemo-preventive activity [6]. Green tea represents one of the most consumed beverages worldwide and

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has a predominant composition of catechins (25-35% dry weight) which provides a strong antioxidant activity [7, 8]. Due to its structure, it can form strong hydrogen bonds with the support and thus can be loaded into transport systems, so that it can be used in different drug delivery systems, being non-toxic [9, 10].

Mesoporous silica materials are of great scientific interest due to their adjustable pore size, high surface area, surface functionalization, chemical stability and pore nature [11]. Silica pores allow it to be loaded with various active substances, drugs or natural extracts to be functionalized or used as controlled release systems. Mesoporous silica can be synthesized in different ways and different structures with variable pore sizes and arrangements can be obtained [12]. The most known structures at the moment are: MCM (Mobile Composition of Matter), SBA (Santa Barbara Amorphous), TUD (Technische Universiteit Delft), HMS (Hollow Mesoporous Silica) or MCF (Meso Cellular Form) [13, 14]. MCM-41 and MCM-48 are part of the MCM family and are two types of mesoporous silica with different pore arrangement. MCM-41 has a hexagonal structure with a uniaxial pore arrangement, and MCM-48 has a cubic structure and a three-dimensional pore arrangement [15]. The properties of mesoporous silica (high surface area, tuned pore size, high specific pore volume, tunable surface functionalization capacity) allow it to be used as a carrier in drug delivery systems [16].

The present study followed the loading of the biologically active substance, catechin, in two types of mesoporous silica from the MCM class, MCM-41 and MCM-48. Catechin were loaded into mesoporous silica, and the two materials obtained, MCM-41@CAT and MCM-48@CAT, were characterized from a morphological and structural point of view to demonstrate the efficient loading of catechin inside the pores. In this experimental study, an in vitro release study was performed by simulating two biological fluids with different pH, simulated gastric fluid and simulated intestinal fluid. The catechin release studies from the mesoporous silica systems were carried out over a period of 5h, and the samples were collected at different time intervals and analyzed.

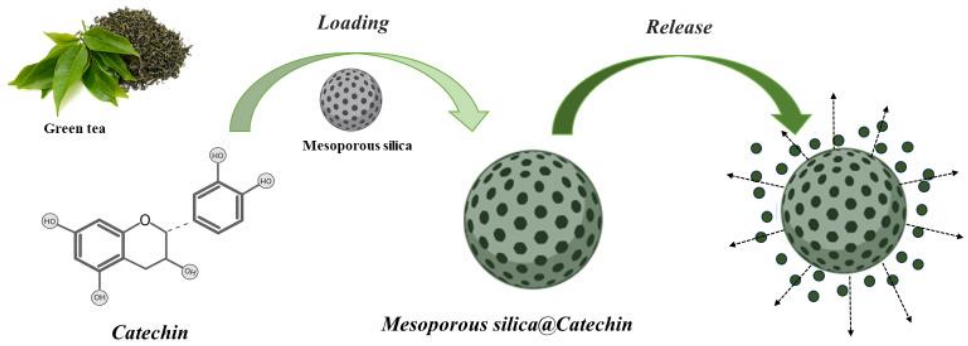


Fig. 1. Synthesis of systems from mesoporous silica loaded with catechin

2. Materials and methods

2.1 ***Materials***

Catechin (CAT, ≥98%) was purchased from Carl Roth and was used for the loading into the mesoporous silicas. Tetraethyl orthosilicate (TEOS), ammonia (NH_3), acetone and ethyl alcohol were produced by Sigma Aldrich while cetyltrimethylammonium bromide (CTAB) by Merck.

The following substances were used for the release study: sodium chloride (NaCl), acetonitrile (HPLC grade) from Sigma Aldrich; sodium hydroxide (NaOH, 1N) and hydrochloric acid (HCl, 2N) from S.C. Silal Trading SRL; sodium dodecyl sulphate (SDS) and potassium dihydrogen phosphate (KH_2PO_4, ≥98%) from Roth.

2.2 ***Preparation of the mesoporous silicas and loading with catechin***

The obtaining and characterization of the two types of mesoporous silica MCM-41 and MCM-48 were described in the previous article [17]. The materials were loaded with catechin by solubilizing 400 mg of catechin in 4 mL of acetone. The adsorption of the catechin solution (saturated solution) in one gram of mesoporous material was done by adsorption under vacuum at room temperature.

2.3 ***Characterization methods***

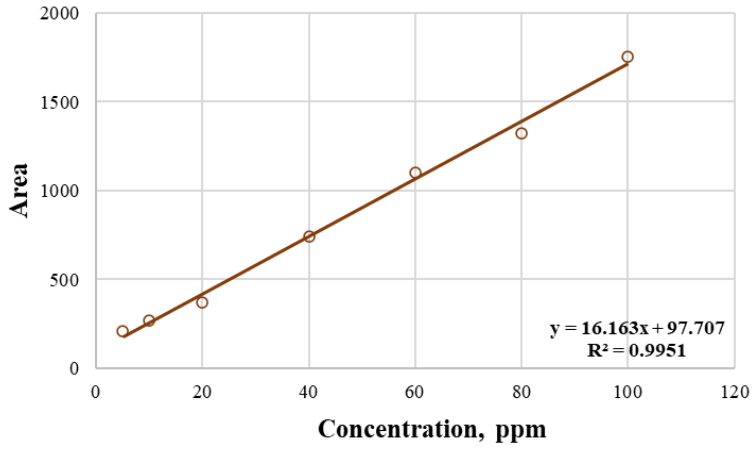
The diffractograms of the mesoporous systems were recorded on Panalytical X'Pert Pro MPD equipment, with Cu-Kα radiation. Scanning electron microscopy images were recorded on QUANTA INSPECT F electron microscope equipped with a field emission gun and an energy dispersive (EDS) detector. The BET analysis of the porous materials and the recording of the adsorption/desorption curves were performed using the 77K Micrometrics Gemini V equipment. To characterize the structure of the materials, FTIR spectra were recorded on Thermo IN50 MX equipment and an FTIR microscope operated in reflection mode was used. Thermogravimetric analyses were recorded using a Netzsch 449C STA Jupiter instrument (Mt. Juliet, TN, USA) at room temperature at 900^{o}C, in an alumina crucible at a heating rate of 10^{o}C/min in dry air (20 mL/min).

2.4 ***Release study***

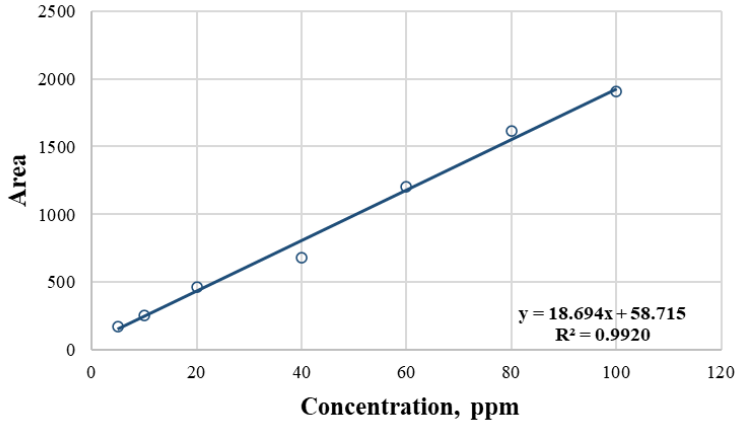
The release study was done following the release of catechin from the mesoporous silica support in two types of simulated biological fluids. Simulated gastric fluid (SGF) was prepared by dissolving 2g of NaCl in one liter of deionized water and adding 2N HCl until pH=1.2. The simulated intestinal fluid (SIF) was obtained by dissolving 6.8 g of KH_2PO_4 and 2 g of SDS in one liter of deionized water and adding 1N NaOH until a pH=6.8.

To study the release of the catechin over time, it was used a High-Performance Liquid Chromatography type Agilent 1260 Infinity with Array Diode Detector (HPLC-DAD). The mobile phase consisted of 30/70 (v/v) ultrapure water and acetonitrile. Separation was achieved on an Aqua C18 column (250 x 4.6 mm, 5µm), the flow rate of mobile phase was 0.750 mL/min and the sample injection volume was 2 µL.

To monitor the release of catechin, two calibration curves (Fig. 2) were made in the range of 5-100 ppm. The release study was performed by adding 50 mg of catechin in a paper bag and suspended in two bottles of 140 mL SGF and SIF. Samples were taken at different time intervals up to 5h and the absorbance was measured by high-performance liquid chromatography (HPLC).



(**a**)



(**b**)

Fig. 2. Calibration curve of catechin in SGF (**a**) and SIF (**b**)

3. Results and discussions

The mesoporous silica loaded with catechin were characterized using X-ray diffraction (XRD), scanning electron microscopy (SEM), BET analysis with adsorption-desorption isotherms, Fourier transform infrared spectroscopy (FTIR) and thermogravimetric analysis with differential scanning calorimetry (TG-DSC).

The corresponding diffractogram MCM-41@CAT (Fig. 3) shows a strong diffraction peaks corresponding to the (100), (110) and (210) feature the ordered hexagonal structure. Peak at (200) is significantly reduced due to loading with the active substance, catechin. The diffractogram recorded on MCM-48@CAT (Fig. 4) shows three major peaks corresponding to the cubic structure of MCM-48 (211), (420), (332) and a peak that has a low intensity (220) due to the loading with catechin [18-20]. By loading the mesoporous silica with catechin, a slight shift of peaks can be observed in both cases compared to the non-loaded mesoporous silica (MCM-41 and MCM-48).

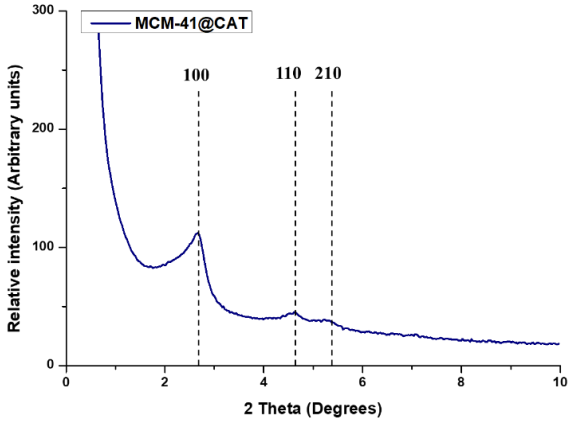


Fig. 3. XRD diffractogram of MCM-41@CAT

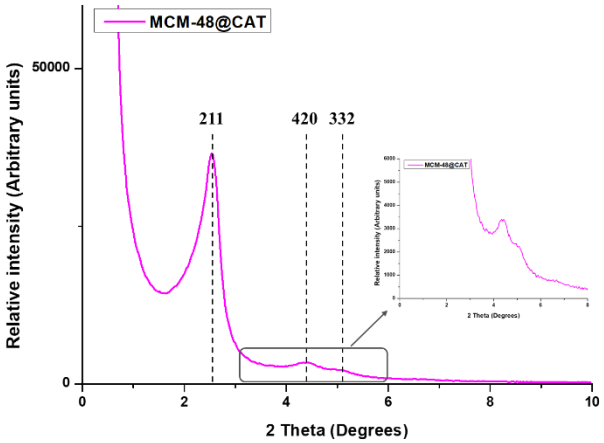
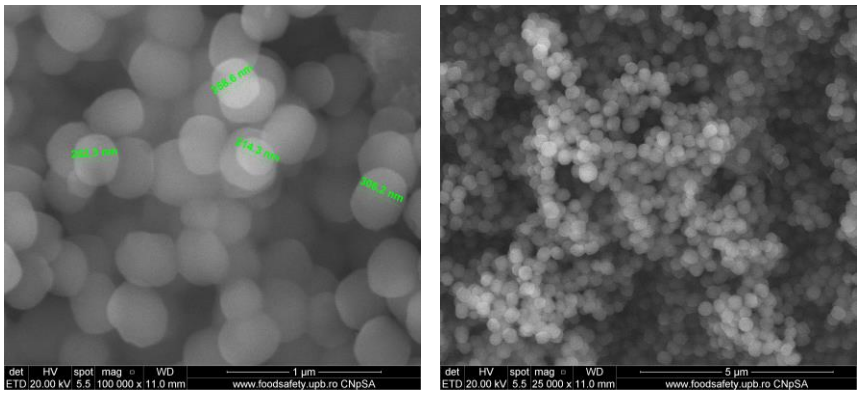
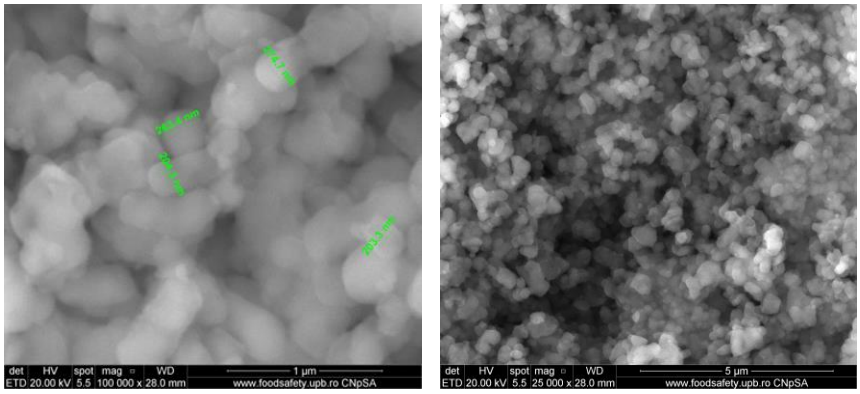


Fig. 4. XRD diffractogram of MCM-48@CAT

Images (Fig. 5) of the mesoporous silica loaded with catechin showed spherical morphology for MCM-41@CAT and the presence of quasi-spherical silica particles for MCM-48@CAT. The loaded materials have silica particles with variable sizes between 200-300 nm and small agglomerations of particles can be observed by loading.



MCM-41@CAT



MCM-48@CAT

Fig. 5. SEM images of MCM-41@CAT and MCM-48@CAT

The BET analysis of the porous materials and the nitrogen absorption/desorption isotherms were determined (Fig. 6) and important characteristics of the pores, such as the pore volume and specific surface area (Table 1). Comparing with the initial BET surface area values of mesoporous silica, MCM-41 (1179.63 m^2/g) and MCM-48 (1482 m^2/g), obtained and described in the previous article [21], can be observed a significant decrease of surface area and pore volumes for materials loaded with catechin. MCM-41@CAT has a BET surface area 11.04 times lower than MCM-41 and MCM-48@CAT 3.36 times lower than MCM-48.

Table 1

Textural parameters of mesoporous silica loaded with catechin

Sample	BET Surface Area (m^2/g)	Langmuir Surface Area (m^2/g)	Volume of pores (cm^3/g)
MCM-41@CAT	106.8464	158.3837	0.7910
MCM-48@CAT	439.8596	648.7318	0.3606

The difference in pore loading between MCM-41 and MCM-48 may be due to the different structure of the pores, hexagonal (MCM-41) and cubic (MCM-48). The Fig. 6 shows the absorption/desorption isotherms of nitrogen at P/P_0 between 0 and 1. The absorption/desorption isotherms are of type IV and are completely reversible, which indicates a uniformity of the pore size.

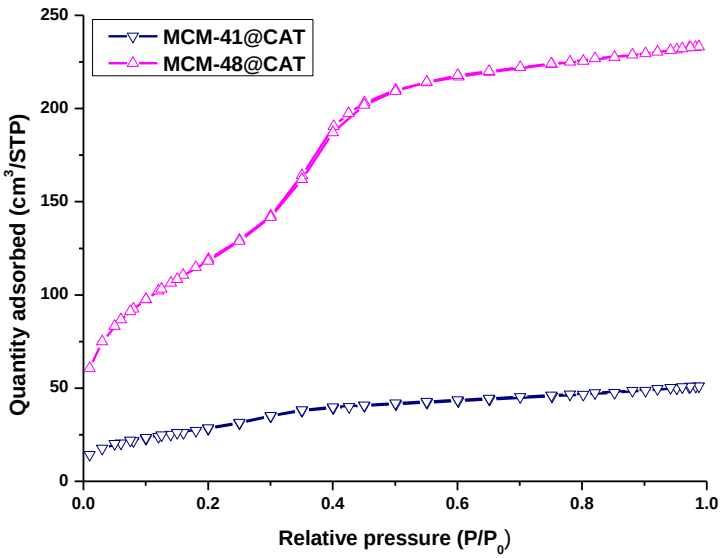


Fig. 6. Nitrogen adsorption–desorption isotherms of MCM-41@CAT and MCM-48@CAT

To characterize the structure of the materials, FTIR spectra of MCM-41@CAT and MCM-48@CAT were recorded. The Fig. 7 shows the FTIR spectra for the two materials in which the absorption bands representative for mesoporous silica can be observed, the band at ~1230 cm^{-1} and ~1047 cm^{-1} which can be attributed to asymmetric Si-O-Si group with stretching vibrations and the band associated with the silanol group at ~965cm^{-1}. At ~815 cm^{-1} the stretching vibrations of the symmetric Si-O-Si are identified while the peak from ~436 cm^{-1} is generated by the Si-O-Si moiety's deformation vibrations [22, 23].

By loading the silica support with the active substance catechin, the absorption band in the area of 3300 cm^{-1} characteristic of the stretching vibrations

the O-H bonds is observed, which corresponds to the phenolic groups. Most of the bonds specific to the catechin structure can be observed in the absorption area ~1100-1700 cm^{-1} due to the high absorptivity of silica, strong intensity bands at ~1700 cm^{-1} and ~1616cm^{-1} for C=C aromatic bonds and medium intensity bands at ~1141 cm^{-1} for C-O-C group [24].

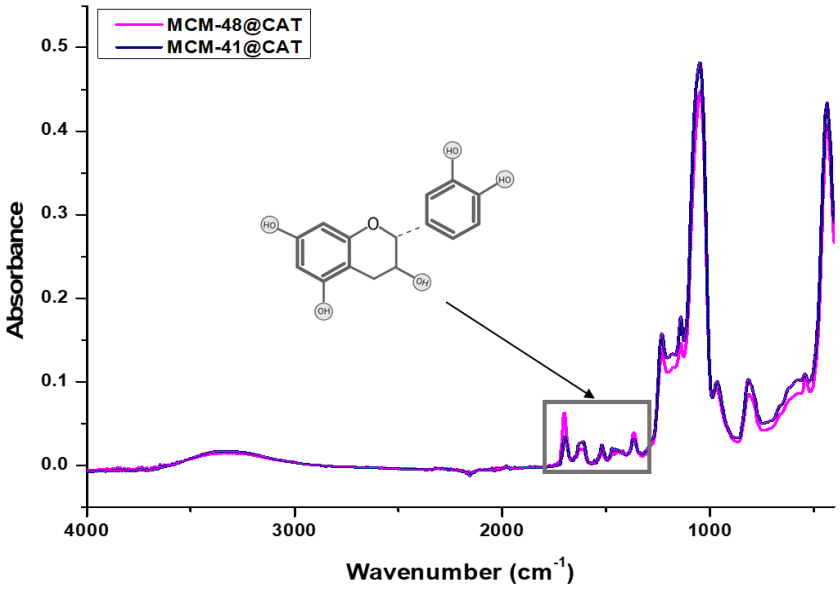


Fig. 7. FTIR spectra of mesoporous materials loaded with catechin

The amount of catechin loaded on mesoporous silica was evaluated by thermal analysis (Fig. 8), together with the behavior at heating.

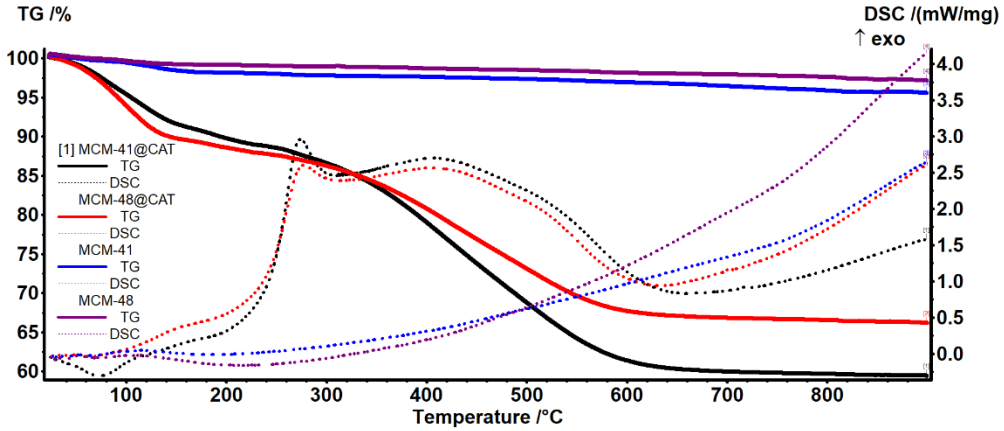


Fig. 8. Thermal analysis for the MCM-41 and MCM-48 mesoporous silica supports and the catechin corresponding loaded materials

In the first process, up to 200ºC, the samples are losing some residual acetone molecules and water bounded into the silica pores or on the particles surface. After 200ºC the organic part is degraded, the catechin being oxidized in two overlapped reactions, as indicated by the shape of the DSC exothermic effects. In the first reaction a partial oxidation is taking place, without a significant mass loss, associated with the effect from ~275ºC. In the second reaction the residual carbonaceous mass is burned away, the process being accompanied by a strong and broad exothermic effect with maximum at 408ºC. The most relevant data derived from thermal analysis are presented in Table 2.

Table 2.

Thermal analysis data for MCM-41/48 and for MCM-41/48@CAT samples

Sample	Mass loss (%) RT-200ºC	Mass loss (%) 200-900ºC	Endo effects (ºC)	Exo effects (ºC)	Estimated load (%CAT)
MCM-41	1.86	2.60	64.1/188.5	-	-
MCM-48	0.97	1.97	68.7/217.8	-	-
MCM-41@CAT	10.21	30.35	73.5	274.1/408.8	37.80
MCM-48@CAT	11.40	22.40	64.7	277.6/408.4	31.89

The estimated loaded catechin onto mesoporous silica is 37.80% for the MCM-41 sample and 31.89% for the MCM-48 support. The differences are in agreement with the results from BET analysis which indicates a better loading efficiency for the MCM-41 support due to its hexagonal pore shape. The results are also in agreement with our previous studies where MCM-41 has exhibited a higher loading capacity for ferulic acid [25], coumaric and caffeic acid [17]. It is worth noting that for gallic acid the loading of various amounts onto MCM-41 and MCM-48 had the same results only for the highest concentration [21]. The process of loading smaller quantities of gallic acid yielded a better percentage for MCM-48 support. This indicates that MCM-48 support has a better entrapment efficiency at low concentrations but has a lower overall capacity.

In the release study, the behavior of catechin is observed in the two simulated biological fluids with different pH. In SGF (Fig. 9), MCM-48@CAT has a maximum degree of catechin recovery of ~23% after 5h and and then decreases probably due to some degradation or precipitation process and additional studies are needed. Unlike MCM-48@CAT, MCM-41@CAT reaches a degree of catechin recovery of ~68 % after 3h and then decreases once with the passage of time.

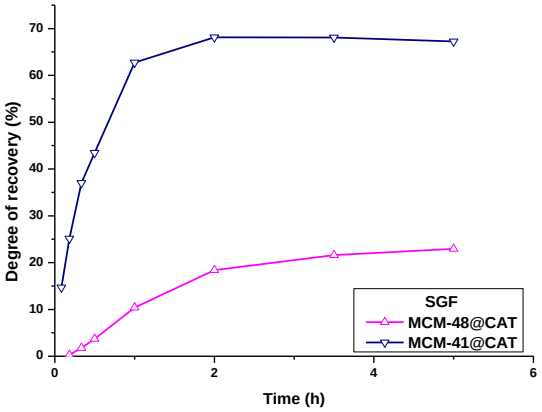


Fig. 9. Degree of recovery from mesoporous silica support in SGF

In SIF (Fig. 10), the behavior of the two materials is maintained, but with a lower degree of catechin recovery. The degree of catechin recovery from MCM-41@CAT was a maximum of ~58% and from MCM-48@CAT was ~20%, but after 4h a small decrease in the percentage of recovered catechins can be observed. In both fluids, the two materials release catechin in different percentages, but after a short period of time (approx. 5h) a decrease in the percentage of catechin is observed, which probably means a degradation of catechins in the working environment.

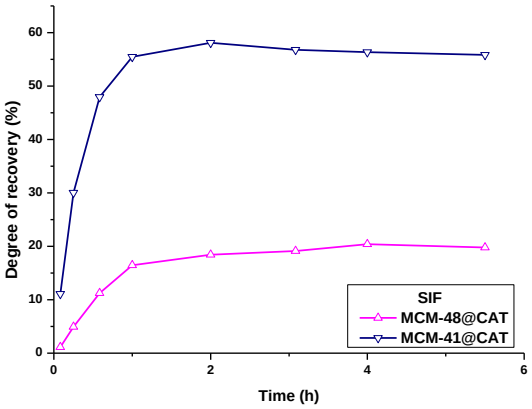


Fig. 10. Degree of recovery from mesoporous silica support in SIF

In the study by Kassem et al. [26] catechin was loaded into the mesoporous silica nanoparticles with a pH-responsive enteric polymer. They did release studies in two simulated biological fluids with acidic pH (1.9) and neutral pH (7.4) and observed that uncharged catechin was released in a proportion of 95% in the first 2 hours while that loaded in mesoporous silica nanoparticles was released approximately 79% in the first 2 hours. Following the study, it was observed that catechin undergoes rapid oxidative and metabolic degradation, which also explains the decrease in the release rate after 2 hours in our study. As can be seen in figures

9 and 10, there are differences in the behavior of the two materials in both simulated biological fluids. Wang et al. [27] studied the loading of the drug cilostazol in MCM-41 and MCM-48 and observed a higher release rate of the drug released from MCM-41 compared to MCM-48, associated with the differences in specific surfaces and pore size. Thus, we noticed that there are differences between BET surface areas and volume pores, and the difference between charged materials compared to non-charged materials is significantly greater, which means that the materials and release have a different behavior.

4. Conclusions

In this study, we obtained two systems made of mesoporous silica support, MCM-41 and MCM-48, loaded under vacuum with 400 mg of catechin/g of mesoporous silica. The obtained materials considerably reduced their surface area and pore volume, determining the surface area for MCM-41@CAT 106.84 m^2/g and for MCM-48@CAT 439.85 m^2/g. Through SEM analysis, the morphology of the nanoparticles was identified and that the materials kept their spherical (MCM-41@CAT) and quasi-spherical (MCM-48@CAT) shape, only small agglomerations were observed, most likely due to the deposition of a small amount of catechin on the outer surface of the nanoparticles. The absorption spectra obtained through FTIR analysis show us the absorption bands related to the silica support, but also part of the absorption bands of catechin. To observe the behavior of catechin in two environments with different pH, the release of catechin from mesoporous materials was studied up to 28h in SGF and SIF. Analyzing the catechin recovery curves we can conclude that MCM-41@CAT has a higher release recovery, but the system must be improved by functionalization or coating with a polymer to further extend the release time. Considering the obtained results, the obtained mesoporous systems have the potential to be used in controlled release systems, but their improvements are necessary and biological analyses should be performed to highlight the antioxidant activity of the systems.

Funding

This work was supported by a grant of the Ministry of Research, Innovation and Digitization, CCCDI—UEFISCDI, project number PN-III-P2-2.1-PED-2021-1788, within PNCDI III; 647PED/2022 “Nutraceutice nanostructurate inovative cu bioactivități sinergice pentru protecție hepato-digestivă”.

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