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Research article

Development and characterization of a zeolite based drug delivery system: Application to cannabidiol oral delivery

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ABSTRACT

The growing interest in the therapeutic potential of cannabidiol (CBD) has led to the need for effective and reliable delivery methods that overcome its low oral absorption. Zeolites, a class of porous nanoparticles, offer unique advantages as drug carriers due to their high surface area and adjustable pore size. In this study, a zeolite-based drug delivery system was developed for the encapsulation of CBD. The zeolite particles were characterized using various techniques such as Scanning Electron Microscopy (SEM), N_2 adsorption analysis, Solid-state Fourier Transform Infrared (FTIR), Direct Light Scattering (DLS), X-ray diffraction (XRD) and thermogravimetric analysis (TGA) before and after the loading. The drug encapsulation efficiency, and the release profile of CBD from the zeolite matrix were evaluated in addition to *in vitro* dissolution experiments in the intestinal and gastric simulated fluids. The results showed that the loaded zeolite particles exhibited high encapsulation efficiency of 73.5 %. XRD analysis proved that the USY structure remained intact after loading with CBD. DLS and N_2 adsorption analysis indicated that CBD was successfully loaded into the zeolite matrix. When compared to CBD containing particles in a commercialized capsule, the in-vitro dissolution rate of CBD loaded zeolite was significantly higher after 30 min in the simulated stomach (pH 1.8) and the intestinal (pH 6.8) fluids, 67.8 % versus 43.6 % and 62.6 % vs 38.4 % respectively. Our findings open new avenues for the use of zeolites as an efficient drug delivery system for drugs with low bioavailability like CBD.

1. Introduction

Zeolites are a class of inorganic microporous crystalline material composed of silica, aluminium, and oxygen tetrahydrate [1]. There are more than 40 known natural zeolite minerals and more than 150 synthetic zeolite types [2]. These basic tetrahedral structures are interconnected by oxygen atoms, creating consistent intracrystalline cavities and narrow channels of molecular

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dimensions [3] that can host drug molecules within [4]. The crystal structure, chemical composition, pore size, and other characteristics of zeolites can be used to classify them [5].

Because of their large surface areas, biocompatibility, and thermal/chemical stability, zeolites are gaining attention in a wide array of biomedical applications, including their use as drug delivery systems [6]. The high porosity of the three-dimensional zeolite structures allows easy optimization and customization to fit the desired active ingredient [7]. Zeolites such as Faujasite (FAU), Zeolite Socony Mobil (MFI), Zeolite Beta (BEA), and Clinoptilolite (CLI) have already been developed and successfully used as drug delivery materials. For instance, they have gained recognition as excipients in system-modified formulations, including anti-inflammatory, cancer therapy, gastric treatments, tuberculosis control, and aspirin formulations [8].

Furthermore, Zeolites have been used to improve the dissolution of drugs with an intrinsic low aqueous solubility [9], or to control the release of drugs, either by controlling the rate of diffusion through their pores or by triggering the release in response to a stimulus such as temperature or pH [10] and in targeted therapy and imaging [11].

Ultrastable Y (H-USY) zeolite has a FAU-type framework consisting of sodalite cages connected through hexagonal prisms. The pores are arranged perpendicular to each other. The USY mesopores may be leveraged to introduce larger molecules in their channels or obtain higher loadings of drugs due to their larger pore geometry. The USY large pore sizes may be used to freely release drug molecules for burst-release applications [12–14].

Moreover, USY zeolite was shown to be safe by Dahm et al., 2004, while testing the cytotoxicity effect on human leukemic monocytic cells (THP-1), the exposure to 13 μg zeolite Y ml^{-1} showed no toxic effect measured over a proliferation time of 3 days [15].

Cannabidiol (CBD) was first FDA-approved in 2018 to treat seizures associated with Lennox–Gastaut syndrome and Dravet syndrome in patients aged two years and above, and later in 2020 to manage seizures associated with tuberous sclerosis complex (TSC) in patients one year of age and older [16,17]. CBD has a low oral bioavailability. Data suggests that its absolute oral bioavailability is about 6 % after fasting, most likely due to the highly lipophilic nature of CBD (Log P 6.3) and significant first-pass metabolism, with up to 75 % of an oral CBD dose potentially removed by the liver before reaching the systemic circulation [18].

Many attempts have been carried out to increase CBD bioavailability after oral administration. The standard method encompassed preparing an oily suspension of CBD that prevents its precipitation in the gastrointestinal tract, hence increasing its absorption rate. An example of a CBD product produced by the standard method is Epidiolex®, delivered orally in an oily solution.

Other methods suggested the use of a piperine pro-nano liposphere [19], the development of a novel nanoemulsion preparation [20] or the use of cocrystal engineering [21] to improve the challenging pharmacokinetic profile of CBD.

In this study, we will develop a zeolite-based drug delivery system and load it with CBD. we will also characterize the physicochemical properties of the loaded zeolite particles and determine their dissolution behaviour while comparing it to commercialized CBD powder particles.

2. Material and methods

2.1. Materials

H-USY zeolite powder (CBV-600) was purchased from Zeolyst International, Si/Al ratio 5.2.

The capsules containing CBD used as control formulation for the dissolution test was purchased from Cannahemp® with a batch number: CBDCAP-05202301. 1.17 g of cannabis oil extract (COE) were extracted from a sample of 10 g of air-dried cannabis flower using ethanol over the course of 48 h and after filtering and concentrating it at 45 °C under low pressure. Drug Enforcement Office in Zahle, Beqaa Governorate, granted the dried samples of Lebanese cannabis strain collected in October 2019 from Yammoune, located in the Beqaa valley (34°07′46.4″North, 36°01′40.8″East; elevation, 1375 ± 10 m). On campus, the plant material was kept in a safe storage facility. A specimen has been added to the Department of Natural Sciences' herbarium at Lebanese American University in Lebanon (ID, 2019–0011). The extracted cannabis oil was fractionated using a normal-phase silica gel column chromatography and eluted with chloroform:hexane:diethyl ether (4:3:3). Fractions were monitored by thin layer chromatography (TLC) using 1 % vanillin/sulfuric acid as locating reagent. Similar fractions were combined and concentrated using a rotary evaporator. GC-MS analysis, and CBD identification was performed using a Shimadzu GCMS-QP2020NX as previously described by Shebaby et al. [22].

2.1.1. Zeolite loading with CBD

Zeolites were first activated by heating H-USY zeolite at 125 °C overnight to remove moisture trapped inside the pores. 400 mg of the dried zeolite were impregnated with different weights of CBD oil (80 mg, 120 mg, 160 mg, 200 mg) diluted in a 10 ml of Ethanol solution added dropwise in volumes approximately equal to the total pore volume of the zeolite used. The wet powder in which the drug has diffused into the pores by capillarity is then dried at room temperature. This led us to prepare 20 %, 30 %, 40 % and 50 % w/w CBD loaded zeolite particles.

2.2. Physico-chemical characterization

Several analytical techniques were adopted in characterizing the physicochemical properties of the CBD loaded zeolites particles.

2.2.1. Scanning electron microscopy (SEM)

SEM imaging of the samples was acquired with a MIRA 3 electron microscope from TESCAN (Brno, Czechia) using the secondary electron (SE) detector with the electron beam set at 20 kV. Prior to SEM imaging, the samples were coated in a 10 μm gold film using

the Q150T ES sputtering machine from Quorum Technologies to prevent sample charging by the electron beam.

2.2.2. N_2 adsorption analysis

Surface properties of the parent zeolite and CBD-loaded samples were acquired by N_2 adsorption analysis at 77 K, performed on Gemini VII 2390 instrument from Micromeritics (Georgia, U.S.). Prior to analysis, the parent zeolite sample was degassed in an N_2 environment at 250 °C for 12 h to remove any volatiles or organic contaminants from the surface and pores of the sample which may interfere with the N_2 adsorption. However, to prevent the thermal degradation of the cannabidiol during conventional high-temperature degassing procedure, the loaded samples were degassed under vacuum at 80° for 24 h. Surface area data was obtained using the Brunauer-Emmett-Teller (BET) theory, which assumes that the adsorbed gas first forms a monolayer on the surface of the analyte, followed by subsequent multiple layers of additional gas molecules. The mathematical model of the BET equation describes how the amount of gas adsorbed on the sample varies with pressure, resulting in an adsorption isotherm graph which is used to calculate the surface area of the sample. Data from the adsorption-desorption isotherm graph is used to infer the pore volume of the sample through the Barrett-Joyner-Halenda (BJH) theory [22].

2.2.3. FTIR analysis

Solid-state Fourier Transform Infrared (FTIR) spectroscopy measurements were made on the TGA-IR Tensor instrument from Bruker (Billerica, U.S.) equipped with diamond ATR detector. The absorbance/transmittance data collection range was set at 500-4500 cm^{-1} with an interval of 1 cm^{-1}.

2.2.4. DLS analysis

Sample particle size was determined using the NanoPlus HD particle size analyzer from Particulate System (Georgia, U.S.). Prior to analysis, the CBD-loaded zeolites were sieved through a stainless-steel mesh sieve with aperture size 0.106 mm. The resultant powder was then vortexed with deionized water for 1 min to obtain a dispersion. The dispersion was transferred to a quartz cuvette, which was left to equilibrate in the chamber for 5 min before particle size readings were taken.

2.2.5. XRD analysis

X-ray diffraction (XRD) analysis was performed on D8 ADVANCE instrument from Bruker (Billerica, U.S.) with a monochromatic Cu K_α radiation, with the beam voltage and current being 40 kV and 40 mA respectively. The angular range (2θ) was chosen from 20° to 80° with an angle step of 0.02° and a time step of 0.1 s. The crystalline species shown in the pattern of the given samples were identified by DIFFRAC-EVA™ equipment software, which contains a database for many known compounds along with their corresponding peaks.

2.3. Content quantification

2.3.1. Thermo-gravimetric analysis

Thermo-gravimetric analysis (TGA) was carried out under a nitrogen atmosphere to determine the change in mass of the CBD loaded zeolite powder against temperature. TGA was performed before and after loading to determine the amount of drug loaded into the zeolite. The TGA analysis was performed on a TG209 F1 Libra analyser from Netzsch (Selb, Germany). A sample of the crushed CBD-loaded zeolite weighing ~15 mg was added to an alumina ceramic crucible and heated from ambient temperature to 500 °C.

Cannabidiol content is determined by using the following equation:

$$\text{Drug content } (\%) = \text{Total percentage weight loss} - \text{Total percentage water loss due to evaporation}$$

$$\text{Theoretical CBD content } (\%) = \frac{\text{CBD weight}}{\text{Total sample weight } (\text{CBD} + \text{zeolite})}\ x\ 100$$

$$\text{Encapsulation efficiency } (\%) = \frac{\text{Drug content}}{\text{Theoretical CBD content}}\ \text{x } 100$$

2.3.2. Forced release method

This method was used to confirm the findings obtained from the TGA described above in order to study dissolution of the preparation with the best encapsulation efficiency. Based on previous characterization results, 30 mg of the sample with the highest encapsulation efficiency was subjected to dissolution in a solvent comprising 200 ml of distilled water with 1 % (w/v) Tween 80, to ensure sink conditions. Full drug release from the sample was facilitated by overnight stirring (200 rpm). The resulting solution was subjected to quantification via High-Performance Liquid Chromatography (HPLC). Drug Content and encapsulation efficiency was determined using the following equation:

$$\text{Drug content } \% = \frac{\text{weight of Canabidiol released}}{\textit{weight of particles}}\ \text{x } 100$$

$$\text{Encapsulation efficiency } \% = \frac{\text{weight of Canabidiol released}}{\textit{initial weight of cannabidiol}}\ \text{x } 100$$

2.4. CBD release from the loaded zeolite particles

2.4.1. In-vitro dissolution

Drug release experiments were performed by keeping 75 mg of the CBD loaded zeolites particle and the powder from the control capsule having the same CBD content in 500 ml containing 0.1 N HCL to stimulate the gastric fluid (SGF) (pH = 1.8 at 37 °C) and in a sodium phosphate buffer to simulate the intestinal fluid (SIF) (pH = 6.8 at 37 °C) and were stirred at 100 rpm over 3 h 0.5 % w/v Tween 80 were added to ensure sink condition. Aliquots of 5 ml were pipetted at 5, 15, 30, 45, 60, 120 and 180 min to determine the CBD released from the control and zeolite particles. Media was refilled every time.

2.4.2. HPLC-UV

CBD released was analysed using a validated HPLC-UV method. Aliquots were filtered with a 0.22 μm Microlab® cellulose acetate membrane and measured by Thermo Scientific Dionex UltiMate 3000 HPLC (Sunnyvale, U.S.) with an autosampler and a UV detector.

Samples were isocratically eluted on a C18 150 mm × 4.6 mm, 5 μm column (ThermoScientific Hypersil Gold™) using an ultraviolet–visible (UV/Vis) detector operating at 214 nm, The mobile phase consisted of 75/25 acetonitrile/water v/v, under a flow rate of 1.5 mL/min [23].

2.4.3. Statistical analysis

Each experiment was conducted with three replicate samples and repeated three times. Data were averaged across replications. The statistical analysis was conducted using R software (version 4.3.1.), with significance set at a p-value of 0.05.

3. Results and discussion

3.1. Physico-chemical characterization

3.1.1. SEM

SEM analysis was used to examine the morphology of the zeolite drug delivery system both before and after CBD was loaded. Following drug loading, there was no significant changes to the morphology and structure of the H-USY zeolite. The usual microporous crystalline aluminosilicate structure was seen in the SEM images of both the CBD loaded zeolite particles and the free zeolite particles (Fig. 1). There was no significant difference in the average particle diameter of the samples before and after drug loading.

SEM images of the free and CBD loaded zeolite particles suggest that most of CBD, was loaded into the pores of zeolites rather than on their surface since drug loading had no noticeable effect on the structure nor the shape of the particles. Similar results were obtained from previous research on microporous drug carriers such as Zeolite loaded with Diclofenac and Curcumin [24,25].

3.1.2. FTIR analysis

FTIR spectra of parent H-USY and 50 % CBD/USY are shown in Fig. 2. The spectrum of the H-USY zeolite in Fig. 2(a) shows a sharp peak at ~450 cm^{-1} corresponding to the internal bending of the Si-O and Al-O of the SiO_4 and AlO_4 tetrahedra. Likewise, the peaks at ~830 and ~1060 cm^{-1} respectively represent the external symmetric and internal asymmetric stretching vibrations of the Si-O-Si and Si-O-Al linkages. The broad peak at ~3390 cm^{-1} represents the Si-OH and Al-OH stretching, and the slight peak at ~1600 cm^{-1} denotes the -OH bending of these groups [26,27]. The FTIR spectrum of the CBD-loaded USY in Fig. 2(b) shows the characteristic peaks

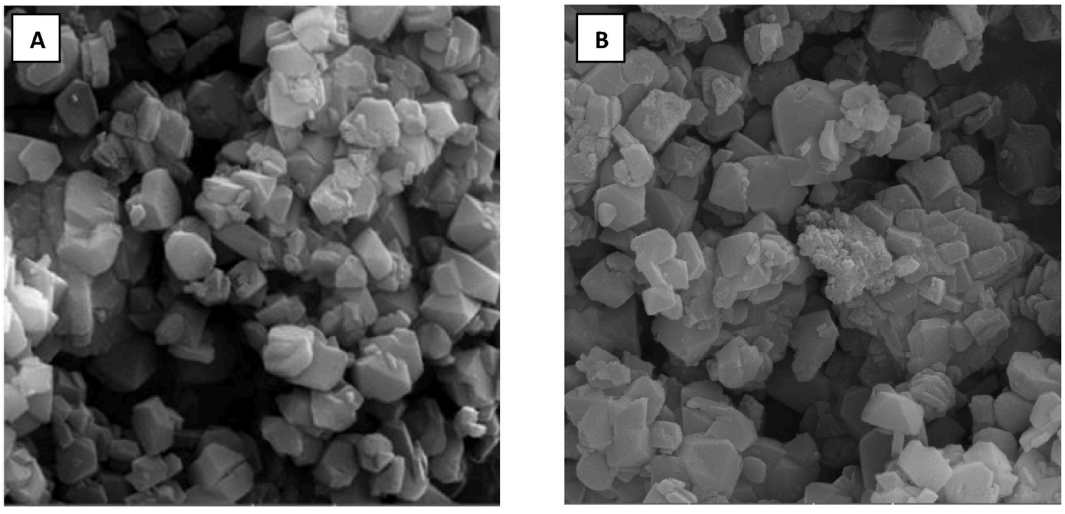

Fig. 1. Scanning electron microscope images of (A) fresh zeolite USY and (B) CBD-loaded zeolite particles.

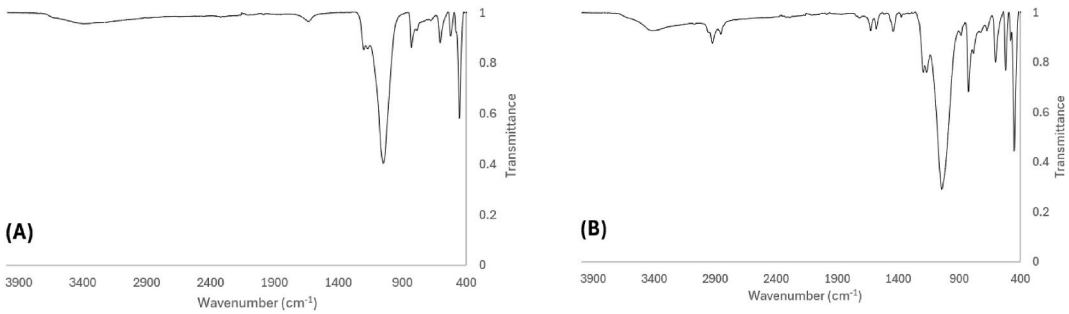

Fig. 2. FTIR spectra of (a) H-USY and (b) 50%CBD/USY.

of the USY zeolite, with additional peaks at ~2930, ~1580, and ~1440 cm^{-1}, respectively corresponding to methyl and methylene groups, phenyl ring C=C stretching, and C-O stretching vibrations, where all these functional groups are found in the structure of CBD oil [28]. The differences in the spectra indicate that the zeolite particles were successfully loaded with CBD.

3.1.3. XRD analysis

The diffractograms of the parent H-USY zeolite and the 50 % CBD/USY sample are shown in Fig. 3. Fig. 3(a). The diffractogram of the USY zeolite support showed peaks indicative of FAU-structured zeolites, with characteristic peaks at $2\theta = 6.3^{\circ}$, 15.8°, and 23.8°, corresponding to the (111), (331), and (533) faces of the zeolite respectively [29]. The diffractogram of the loaded sample in Fig. 3(b) exhibited similar XRD patterns to the parent zeolite with no additional peaks present, indicating that the framework remained intact during and after the drug loading process. However, some changes in the peak intensity were noted, suggesting the encapsulation of the CBD within the zeolite structure [25].

3.1.4. DLS analysis

Results of the DLS analysis to determine the particle size of the parent zeolite and loaded 50 % CBD/USY sample are shown in Fig. 4. The USY zeolite exhibited a well-defined sharp peak indicating a hydrodynamic diameter of 0.95 μm, whereas the 50%CBD/USY sample exhibited a broad peak which showed a hydrodynamic diameter of 1.03 μm. The results confirm the change in size after loading with cannabidiol (CBD). The slight change of only 0.08 μm is concurrent with the findings of the SEM imaging, and it is likely why there were no obvious changes in the size of the particle observed in the SEM.

3.1.5. N_2 adsorption analysis

The isotherms resultant from N_2 adsorption analysis on the unloaded and CBD-loaded zeolite are shown in Fig. 5. The isotherm of the parent USY zeolite follows a type IV isotherm as described by the IUPAC classification of adsorption isotherms, which denotes that the material is of a mesoporous type. However, the isotherm of the loaded 50 % CBD/USY sample showed a drastically reduced adsorbed quantity of N_2 compared to that adsorbed on the parent zeolite, indicating that the surface of the zeolite and its pores were loaded with CBD [2,30].

Table 1 illustrates the observed decrease in surface areas and pore size in zeolite samples after drug loading with different concentration. Therefore, it can be concluded that CBD was present in the vacant pores in H-USY Zeolite during the loading phase. BET results were evaluated, and the comparison between the different formulations prepared (w/w: 20 %, 30 %, 40 %, 50 %) favoured the selection of the formulation with the most reduction in surface area and in pore size to be submitted for the in-vitro dissolution test.

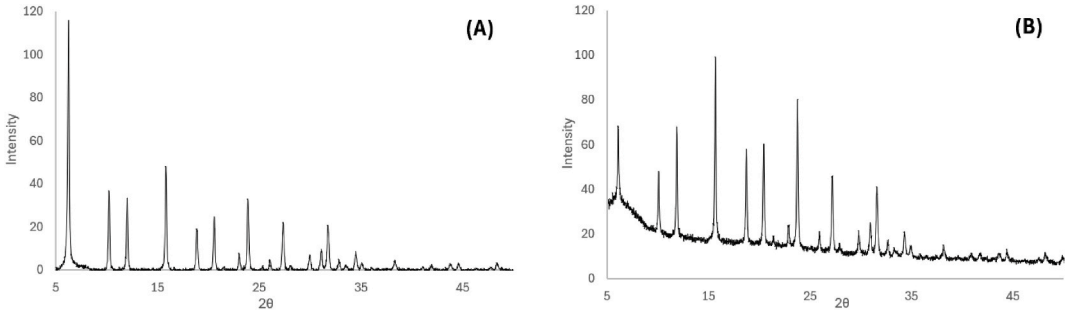

Fig. 3. XRD diffractograms of (a) H-USY and (b) 50%CBD/USY samples.

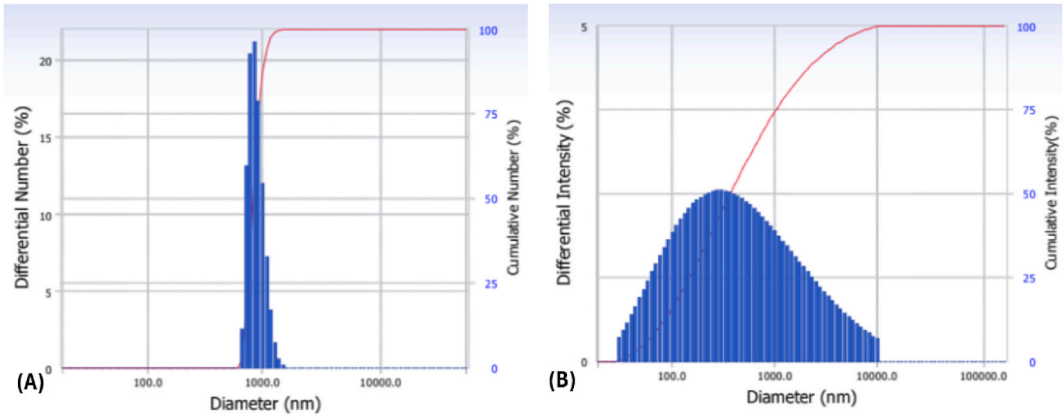

Fig. 4. DLS measurements for hydrodynamic diameter calculations of (a) H-USY zeolite and (b) 50%CBD/USY samples.

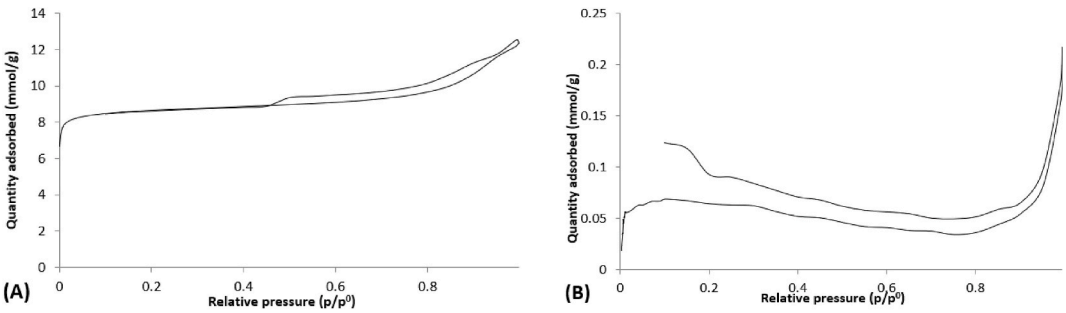

Fig. 5. N_2 adsorption isotherms resulting from analysis of (a) H-USY and (b) 50%CBD/USY.

Table 1
Surface area (m^2/g) and pore size (cm^3/g) of the free USY zeolite and of the different CBD loaded particles prepared.

Preparation	Surface Area (m^2/g)	Pore Volume (cm^3/g)
Free H-USY	626.3	0.15
20 % CBD loaded zeolite	11.57	0.0099
30 % CBD loaded zeolite	10.36	0.0084
40 % CBD loaded zeolite	9.47	0.0055
50 % CBD loaded zeolite	3.64	0.0035

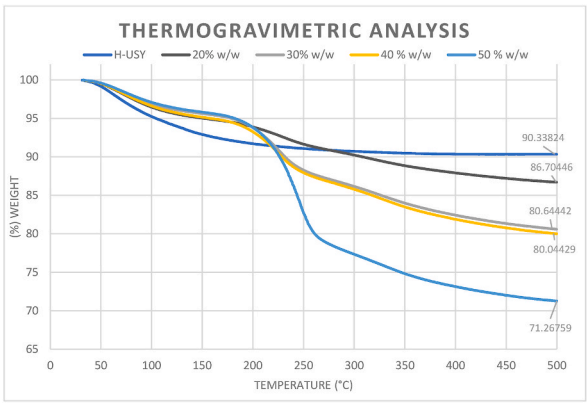

Fig. 6. Thermal gravimetric analysis of different formulations of Cannabidiol loaded USY Zeolite.

3.2. Content quantification

3.2.1. TGA

TGA has been used to determine the loading capacity of H-USY Zeolite. In this method, drug components decomposition and desorption, and weight loss in samples, are monitored in relation to gradually increasing temperatures from 30 °C to 500 °C. In Fig. 6, The TGA curves of pure H-USY zeolite shows a one stage weight loss due to the evaporation of physically adsorbed water. On the other hand, a three-stage weight loss is seen in the TGA curves of the various concentrations of H-USY loaded formulations. Cannabidiol decomposition starts between 175 and 200 °C (melting point of CBD = 180 °C). The initial weight loss is ascribed to moisture desorption with a maximum loss of 4.3 % of its original weight (between 100 °C and 150 °C), whereas the subsequent two weight losses appear to be associated with the evaporation and thermal breakdown of CBD, slightly present on the external surface (between 175 and 200 °C) and in the pore structure of the H-USY zeolite (between 200 and 500 °C). This trend has previously been noted when using Zeolite X as a drug delivery system for ketoprofen, where the multiple stages of mass loss being attributed to the strong interaction and binding of the drug to the zeolite surface [2]. Encapsulation efficiency of the CBD loaded zeolite particles were determined between 54.0 % and 73.5 % with the highest efficiency and content attributed for the 50 % w/w preparation as presented in Table 2.

3.2.2. Forced release method

There were no significant differences between the forced release method and TGA regarding the loading content for the preparation with the highest encapsulation efficiency. After 6 h, 7.06 mg cannabidiol were released from 30 mg CBD loaded zeolite sample, suggesting a 23.52 % drug content vs 24.5 % in the TGA analysis as presented in Table 3.

3.3. CBD release from the loaded zeolite particles

3.3.1. In-vitro dissolution studies

Using the Calibration curve of CBD in Ethanol solution ($r^2 = 0.98$), we calculated the percent release profile in SGF and SIF.

The CBD loaded zeolite particles released most of their content within 120 min, 95.7 % was released in the gastric simulated fluid and 87.6 % in the intestinal simulated fluid. Additionally, CBD released from the loaded zeolite particles was relatively faster than the control sample in both simulated biological media. After 30 min, 67.8 % was released in the SGF compared to 43.6 % released from the control sample, and 62.6 % compared to 38.4 % in the SIF respectively as shown in Fig. 7(a) and b.

The release profiles in each media showed that the zeolite loaded particles differed significantly at pH = 1.8 (*t*-test, $p = 0.03 < 0.05$) and at pH = 6.8 (*t*-test, $p = 0.03 < 0.05$) from commercialized control samples. The unique structure and porous architecture may facilitate rapid diffusion of CBD molecules out of the zeolite particles. Moreover, the hydrophilic nature of zeolites could enhance the solubility and dissolution rate of CBD, a relatively hydrophobic compound [9,31].

The enhancement in dissolution rate of CBD observed in our study is comparable to the results of Karavasili et Al., 2016. When nifedipne is formulated with zeolite beta via spray drying, a 4-fold and 6-fold increase in the dissolution rate compared to the pure drug was seen within 15 min in both gastric and intestinal fluids, respectively [9]. Similar results were also seen with danazol-loaded NaX-FAU zeolitic particles which showed a gradual increase in dissolution reaching 70 % of its original content in 2 h compared to a rapid and stagnant 50 % for the crystalline form in both media [32].

4. Conclusion

This work achieved the successful development and characterization of novel zeolite-based particles. These particles demonstrably enhanced the dissolution rate of cannabidiol (CBD), a highly lipophilic compound with poor oral bioavailability. This innovative approach presents promising potential for significantly improved CBD oral delivery, potentially revolutionizing the administration of this increasingly popular therapeutic agent. Furthermore, the applicability of this approach extends beyond CBD, offering exciting possibilities for enhancing the oral delivery of a broad spectrum of drugs that currently suffer from low bioavailability.

This study has limitations that are currently being addressed in ongoing research: i. The current research focused on characterization and dissolution testing. The translation of these findings to in vivo conditions will help understand and predict further the CBD release; ii. Although zeolites have been explored in various applications, their long-term biocompatibility and potential toxicity when used as drug carriers require further investigation, particularly in the context of repeated or prolonged administration.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Fouad Dernaika: Writing – original draft, Methodology, Formal analysis. **Layal Halawy:** Methodology. **Joseph Zeaiter:** Writing –

Table 2
Loading content (%) and encapsulation efficiency (%) of the different CBD loaded zeolite formulations after calculating total sample weight loss (%) using thermogravimetric analysis.

Cannabidiol loaded H-USY Zeolite	% w/w	Theoretical weight loss	Thermogram Total weight loss	Water weight loss	CBD weight loss (Loading content)	Encapsulation efficiency
1	20 %	16.6 %	13.3 %	4.3 %	9 %	54.01 %
2	30 %	23.07 %	19.4 %	4.3 %	15.1 %	64.45 %
3	40 %	28.57 %	19.9 %	4.3 %	15.6 %	54.6 %
4	50 %	33.33 %	28.8 %	4.3 %	24.5 %	73.5 %

Table 3
Loading content (%) and encapsulation efficiency (%) of the 50 % w/w CBD loaded zeolite particles after calculating its weight loss (mg) using forced release method.

Cannabidiol loaded H-USY Zeolite	% w/w	Theoretical weight loss	Weight of cannabidiol released	Sample weight	CBD weight loss (Loading content)	Encapsulation efficiency
1	50 %	33.33 %	7.058 mg	30 mg	23.52 %	70.58 %

a

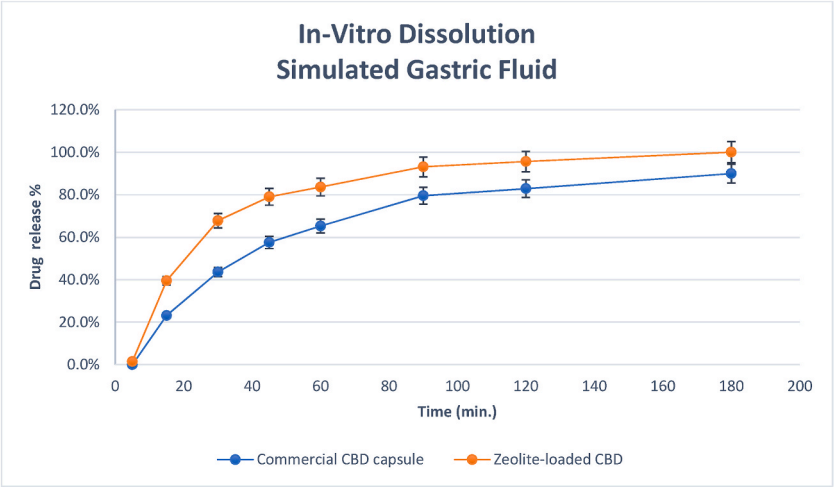

Fig. 7a. Cannabidiol loaded zeolite delivery system release profile vs. control sample in simulated gastric fluid.

b

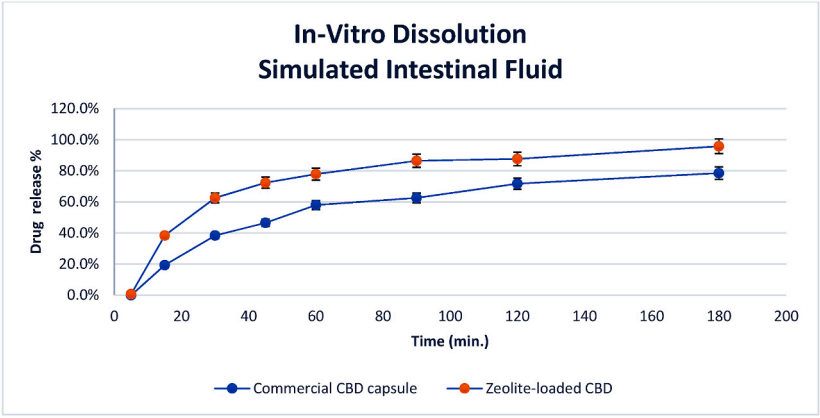

Fig. 7b. Cannabidiol loaded zeolite delivery system release profile vs. control sample in simulated intestinal fluid.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R. Amorim, N. Vilaça, O. Martinho, et al., Zeolite structures loading with an anticancer compound as drug delivery systems, J. Phys. Chem. C 116 (48) (2012) 25642–25650, https://doi.org/10.1021/jp3093868.

[2] M.G. Rimoli, M.R. Rabaioli, D. Melisi, et al., Synthetic zeolites as a new tool for drug delivery, J. Biomed. Mater. Res. 87A (1) (2008) 156–164, https://doi.org/10.1002/jbm.a.31763.

[3] C.C. Villa, G.A. Valencia, A. López Córdoba, R. Ortega-Toro, S. Ahmed, T.J. Gutiérrez, Zeolites for food applications: a review, Food Biosci. 46 (2022) 101577, https://doi.org/10.1016/j.fbio.2022.101577.

[4] M. Servatan, P. Zarrintaj, G. Mahmodi, et al., Zeolites in drug delivery : progress , challenges and opportunities, Drug Discov. Today 25 (4) (2020) 642–656, https://doi.org/10.1016/j.drudis.2020.02.005.

[5] A. Miteva, V. Stoyanova, Zeolites application in terrestrial and space industry – a review, Aerospace Research in Bulgaria 32 (2020) 209–223, https://doi.org/10.3897/arb.v32.e17.

[6] H. Derakhshankhah, S. Jafari, S. Sarvari, et al., Biomedical applications of zeolitic nanoparticles, with an emphasis on medical interventions, Int. J. Nanomed. 15 (2020) 363–386, https://doi.org/10.2147/IJN.S234573.

[7] E. Khodaverdi, H.A. Soleimani, F. Mohammadpour, F. Hadizadeh, Synthetic zeolites as controlled-release delivery systems for anti-inflammatory drugs, Chem. Biol. Drug Des. 87 (6) (2016) 849–857, https://doi.org/10.1111/cbdd.12716.

[8] G.T.M. Kadja, N.T.U. Culsum, R.M. Putri, Recent advances in the utilization of zeolite-based materials for controlled drug delivery, Results Chem 5 (2023) 100910, https://doi.org/10.1016/j.rechem.2023.100910.

[9] C. Karavasili, L. Kokove, I. Kontopoulou, G.K. Eleftheriadis, N. Bouropoulos, D.G. Fatouros, Dissolution enhancement of the poorly soluble drug nifedipine by co-spray drying with microporous zeolite beta, J. Drug Deliv. Sci. Technol. 35 (2016) 91–97, https://doi.org/10.1016/j.jddst.2016.06.004.

[10] M. Arruebo, R. Fernández-Pacheco, S. Irusta, J. Arbiol, M.R. Ibarra, J. Santamaría, Sustained release of doxorubicin from zeolite–magnetite nanocomposites prepared by mechanical activation, Nanotechnology 17 (16) (2006) 4057–4064, https://doi.org/10.1088/0957-4484/17/16/011.

[11] N. Ndiege, R. Raidoo, M.K. Schultz, S. Larsen, Preparation of a versatile bifunctional zeolite for targeted imaging applications, Langmuir 27 (6) (2011) 2904–2909, https://doi.org/10.1021/la2000409.

[12] M. Servatan, P. Zarrintaj, G. Mahmodi, et al., Zeolites in drug delivery: progress, challenges and opportunities, Drug Discov. Today 25 (4) (2020) 642–656, https://doi.org/10.1016/j.drudis.2020.02.005.

[13] M. Spanakis, N. Bouropoulos, D. Theodoropoulos, et al., Controlled release of 5-fluorouracil from microporous zeolites, Nanomedicine 10 (1) (2014) 197–205, https://doi.org/10.1016/j.nano.2013.06.016.

[14] G. Lutzweiler, Y. Zhang, F. Gens, et al., Deciphering the role of faujasite-type zeolites as a cation delivery platform to sustain the functions of MC3T3-E1 pre-osteoblastic cells, Mater Adv 3 (23) (2022) 8616–8628, https://doi.org/10.1039/D2MA00768A.

[15] Å. Dahm, H. Eriksson, Ultra-stable zeolites—a tool for in-cell chemistry, J. Biotechnol. 111 (3) (2004) 279–290, https://doi.org/10.1016/j.jbiotec.2004.04.008.

[16] Greenwich Biosciences Inc, Epidiolex (cannabidiol) oral solution. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210365s015lbl.pdf, February 2022. (Accessed 15 November 2023).

[17] GW Pharmaceuticals, FDA approves EPIDIOLEX® (Cannabidiol) oral solution to treat seizures associated with tuberous sclerosis complex. https://www.globenewswire.com/news-release/2020/08/03/2071601/0/en/FDA-Approves-EPIDIOLEX-cannabidiol-Oral-Solution-to-Treat-Seizures-Associated-with-Tuberous-Sclerosis-Complex.html, 2020. (Accessed 11 June 2022).

[18] B. Stella, F. Baratta, C. Della Pepa, S. Arpicco, D. Gastaldi, F. Dosio, Cannabinoid formulations and delivery systems: current and future options to treat pain, Drugs 81 (13) (2021) 1513–1557, https://doi.org/10.1007/s40265-021-01579-x.

[19] I. Cherniakov, D. Izgelov, D. Barasch, E. Davidson, A.J. Domb, A. Ho, Piperine-pro-nanolipospheres as a novel oral delivery system of cannabinoids : pharmacokinetic evaluation in healthy volunteers in comparison to buccal spray administration 266 (August) (2017) 1–7, https://doi.org/10.1016/j.jconrel.2017.09.011.

[20] Y. Nakano, M. Tajima, E. Sugiyama, V.H. Sato, H. Sato, Development of a Novel Nano Emulsion Formulation to Improve Intestinal Absorption of Cannabidiol, vol. 8555, 2019, pp. 35–42, https://doi.org/10.1159/000497361.

[21] S.A. Millar, R.F. Maguire, A.S. Yates, S.E. O'Sullivan, Towards better delivery of cannabidiol (CBD), Pharmaceuticals 13 (9) (2020) 219, https://doi.org/10.3390/ph13090219.

[22] F. Ambroz, T.J. Macdonald, V. Martis, I.P. Parkin, Evaluation of the BET theory for the characterization of meso and microporous MOFs, Small Methods 2 (11) (2018), https://doi.org/10.1002/smtd.201800173.

[23] S. Analakkattillam, V.K. Langsi, J.P. Hanrahan, E. Moore, Analytical method validation for assay determination of cannabidiol and tetrahydrocannabinol in hemp oil infused products by RP-HPLC, Sci. Rep. 12 (1) (2022) 12453, https://doi.org/10.1038/s41598-022-13737-6.

[24] C. Serri, B. de Gennaro, V. Quagliariello, et al., Surface modified zeolite-based granulates for the sustained release of diclofenac sodium, Eur. J. Pharmaceut. Sci. 99 (2017) 202–208, https://doi.org/10.1016/j.ejps.2016.12.019.

[25] Abadeh Z. Ahali, G. Saviano, P. Ballirano, M.G. Santonicola, Curcumin-loaded zeolite as anticancer drug carrier: effect of curcumin adsorption on zeolite structure, Pure Appl. Chem. 92 (3) (2020) 461–471, https://doi.org/10.1515/pac-2018-1213.

[26] Y. Hidayat, K.D. Nugrahaningtyas, P.J. Hendrastuti, Activated carbon addition methods on the pre-impregnation process of Co-Mo in Y-zeolite ultra stable: a properties exploration and enhancement of metals loaded, Jurnal Riset Kimia 12 (2) (2021), https://doi.org/10.25077/jrk.v12i2.384.

[27] C. Huang, A. Li, Z.S. Chao, Heterogeneous catalytic synthesis of quinoline compounds from aniline and C_1 –C_4 alcohols over zeolite-based catalysts, RSC Adv. 7 (76) (2017) 48275–48285, https://doi.org/10.1039/C7RA08442K.

[28] T. Moqejwa, T. Marimuthu, P.P.D. Kondiah, Y.E. Choonara, Development of stable nano-sized transfersomes as a rectal colloid for enhanced delivery of cannabidiol, Pharmaceutics 14 (4) (2022) 703, https://doi.org/10.3390/pharmaceutics14040703.

[29] N. Songsiri, G.L. Rempel, P. Prasassarakich, Isoprene synthesis using MIL-101(Cr) encapsulated silicotungstic acid catalyst, Catal. Lett. 149 (9) (2019) 2468–2481, https://doi.org/10.1007/s10562-019-02837-0.

[30] E. Khodaverdi, R. Honarmandi, M. Alibolandi, R.R. Baygi, R. Hadizadeh, F. Gholamhossein, Evaluation of Synthetic Zeolites as Oral Delivery Vehicle for Anti-inflammatory Drugs, vol. 17, 2014.
[31] M. Karimi, M. Habibizadeh, K. Rostamizadeh, M. Khatamian, B. Divband, Preparation and characterization of nanocomposites based on different zeolite frameworks as carriers for anticancer drug: zeolite Y versus ZSM-5, Polym. Bull. 76 (5) (2019) 2233–2252, https://doi.org/10.1007/s00289-018-2472-1.
[32] E. Kontogiannidou, C. Karavasili, M.G. Kouskoura, et al., In vitro and ex vivo assessment of microporous Faujasite zeolite (NaX-FAU) as a carrier for the oral delivery of danazol, J. Drug Deliv. Sci. Technol. 51 (2019) 177–184, https://doi.org/10.1016/j.jddst.2019.02.036.