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Zn/La^{3+}-Based MOFs: A Novel Approach for Controlled and Sustained Release of Captopril

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Abstract
This study presents the synthesis of Zn/La^{3+}-based metal-organic frameworks (MOFs) using a co-precipitation assisted microwave method. Characterization through SEM and TEM revealed uniform nanoparticles around 80 nm. FT-IR spectroscopy confirmed the presence of key functional groups. Dynamic light scattering (DLS) showed highly uniform particle sizes. In vitro release studies of captopril from Zn/La^{3+}/MOFs demonstrated a 41% release rate over 300 min, compared to 64% for pure captopril. Encapsulation within the MOF matrix ensured controlled and sustained drug release, with the first -order kinetic model fitting best. These Zn/La^{3+}/MOFs show promise for enhanced and controlled drug delivery systems.

Keywords
Metal-organic Frameworks; Drug release; Captopril.

1.INTRODUCTION

Cardiovascular diseases (CVDs) pose a significant global health challenge, representing a leading cause of morbidity and mortality worldwide [1]. Pharmacotherapy, including the use of drugs like captopril, remains a cornerstone in the management of CVDs [2]. Captopril, an angiotensin-converting enzyme (ACE) inhibitor, has demonstrated efficacy in treating hypertension, heart failure, and various other cardiovascular conditions[3]. However, despite its widespread use, challenges persist in optimizing its therapeutic effectiveness and ensuring patient safety [4].

A major obstacle in the pharmacotherapy of CVDs lies in achieving precise control over drug release kinetics, which directly influences the drug's pharmacokinetic and pharmacodynamic profiles [5]. Ensuring optimal drug release is vital for maintaining therapeutic plasma concentrations, minimizing adverse effects, and improving patient adherence to treatment regimens [6]. Additionally, ensuring the chemical stability of these drugs during storage and administration is crucial to preserving their efficacy and safety [7].

To address these challenges, novel drug delivery systems have emerged as promising avenues of research [8]. Metal- Organic Frameworks (MOFs), characterized by their tunable properties and potential for controlled drug release, offer an innovative platform for enhancing drug delivery efficiency and therapeutic outcomes [9]. By integrating captopril into MOF, it may be possible to circumvent limitations associated with traditional dosage forms and optimize the drug's pharmacological properties [10].

In the pursuit of improved drug delivery strategies, the utilization of MOFs holds promise due to their unique physicochemical properties and customizable structures [11]. These frameworks, composed of organic ligands coordinated to metal ions or clusters, offer a versatile platform for encapsulating and delivering therapeutic agents [9].

By harnessing the modularity of organic ligands and the diverse coordination geometries of metal ions, MOFs can be tailored to accommodate a wide range of drug molecules, including captopril [12].Through precise control over framework composition and architecture, it becomes feasible to regulate drug release kinetics and optimize therapeutic outcomes [13].

Moreover, MOFs exhibit inherent biocompatibility and biodegradability, mitigating concerns regarding cytotoxicity and long-term safety [14]. Their nanoporous structures also facilitate high drug loading capacities and enhanced drug stability, further enhancing their utility as drug delivery vehicles [15].

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In this study, we propose the synthesis and characterization of MOFs for captopril encapsulation and delivery. Through a combination of synthetic methodologies and advanced characterization techniques, we aim to elucidate the structural properties of these frameworks and evaluate their performance as drug carriers.

Furthermore, we will investigate the impact of MOFs on the antioxidant properties of captopril, aiming to enhance its therapeutic efficacy in combating oxidative stress-related cardiovascular complications. By elucidating the relationship between framework composition, drug release kinetics, and antioxidant activity, we seek to lay the groundwork for the development of next-generation drug delivery systems for cardiovascular therapy.

Overall, this research endeavors to bridge the gap between fundamental materials science and translational medicine, offering insights into the design principles of MOFs for drug delivery applications. Through interdisciplinary collaboration and innovative approaches, we aim to propel the field of cardiovascular drug delivery forward, ultimately improving patient outcomes and quality of life.

2.EXPERIMENTAL

2.1. Materials

Captopril (C_9H15NO_3S, MW: 217.29 g/mol), along with lanthanum (III) chloride hydrate (99.9%) and $Zn(NO_3)_2{\cdot}6H_2O$, served as the starting precursors. The linker used was 1,3,5-benzenetricarboxylic acid (98%, purchased from Sigma-Aldrich, Germany), all chemicals were of analytical grade and were obtained from Sigma-Aldrich without further purification. All solutions were prepared using deionized water at room temperature.

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2.2. Synthesis of Zn/La^{+3}- based MOF

The synthesis was performed in accordance with the procedure outlined in the previous study [16]. As reported in the earlier work, Zn/La³⁺/MOF structures were synthesized by dissolving 1.62 mmol of $Zn(NO_3)_2{\cdot}6H_2O$ in 10 mL of distilled water. Subsequently, 0.05 mmol of lanthanum (III) chloride hydrate and 0.02 g of 1,3,5-benzenetricarboxylic acid were gradually added to the solution under vigorous stirring at 800 rpm, maintaining the temperature at 50°C for 2 hours. The resulting mixture was transferred to a 150 mL beaker and subjected to microwave irradiation at 300 W. The obtained precipitate was separated by centrifugation, washed thoroughly with distilled water, and dried at 60°C for 10 hours.

2.3. Physiochemical characterization and study of encapsulation efficiency

Before loading Captopril, Fourier-transform infrared (FT-IR) spectroscopy was conducted to verify the formation of Zn/La³⁺/MOF. To achieve this, the dried potassium bromide was evenly dispersed on the sample surface, and the spectrum was recorded within the wavenumber range of 4000 to 400 cm^{-1} (IRTracer-100, Spectrophotometers, Shimadzu, Japan). Additionally, the prepared MOF was subjected to physical stability screening tests, including thermodynamic accelerated stability tests (heating-cooling and freeze-thaw cycles) and centrifugation cycle durability. Visual inspection was also performed to detect any observable changes.

Based on previously reported studies, the encapsulation efficiency (EE) of captopril-loaded MOF was determined [17]. To achieve this, a calibration curve for captopril was constructed using its absorption maximum (λmax) at 518.88 nm, and its linearity was verified based on the regression equation. [18].

To assess the encapsulation efficiency (EE%), initially, a solution containing 100 mg of captopril dissolved in a 50 ml ethanol-water mixture (1:1 ratio) was prepared.

A total of 100 mg of Zn/La³⁺/MOF was added to the solution under constant magnetic stirring at 200 rpm, and the mixture was maintained at a temperature of 40°C. After a 24-hour incubation period, the solvent, consisting of an ethanol-water mixture, was evaporated, resulting in the formation of dried Cap-Zn/La³⁺/MOF particles.

These particles underwent multiple washes and were then subjected to vacuum drying at room temperature for 24 hours to eliminate any unloaded captopril molecules. This procedure was repeated three times, and each sample was subjected to analysis using UV-visible spectrophotometry (Optizen 3220 UV, Mecasys, South Korea). Additionally, the unloaded MOF served as a blank to confirm the absence of interference from formulation components.

The percentage of captopril content in Zn/La³⁺/MOF was determined using Equation 1:

$$EE\ \% = (Wt/Wi) \times 100 \qquad \text{Equation 1}$$

Where Wt represents the amount of captopril encapsulated in Zn/La³⁺/MOF, and Wi is the total quantity of captopril used. This experiment was repeated, and the captopril content was reassessed over a period of 60 days of storage at room temperature.

To assess the characteristics of Cap@ Zn/La³⁺/MOF, Dynamic Light Scattering (DLS) analysis was conducted to determine their average size and size distribution. DLS is a rapid and non-destructive technique that allows for the evaluation

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of particle sizes ranging from 0.3 nm to 10000 nm based on their Brownian motion in a liquid medium. To perform the analysis, the encapsulated formulation was diluted in 2 mL of distilled water and examined using a DLS instrument (VASCO®, Cordouan Technologies, France).

Furthermore, the morphology, uniformity, and diameter of the Cap-Zn/La^{3+}/MOF were investigated using Scanning Electron Microscopy (SEM) analysis, following established protocols described in the literature. After drying at room temperature, the formulation was mounted onto aluminum stubs and coated with a thin layer of gold to enhance conductivity. Subsequently, SEM imaging was conducted using a field emission scanning electron microscope (FE-SEM, MIRA 3 XM, Tescan Inc., USA) at an acceleration voltage of 15 kV.

3. RESULTS AND DISCUSSION

Surface properties and particle size distributions of the nanostructures were analyzed using scanning electron microscopy (SEM) images. As illustrated in Figure 1a, the SEM image of the Zn/La^{3+}/MOF shows particles approximately 80 nm in size. The particle size distribution indicates that the particles are consistently within a specific size range. To further investigate the morphology and particle size distribution, TEM imaging was employed. The TEM results revealed a uniform and self-assembling Zn/La^{3+}/MOF, corroborating the observations from the SEM image. Figure 1b shows the TEM image of the Zn/La^{3+}/MOF. To identify the functional groups and chemical bonds in the nanoparticles, Fourier transform infrared (FT-IR) spectroscopy was utilized on the synthesized Zn/La^{3+}/MOF samples, as illustrated in Figure 2a. The pronounced absorption peak at 3406 cm^{-1} is attributed to the O-H bond, which signifies moisture and environmental molecules absorbed onto the surface of the structures. The characteristic absorbance at 2396 cm^{-1} confirmed the presence of C-C bonds in 1,3,5-benzenetricarboxylic acid. A weak peak observed at 1763 cm^{-1} is associated with C=O stretching vibrations and symmetric stretching vibration bands. Additionally, the absorption bands around 825 cm^{-1} are attributed to Zn-C-La bonds in the metal-organic framework samples. Figure 2b presents the particle size analysis. According to the DLS diagram, the Dn 10%, Dn 50%, and Dn 90% values are 38.94 nm, 49.06 nm, and 81.59 nm, respectively. This data indicates that the particles were synthesized with a highly uniform dispersion, falling within the particle size range of 30-80 nm. [16]

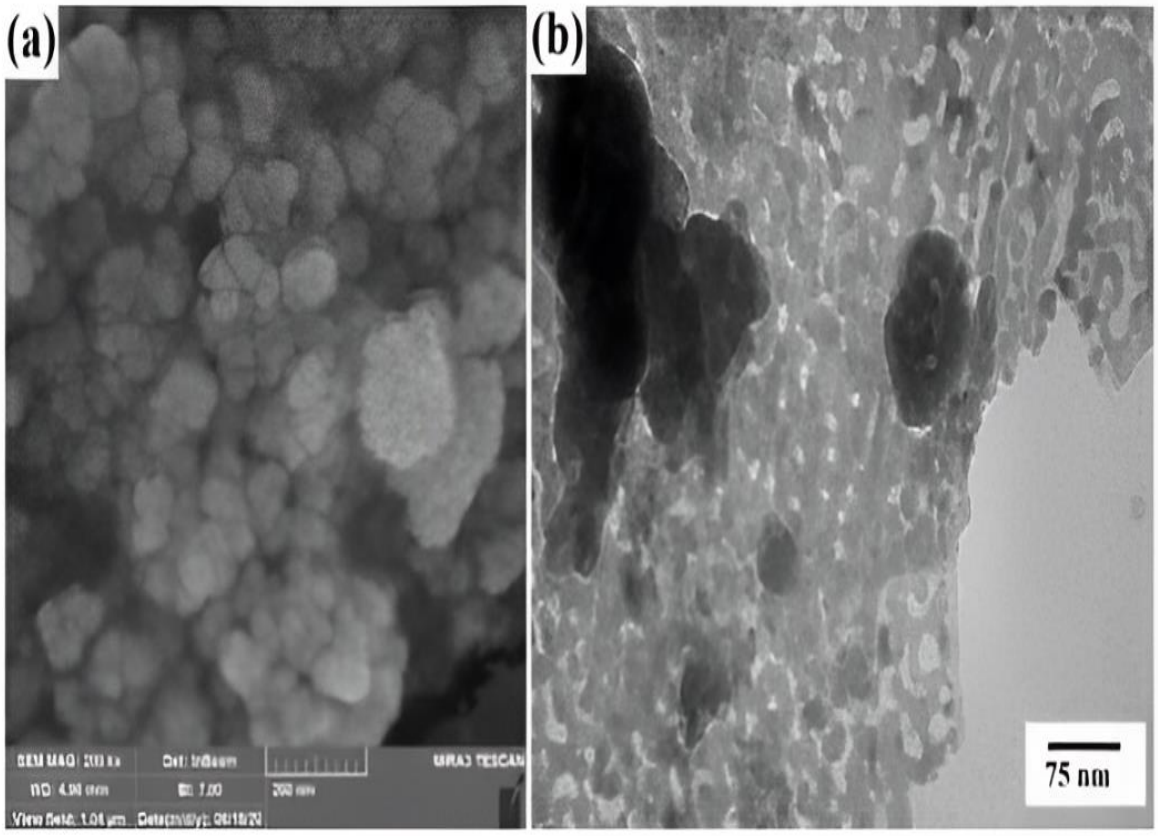

Fig. 1. The SEM (a) and TEM (b) image of the as-synthesized Zn/La^{3+}/MOF [16]

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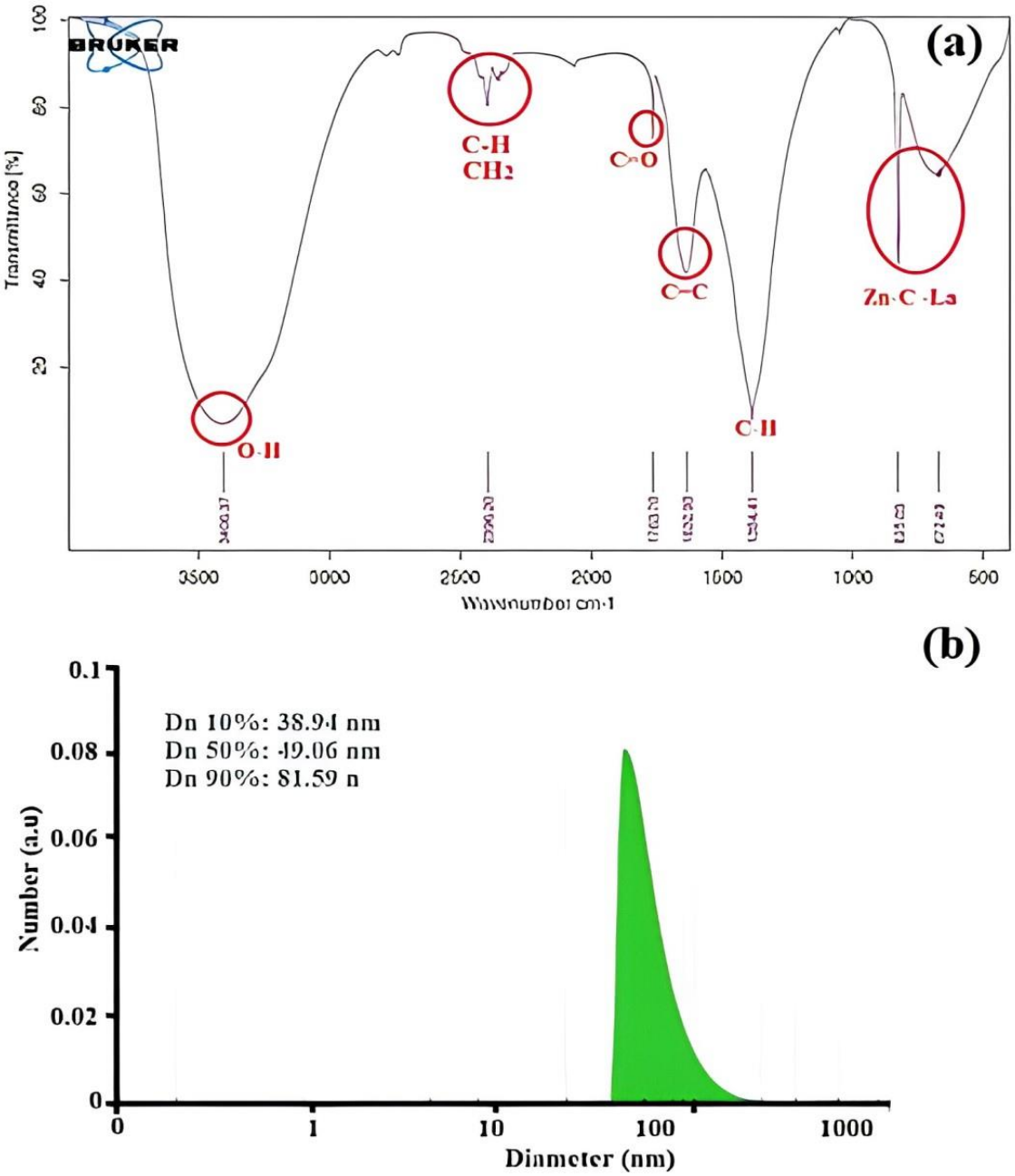

Fig. 2. The fourier transformed infrared (a) and dynamic light scattering diagram of the as synthesized Zn/La^{3+}/MOF [16]

3.1. Study of drug release

The release behavior of Captopril from Zn/La^{3+}/MOF was investigated using a modified Franz diffusion cell method. To ensure complete saturation, a synthetic semi-permeable membrane with a molecular weight cut-off of 12 kDa (cellulose acetate) was immersed overnight in a receiving medium consisting of a 1:1 mixture of ethanol and water. The Captopril- loaded La-MOFs were placed in the donor compartment of the diffusion cell. Samples were collected at predetermined time intervals under constant conditions (stirring at 200 rpm and maintained at 34 ± 1°C). The released amount of Captopril was determined using UV-visible spectrophotometry at λmax. Additionally, the release profile of pure Captopril dissolved in ethanol-water mixture was evaluated for comparison. All experiments were conducted in triplicate, and the results were expressed as mean ± SD deviation. Various mathematical models, including zero order, first order, Hixon Crowell, Higuchi, and Korsmeyer-Peppas, were employed to analyze the release kinetics and diffusion characteristics. The best-fitting model was determined based on the coefficient of determination (R^2), aiming for a value approaching unity [19].

The cumulative in-vitro release of Captopril from Zn/La^{3+}/MOF is delineated in Figure 3. The release study spanned 300 min and was juxtaposed with

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the release trajectory of pure Captopril. Accordingly, Zn/La^{3+}/MOF exhibited a 41% Captopril release rate, while the unencumbered pure Captopril displayed a 64 % release rate.

Furthermore, the encasement of active agents within such a MOF matrix not only shields them from instantaneous deterioration but also implies a sustained release pattern. This is owing to the ability to tailor the platform's pore size marginally larger than the dimensions of the drug molecule, thereby diminishing its mobility.

Various kinetic models were employed to delineate the liberation pattern. Consequently, the data were scrutinized, and the most fitting kinetic model was determined based on the correlation coefficient (R^2) value. In this context, the first-order liberation kinetics emerged as the most suitable curve-fitting model Figure 4 (a, b).

The release kinetics of captopril, as illustrated in Figure 4 (c, d), exhibit a pattern consistent with the Higuchi equation. This observation indicates that the drug release is diffusion-controlled, aligning with the principles of the Higuchi model. The Higuchi model describes the release of solutes from homogeneous matrices under specific conditions. This model is particularly applied in pharmaceutical formulations where diffusion is the primary mechanism governing the release rate.

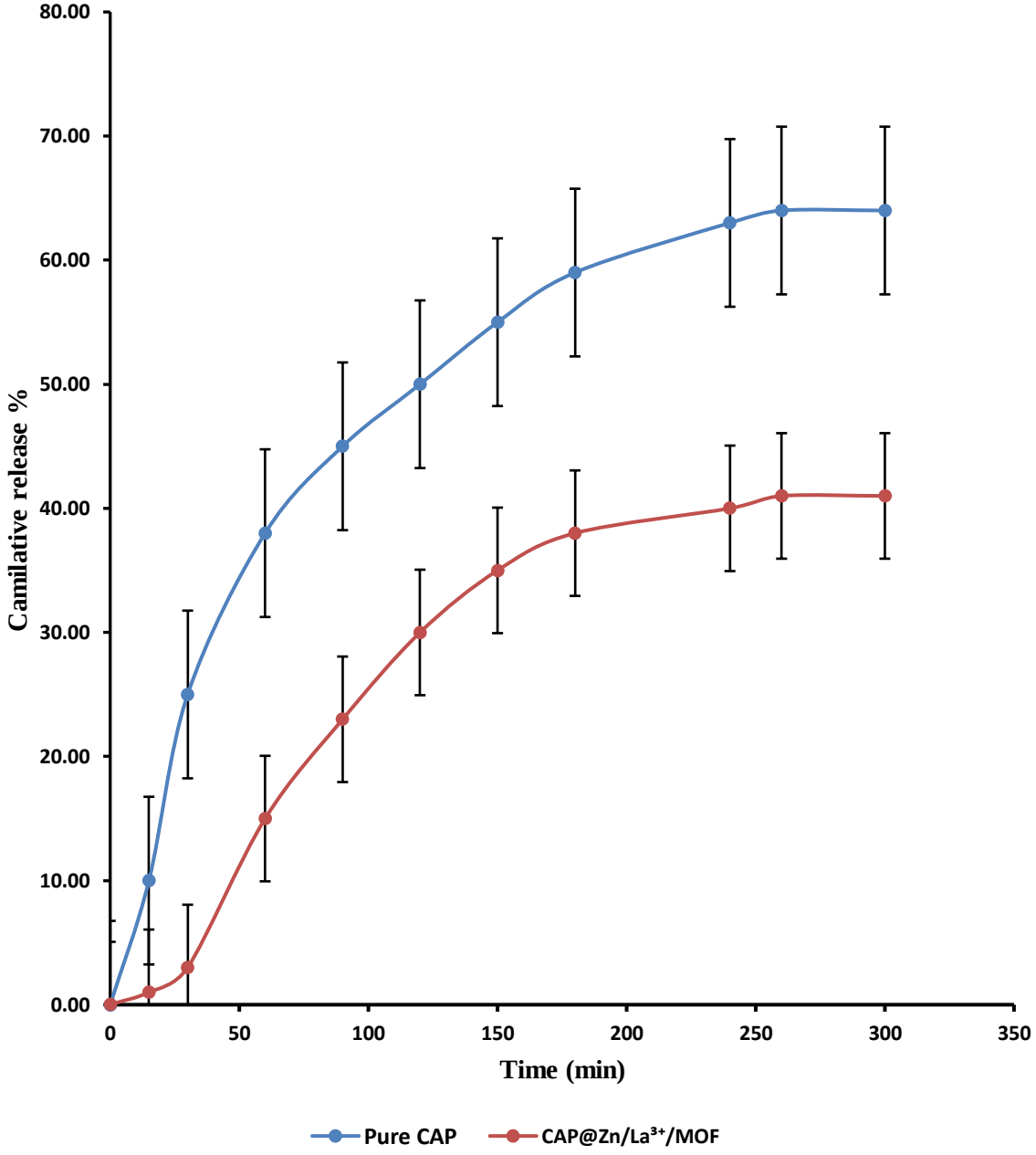

Fig. 3. The results of cumulative release for Captopril loaded Zn/La^{3+}/MOF and pure Captopril (Mean ± SD, n=3).

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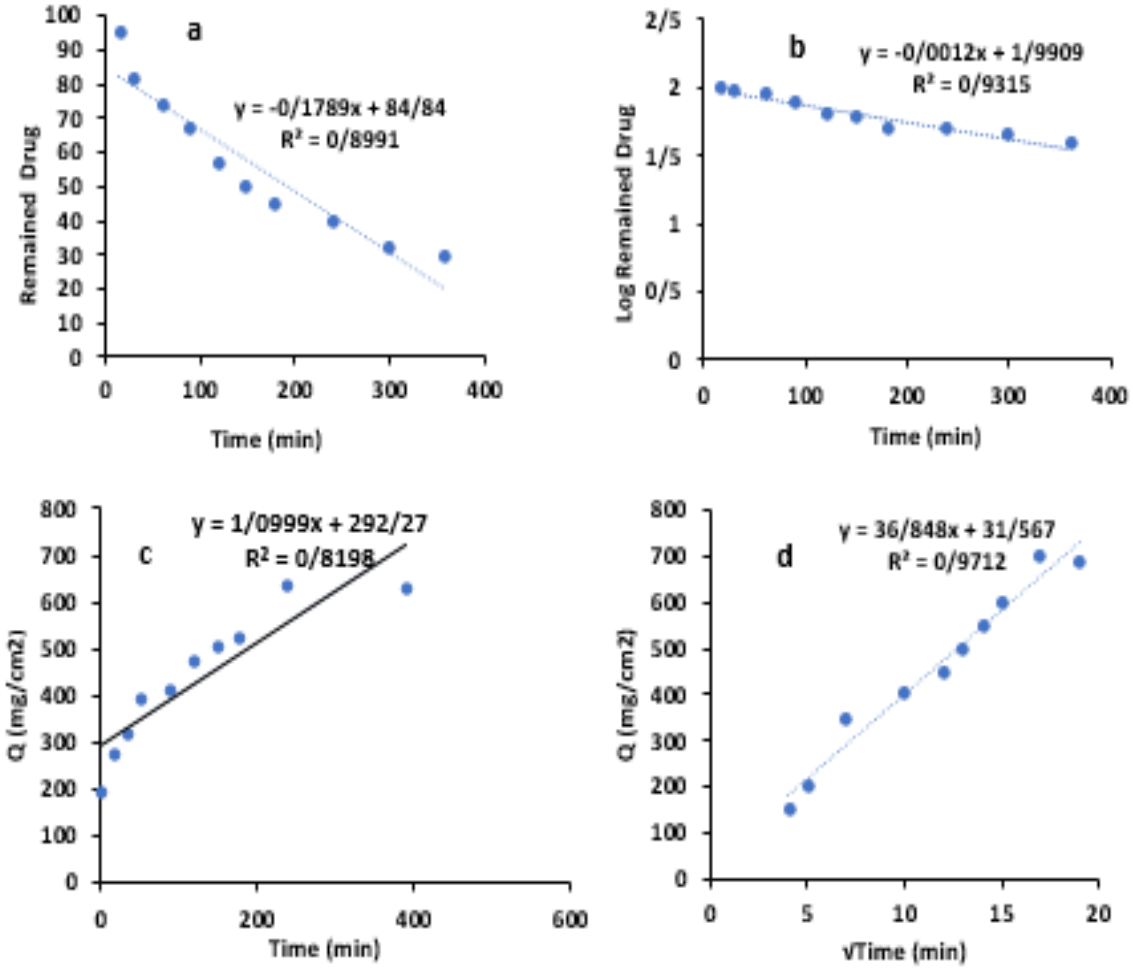

Fig. 4. (a) The percentage of remaining drug within the Zn/La³⁺/MOF system versus time, **(b)** Logarithm of the percentage of remaining drug versus time, **(c)** Cumulative release of the active substance from Zn/La³⁺/MOF per unit surface area versus time, **(d)** Cumulative release of the active substance per unit surface area as a function of the square root of time (Mean ± SD, n=3).

4.CONCLUSIONS

In this study, we successfully synthesized Zn/La³⁺-based metal-organic frameworks (MOFs) using a co-precipitation assisted microwave method. The synthesized MOFs were characterized by SEM, TEM, FT-IR, and DLS, confirming their uniform particle size and the presence of functional groups essential for drug encapsulation. The in vitro release studies indicated that Zn/La³⁺/MOFs provide a sustained release profile for captopril, with a release rate of 41% over 300 minutes, compared to 64% for pure captopril. The zero-order kinetic model was identified as the most suitable for describing the drug release behavior. These findings suggest that Zn/La³⁺/MOFs are a promising platform for controlled drug delivery, offering protection and sustained release of therapeutic agents. Future work should focus on further optimizing the MOF synthesis and expanding the range of encapsulated drugs to fully realize the potential of this delivery system.

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چارچوب‌های آلی–فلزی بر پایه Zn/La^{3+} : رویکردی نوین برای رهایش کنترل‌شده و پایدار کاپتوپریل

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چکیده

این مطالعه به سنتز چارچوب‌های آلی–فلزی بر پایه Zn/La^{3+} با استفاده از روش هم‌رسوبی به کمک ماکروویو می‌پردازد. شناسایی توسط میکروسکوپ الکترونی روبشی (SEM) و میکروسکوپ الکترونی عبوری (TEM) نشان داد که نانوذرات با اندازه یکنواخت حدود ۸۰ نانومتر تولید شده‌اند. طیف‌سنجی FT-IR حضور گروه‌های عاملی کلیدی را تأیید کرد. پخش نور دینامیکی (DLS) اندازه‌های بسیار یکنواخت ذرات را نشان داد. مطالعات رهایش در شرایط آزمایشگاهی کاپتوپریل از چارچوب‌های آلی–فلزی Zn/La^{3+} نشان داد که نرخ رهایش ۴۱٪ طی ۳۰۰ دقیقه بوده است، در حالی که برای کاپتوپریل خالص این میزان ۶۴٪ بوده است. انکپسولاسیون در ماتریس چارچوب آلی–فلزی رهایش کنترل‌شده و پایدار دارو را تضمین کرد و مدل سینتیک مرتبه اول بهترین تطابق را نشان داد. این چارچوب‌های آلی–فلزی Zn/La^{3+} نشان‌دهنده پتانسیل بالایی برای سیستم‌های دارورسانی کنترل‌شده و بهبود یافته هستند.

کلید واژه ها

چارچوب‌های آلی–فلزی؛ رهایش دارو؛ کاپتوپریل.

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