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Development and Characterization of Zinc-Based Metal–Organic Frameworks for Sustained Delivery of Clonidine Hydrochloride

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Abstract

The present study focuses on the development and characterization of zinc-based metal–organic frameworks (MOFs) for the sustained oral delivery of clonidine hydrochloride, a centrally acting antihypertensive drug with a short biological half-life and dose-related adverse effects. Zinc acetate was employed as the metal source, while fumaric acid and succinic acid were investigated as organic linkers to evaluate their influence on framework formation, drug entrapment, and release behavior. MOFs were synthesized using precipitation and solvent evaporation techniques, and drug loading was achieved through in-process and post-synthetic methods. Eight formulations (C1–C8) were prepared and screened based on percentage yield and entrapment efficiency. Fumaric acid-based MOFs (C1–C4) exhibited poor yield and low drug entrapment, leading to their exclusion from further optimization.

In contrast, succinic acid-based MOFs (C5–C8) demonstrated significantly improved performance, with formulation C7 showing the highest entrapment efficiency (68.00 ± 0.08%) and percentage yield (69.33 ± 0.77%). The optimized formulation was subjected to detailed physicochemical characterization using powder X-ray diffraction, scanning electron microscopy,

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Fourier-transform infrared spectroscopy, differential scanning calorimetry, and particle size analysis, confirming successful drug encapsulation, structural integrity, and nanoscale particle size. In vitro drug release studies revealed a sustained release of clonidine hydrochloride over 8 hours, following diffusion-controlled kinetics best described by the Korsmeyer–Peppas model. Accelerated stability studies conducted according to ICH guidelines demonstrated good physicochemical stability and acceptable shelf-life characteristics. Overall, the findings suggest that succinic acid-based zinc MOFs represent a promising platform for sustained oral delivery of clonidine hydrochloride, with potential to improve therapeutic efficacy and patient compliance in hypertension management.
Keywords: Clonidine Hydrochloride, Drug Delivery, Metal-Organic Frameworks, Sustained Release, Zinc-Based MOFs.

1. Introduction

Hypertension (high blood pressure) is a chronic and progressive cardiovascular condition typified by abnormally high arterial pressure. It is a major worldwide public health problem with more than 1.3 billion people affected globally, and leads to significant cardiovascular morbidity and mortality, stroke, myocardial infarction, heart failure, and chronic kidney disease [1]. It remains asymptomatic for many in its early stages and is nicknamed the “silent killer” because it can damage organs slowly over time before people even realize they have hypertension [2]. As a result, the early detection and control of hypertension are critical for minimizing disease burden and averting complications [3].

Current treatment for hypertension despite the development of numerous pharmacological agents such as thiazide diuretics, β-adrenergic blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) as hypotensive agents, the therapies for hypertension are still limited [4]. Acting in general as good anti-hypertensive agents, medications of such class are, however, often associated with limited clinical utility due to lower aqueous solubility, low oral bioavailability, and poor biological half-lives. These pharmacokinetic constraints frequently require dosing that is overly complicated, leading to low patient compliance, particularly in those with chronic diseases where lifelong treatment is needed. In addition, a number of these agents are accompanied by systemic side effects, for example, electrolyte imbalance, fatigue, dizziness, and orthostatic hypotension, which may have an adverse impact on treatment [5,6].

Clonidine Hydrochloride (HCl) is a centrally acting antihypertensive α_2-adrenergic receptor agonist. Clonidine HCl attenuates the sympathetic outflow from the CNS and thereby decreases peripheral vascular resistance and heart rate resulting in lower arterial blood pressure [7,8]. It is extremely useful in the treatment of resistant hypertension and hypertensive emergencies. However, use of Clonidine HCl is restricted due to a short half-life of elimination (approximately 12–16 hours), central nervous system side effects (especially sedation and dry mouth), and possibility of rebound hypertension with abrupt withdrawal[8,9]. These limitations justify the need for the design of more sophisticated drug carrier systems to improve its therapeutic profile [10].

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In recent years, MOFs have shown great potential for use as drug delivery materials. Metal-organic frameworks (MOFs) are a class of porous crystalline materials comprised of metal ions or clusters and organic ligands that are built into highly ordered three-dimensional networks [11]. Their unique features, including a very high surface to volume ratio, adjustable pore size, versatile chemistry and possibility of functionalization can be used to incorporate therapeutic drugs and control and sustain their delivery [12,13]. These features render MOFs very appealing for the oral delivery of drugs possessing low pharmacokinetics or a narrow therapeutic range [14].

There are many MOF systems but zinc-based MOFs have received more attention as they are biocompatible, easy to synthesize and have promising degradation pattern. Zinc, a necessary trace element in the body of a human being, also contributes to the other biosafety aspects of these frameworks [15,16]. Succinic acid and fumaric acid (both are FDA approved, low cost, and pharmaceutically acceptable carboxylic acid) are typical organic linkers in the synthesis of ZN-based MOFs. The linkers are key to adjust the physicochemical properties of the MOFs (e.g., crystallinity, stability, porosity which in turn influence drug encapsulation efficiency, and release kinetics due to the different pore sizes and properties [17].

The incorporation of Clonidine HCl in zinc-based MOFs offers a new approach to overcome short-comings associated with the conventional clonidine. Non-burst release is one of the disadvantages of MOF-based delivery systems, however, it has the advantage of sustained release which could help to decrease the dosing frequency and improve patient compliance, and avoid the peak-trough plasma concentration fluctuation. In addition, slow release may minimize the frequency of side effects related to dosage and optimize therapeutic effectiveness [18]. The flexibility of MOFs also allows post-synthetic or in-situ drug loading, which should be useful to optimize drug loading capacities as well as drug release.

Therefore, the aim of the present investigation is to prepare and assess *in vitro* drug release behavior of Clonidine HCl loaded zinc metal-organic frameworks using succinic acid and fumaric acid as organic linkers. MOFs with desired structure and functions are synthesized by two routes, precipitation and solvent evaporation. The formulations are characterized for their physicochemical and pharmaceutical characteristics such as particle size study, micromeritic properties, surficial morphology, drug loading efficiency and *in vitro* drug release studies. Additionally, accelerated stability studies & Shelf-Life (T90) estimation were conducted as per ICH guidelines to assess the formulation's robustness and shelf life. The ultimate goal is to develop a well-designed MOF -based DDS to improve the bioavailability, therapeutic performance and patient compliance of Clonidine HCl, leading to improved hypertension treatment.

To systematically develop a sustained-release formulation, the study began with preliminary screening of fumaric acid as a linker. Due to its poor entrapment and release performance, succinic acid was then selected for further optimization. Both phases are included to provide a complete development approach.

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2. Material of MOF

Clonidine HCl, the drug used as , the active pharmaceutical ingredient (API), was received from Nectar Lifesciences Ltd., India. Zinc acetate dihydrate (as metal ion source) and succinic acid (as organic linker for MOF synthesis) were procured from Loba Chem Pvt. Ltd., Mumbai. Ethanol (analytical grade) and distilled water were the solvents for synthesis and purification of MOFs. All the reagents and solvents were of analytical grade and used as received without further purification.

2.1. Synthesis of Metal–Organic Frameworks (MOFs)

To evaluate the impact of synthesis method and organic linker type on drug entrapment efficiency, metal-organic frameworks (MOFs) were synthesized using two different dicarboxylic acid linkers—succinic acid and fumaric acid—via two distinct fabrication techniques: precipitation and solvent evaporation.

2.1.1. Precipitation Method

For the preparation of MOFs via the precipitation method, 0.41 g (3.5 mmol) of succinic acid was accurately weighed and dissolved in 9.214 mL of ethanol to prepare the organic linker solution. Separately, 1.56 g (7.24 mmol) of zinc acetate dihydrate was dissolved in 11 mL of distilled water to form the metal ion solution. The zinc solution was added dropwise to the succinic acid solution with continuous magnetic stirring at room temperature. Within 15 minutes, a white precipitate began to form. Stirring was continued for a total of 24 hours to ensure complete coordination and formation of the metal–organic framework. The resulting precipitate was filtered, washed thoroughly with ethanol to remove unreacted materials, and dried overnight at room temperature in a desiccator.

For MOF preparation with fumaric acid (MOF-F), the same procedure was followed using 0.42 g (3.6 mmol) of fumaric acid dissolved in 14.96 mL of ethanol as the organic linker solution [19].

2.1.2. Solvent Evaporation Method

The solvent evaporation method was employed to investigate the effect of heat-assisted synthesis on framework formation.

In this method, 0.41 g of succinic acid was dissolved in 9.214 mL of ethanol, while 1.56 g of zinc acetate dihydrate was dissolved in 11 mL of distilled water. The metal solution was added slowly to the organic linker solution under constant stirring. The reaction mixture was then subjected to controlled heating at 60–70 °C to facilitate gradual solvent evaporation and crystallization. As the solvent evaporated, a white crystalline slurry was formed. Stirring and heating continued until a dense paste-like consistency was reached. The solid product was filtered, washed with ethanol, and dried overnight at ambient conditions.

The same process was repeated for fumaric acid-based MOF synthesis (MOF-F-SE) using 0.42 g of fumaric acid dissolved in 14.96 mL of ethanol [20].

2.2. Drug Loading Techniques

Two distinct loading strategies were employed to evaluate the influence of drug incorporation method on entrapment efficiency: in-process loading and post-synthetic loading.

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2.2.1. In-Process Loading (Co-Synthesis Method)

In this method, 100 mg Clonidine HCl was directly dissolved in zinc acetate solution before adding to the organic linker solution. The MOF was subsequently synthesized by using precipitation or solvent evaporation as mentioned above. This approach can help in trapping drug inside the MOF network while framework is being formed leading to evenly distributed drug molecules throughout the porous matrix [21].

2.2.2. Post-Synthetic Loading (Incubation Method)

For post-loading method 1gm of filtered oven dried MOF was dispersed in 20 mL of aqueous solution (100 mg of Clonidine HCl). The solution was continuously stirred at room temperature for 24 h to facilitate the penetration of drug in the internal pores of the MOF's structure. After incubation the material was filtered and washed gently with ethanol to ensure the removal of surface bound or unencapsulated drug and left at room temperature to dry [20]. **Table 1-2, Figure 1-2**

Table 1.: Quantitative composition of Clonidine HCl-loaded metal–organic frameworks using Fumaric acid as the organic linker

S. No.	Name of Ingredient	C1	C2	C3	C4
1.	Zinc Acetate	1.546	1.546	1.546	1.546
2.	Fumaric Acid	0.476	0.476	0.476	0.476
3.	Ethanol	14.960	14.960	14.960	14.960
4.	Distilled Water	11.040	11.040	11.040	11.040
5.	Clonidine HCl	0.100	0.100	0.100	0.100
6.	Total Weight of MOFs	2.122	2.122	2.122	2.122
7.	Manufacturing Process	Solvent Evaporation	Precipitation Method	Solvent Evaporation	Precipitation Method
8.	Drug Loading Process (Before/After MOF Formation)	Before	After	Before	After

Table 2.: Quantitative composition of Clonidine HCl - loaded metal-organic frameworks using Succinic acid as organic linker

S. No.	Formulation No.	C5	C6	C7	C8
	Name of ingredient	Quantity (in grams) per batch			
1.	Zinc Acetate	1.546	1.546	1.546	1.546
2.	Succinic acid	0.484	0.484	0.484	0.484
3.	Ethanol	9.214	9.214	9.214	9.214
4.	Distilled water	11.040	11.040	11.040	11.040
5.	Clonidine HCl	0.100	0.100	0.100	0.100

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6.	**Total weight of MOFs**	**2.130**	**2.130**	**2.130**	**2.130**
7.	Manufacturing process	Solvent Evaporation		Precipitation Method	
8.	Drug Loading process (Before/After MOFs Formation)	Before	After	Before	After

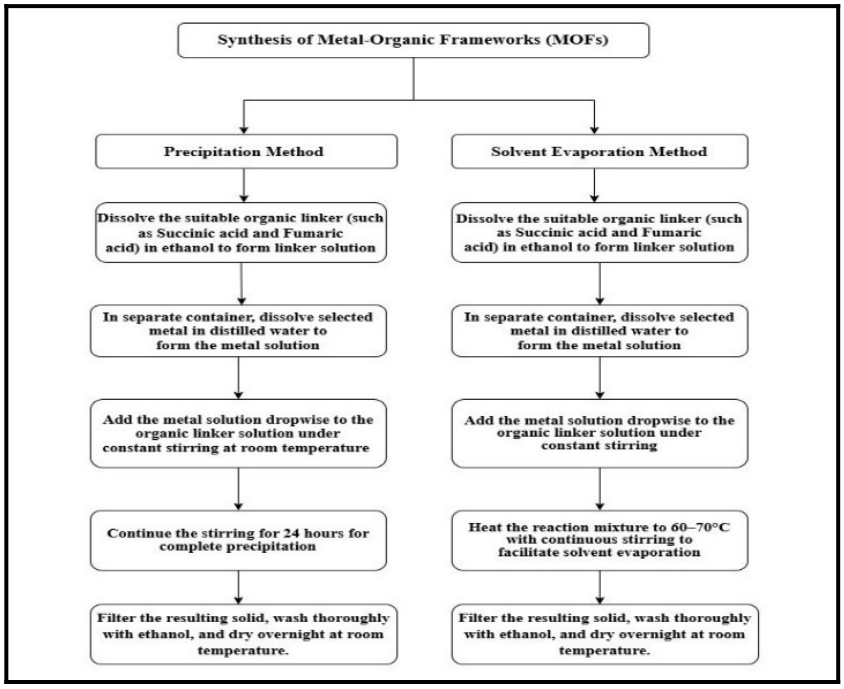

Figure 1.: Synthesis of Metal-Organic Frameworks (MOFs)

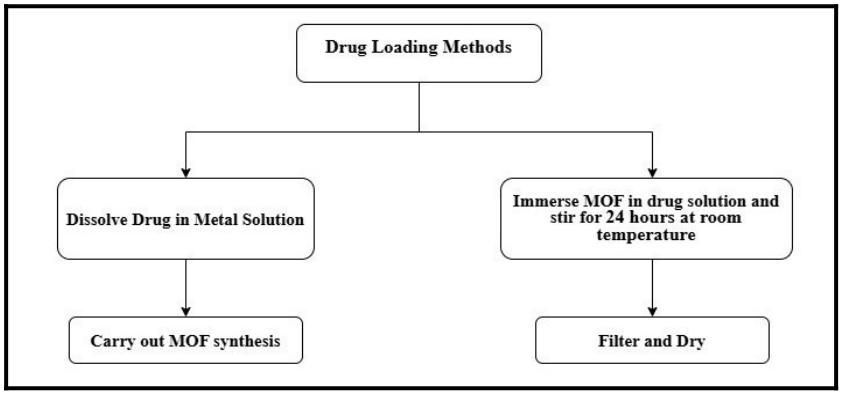

Figure 2.: Drug Loading Methods

3. Experimental Design

Eight formulations of Clonidine HCl loaded metal-organic frameworks (MOFs) were prepared in this study (C1–C8) using two organic linkers, namely the succinic acid and fumaric acid and by two different synthesis methods namely precipitation method and

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solvent evaporation method.

Drug loading was carried out through in situ loading in addition to post-synthetic loading. All these formulations were prepared with equal quantity of excipients, the difference in results was attributed only to linker type, synthesis method and method of drug loading.

Entrapment efficiency and percentage yield were the overall primary screening parameters for each formulation. Formulation C7, prepared with succinic acid through precipitation method employing in process drug loading, exhibited maximum entrapment efficiency (68.00±0.70%) and yield (69.33±0.77%) and hence chosen as the optimized formulation.

Additional physicochemical characterization (Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry, Powder X-ray Diffraction, Scanning Electron Microscopy and particle size analysis) was performed with the optimized formulation to verify its structural and thermodynamic characteristics. Since all the formulation contained the same excipient ratios and only the synthetic variables varied, further characterizations of non-optimized batches were not carried.

Formulations C1–C4 using fumaric acid served as the screening set, while C5–C8 using succinic acid were optimized based on performance. This progression guided the formulation development strategy.

3.1. Characterization Methods of Metal–Organic Frameworks (MOFs)

3.1.1. Preliminary Screening – Fumaric Acid-Based MOFs (C1–C4)

In the initial screening phase, four MOF formulations (C1–C4) were prepared using zinc acetate dihydrate as the metal source and fumaric acid as the organic linker. Two synthesis methods were employed: solvent evaporation and precipitation. Each method was combined with two different drug-loading strategies — in-process loading and post-synthetic loading.

- C1: Solvent evaporation + in-process drug loading
- C2: Precipitation + in-process drug loading
- C3: Solvent evaporation + post-synthetic drug loading
- C4: Precipitation + post-synthetic drug loading

The aim of this phase was to evaluate basic feasibility based on percentage yield and drug entrapment efficiency. Due to poor performance, no further characterization (e.g., PXRD, FTIR) was conducted on these batches.

Percentage Yield (%): The synthesis yield of MOFs was calculated to evaluate process efficiency using the formula:

$$\textbf{Percentage Yield (\%)} = (\text{Actual Yield}/\text{Theoretical Yield}) \times 100$$

Percentage Entrapment Efficiency: A fixed quantity of MOF was dispersed in 0.1 N HCl, sonicated, and centrifuged to release the drug. The supernatant was filtered and analyzed at 271 nm using a UV spectrophotometer.

$$\text{Entrapment Efficiency (\%)} = \frac{Amount\ of\ drug\ entrapped \in MOF}{Total\ amount\ of\ drug\ used\ for\ loading} \times 100$$

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3.1.2. Optimization Phase – Succinic Acid-Based MOFs (C5–C8)

Based on the findings from the preliminary screening phase, succinic acid was selected as the organic linker for further optimization. Four formulations (C5–C8) were prepared using the same synthesis strategies as in the screening phase, involving solvent evaporation and precipitation methods combined with in-process or post-synthetic drug loading. Specifically, formulation C5 was prepared by solvent evaporation with in-process drug loading, C6 by precipitation with in-process loading, C7 by precipitation with post-synthetic loading, and C8 by solvent evaporation with post-synthetic loading. These formulations were subjected to comprehensive physicochemical and performance characterization, including percentage yield, entrapment efficiency, particle size analysis, Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and *in vitro* drug release studies.

Powder X-ray Diffraction (PXRD): PXRD measurements were carried out in order to verify the crystalline nature and phase purity of the obtained MOF. The characteristic diffraction peaks can confirm that the anticipated crystal structure was obtained by the experimental reactions and the stability of MOF framework after drug loading [22].

Scanning Electron Microscopy (SEM): SEM was used to view the surface morphology and particle shape of the MOFs. This approach will offer insight into particle texture, surface roughness and aggregation [23].

Particles Size Analysis: The particle size of the drug loaded MOF formulation was determined so that its physical properties could be investigated, which could have an impact on drug release and bioavailability. Measurements comprised Z-average diameter and polydispersity index (PDI) based on dynamic light scattering methods [24].

Differential Scanning Calorimetry (DSC): DSC was employed to characterize the thermal features and physical state of Clonidine HCl when incorporated in MOF. The presence or absence of shift in the melting point of the drug implied changes in crystallinity and drug–excipient interactions [25].

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectroscopy was employed to identify functional groups and confirm the coordination between metal ions and organic linkers. Successful drug incorporation was verified by detecting characteristic peaks of both Clonidine HCl and the MOF framework [26].

Percentage Yield (%): The synthesis yield of MOFs was calculated to evaluate process efficiency using the formula:

$$\textbf{Percentage Yield (\%)} = (\text{Actual Yield}/\text{Theoretical Yield}) \times 100$$

3.1.2.1. Percentage Entrapment Efficiency: A fixed quantity of MOF was dispersed in 0.1 N HCl, sonicated, and centrifuged to release the drug. The supernatant was filtered and analyzed at 271 nm using a UV spectrophotometer.

$$\text{Entrapment Efficiency (\%)} = \frac{\textit{Amount of drug entrapped} \in \textit{MOF}}{\textit{Total amount of drug used for loading}} \times 100$$

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In-Vitro Drug Release Study: For controlled release studies assessment, in-vitro release pattern of Clonidine Hydrochloride was studied in simulated gastric fluid from drug loaded drug-loaded metal–organic framework (MOF). The investigations were performed in a USP Type II dissolution apparatus (paddle method). Drug loaded MOF was then added in a known quantity in 900 mL 0.1 N hydrochloric acid (pH 1.2) controlled at 37±0.5°C. The paddle stirrer operated at a speed of 50 rpm to ensure homogenous distribution of dissolution medium.

1mL aliquots were taken at the following sampling periods: 0, 15, 30, 45, 60, 90, 120, 240, 360, and 480 minutes. At the end of each sampling, 0.1 N HCl (pre-warmed to the same temperature) was added to the solution to ensure the sink condition and a constant volume in the receptor compartment. These samples were filtered to eliminate solid, when necessary, diluted and analyzed with a UV-visible spectrophotometer at 271 nm. All experiments were conducted in triplicate and presented as the cumulative percent drug release, mean ± SD [27].

Release Kinetics Analysis: The release kinetics of Clonidine HCl loaded MOF was studied using drug release data of the *in vitro* and were calculated according to Zero-order, First-order, Higuchi and Korsmeyer–Peppas models of kinetic models to establish the release mechanism. The most appropriate model was selected according to the highest R^2 value of the plot. Moreover, the release exponent (n) of the Korsmeyer–Peppas model was considered to interpret the mechanism of drug release, where n of about 0.45 represents Fickian diffusion, n between 0.45 and 0.89 indicates non-Fickian (anomalous) transport, and $n \geq 0.89$ refers to case-II transport. The release study confirmed the controlled and prolonged release pattern of the MOF-based formulation [27].

Stability Study and Shelf-life Estimation (T_{90}) : Stability studies were carried out on the optimized Clonidine Hydrochloride-loaded Metal-Organic Framework (C7) to evaluate its physicochemical and functional integrity under accelerated conditions, in accordance with ICH Q1A(R2) guidelines. The C7 formulation was stored at 40 ± 2 °C / 75 ± 5 % RH for a period of 30 days. Samples were packed in amber-colored glass vials and analyzed at 0, 7, 14, 21, and 30 days.

The evaluated parameters included physical appearance, percent drug content, entrapment efficiency, and *in vitro* drug release. All analyses were performed in triplicate using validated, stability-indicating analytical methods. Drug release profiles before and after storage were statistically compared using model-independent approaches, namely the difference factor (f_1) and similarity factor (f_2). An f_1 value below 15 and an f_2 value above 50 indicate similarity between dissolution profiles, thereby confirming formulation stability.

In addition, shelf-life estimation (t_{90}) was carried out based on the degradation kinetics of clonidine hydrochloride under accelerated storage conditions. The t_{90} value, defined as the time required for the drug content to decline to 90 % of its initial value, was calculated using regression analysis of percent drug remaining versus time.

The estimated t_{90} indicates that the optimized C7 formulation possesses acceptable stability and is expected to maintain its potency within pharmacopeial limits during storage [28,29].

4. Results

4.1. Preliminary Screening – Fumaric Acid-Based MOFs (C1–C4)

The fumaric acid-based formulations exhibited lower percentage yield and entrapment efficiency compared to their succinic acid counterparts. These outcomes guided the shift toward succinic acid for further optimization.

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Percentage Yield (%): The percentage yield of the MOF formulations prepared using fumaric acid (C1–C4) is summarized in Table 3. Among these, the highest yield was observed in formulation C4 (36.48 ± 0.29%), followed by C3 (35.34 ± 0.51%), C2 (30.25 ± 0.51%), and the lowest in C1 (25.16 ± 0.21%). These results reflect relatively poor product recovery and suggest that fumaric acid-based formulations were less efficient under the given synthetic conditions. The low yield may be attributed to weaker coordination interactions between fumaric acid and zinc ions, leading to incomplete or unstable framework formation. These findings emphasized the need for formulation optimization, which was addressed in the subsequent phase using succinic acid as the linker as demonstrated in **Table 3 and Figure 3.**

Table 3: Screening phase: Percentage yield of MOFs formulated using fumaric acid

Formulation	Yield (%)
C1	25.16 ± 0.21
C2	30.25 ± 0.51
C3	35.34 ± 0.51
C4	36.48 ± 0.29

* Data has been expressed as Mean ± SD, n = 3

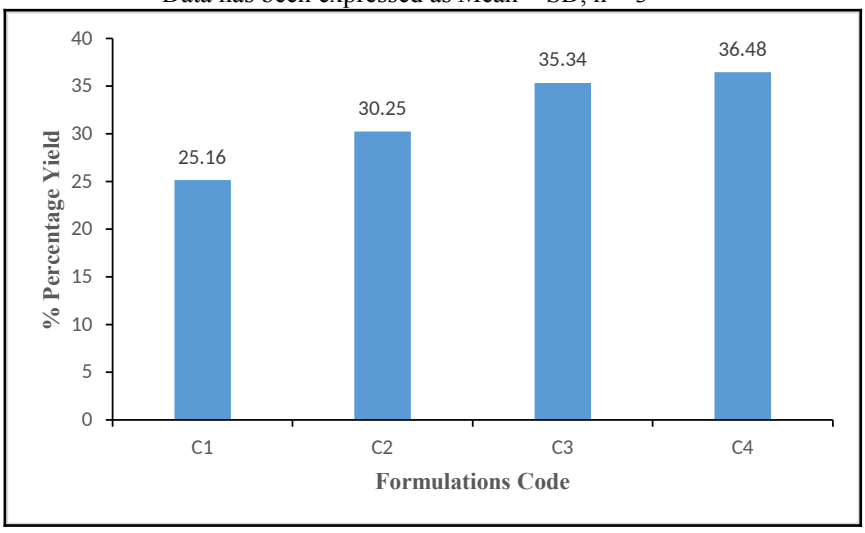

Figure 3.: Percentage Yield of Clonidine Hydrochloride-Loaded MOF Formulations (C1–C4)

Percentage Entrapment Efficiency: The entrapment efficiencies for the screening-phase MOF formulations (C1–C4), prepared using fumaric acid as the organic linker, are presented in **Table 4**. Among these, formulation C4 exhibited the highest entrapment efficiency of 12.35 ± 0.07%, while the lowest was observed in C1 (4.45 ± 0.05%). Moderate values were seen in C2 (5.00 ± 0.10%) and C3 (8.48 ± 0.08%). These findings indicate that fumaric acid-based MOFs demonstrated relatively poor drug loading capacity, likely due to weaker coordination with zinc ions or suboptimal framework formation under the selected synthetic conditions (**Figure 4)**

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Table 4: Screening phase: Entrapment efficiency of MOFs formulated using fumaric acid

Formulation	Entrapment Efficiency (%)
C1	4.45 ± 0.05
C2	5.00 ± 0.10
C3	8.48 ± 0.08
C4	12.35 ± 0.07

* Data has been expressed as Mean ± SD, n = 3

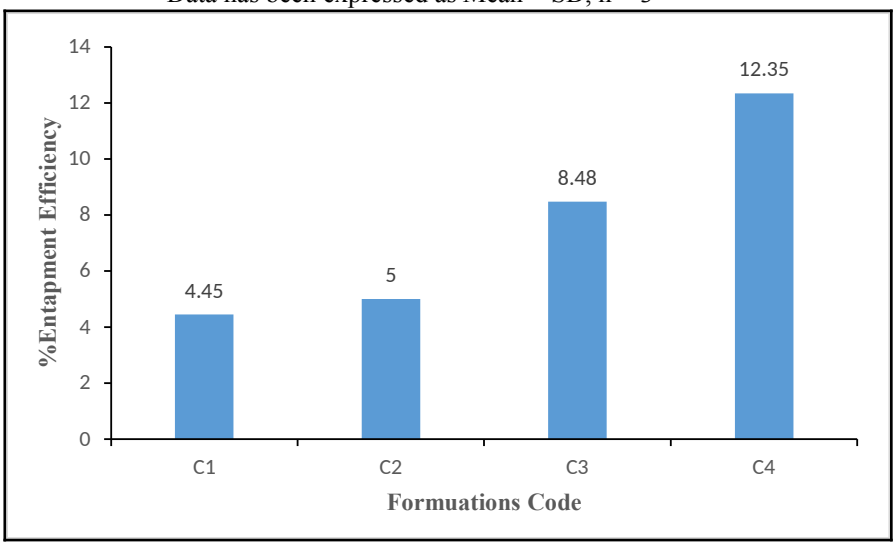

Figure 4.: Percentage entrapment efficiency of different formulations (C1-C4)

4.2. Optimization Phase – Succinic Acid-Based MOFs (C5–C8)

Succinic acid-based formulations demonstrated significantly improved outcomes in both yield and entrapment efficiency. This confirmed succinic acid as the more effective linker for further development.

Percentage Yield (%): The percentage yield of the optimized MOF formulations using succinic acid (C5–C8) is presented in **Table 5**. The highest yield was recorded with formulation C8 (67.07 ± 0.39%), followed by C7 (69.33 ± 0.77%), C6 (69.71 ± 0.34%), and C5 (58.40 ± 0.60%).

These values indicate a marked improvement over the fumaric acid-based formulations and reflect the enhanced efficiency of succinic acid in MOF formation. The higher yields observed in this phase can be attributed to better solubility and stronger coordination between succinic acid and zinc ions, resulting in more stable and well-formed frameworks. These findings confirm the effectiveness of succinic acid as a suitable organic linker for achieving improved synthesis and product recovery as demostrated in **Figure 5**

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Table 5: Optimization phase: Percentage yield and entrapment efficiency of MOFs formulated using succinic acid

Formulation	Yield (%)
C5	58.40 ± 0.60
C6	69.71 ± 0.34
C7	69.33 ± 0.77
C8	67.07 ± 0.39

* Data has been expressed as Mean ± SD, n = 3

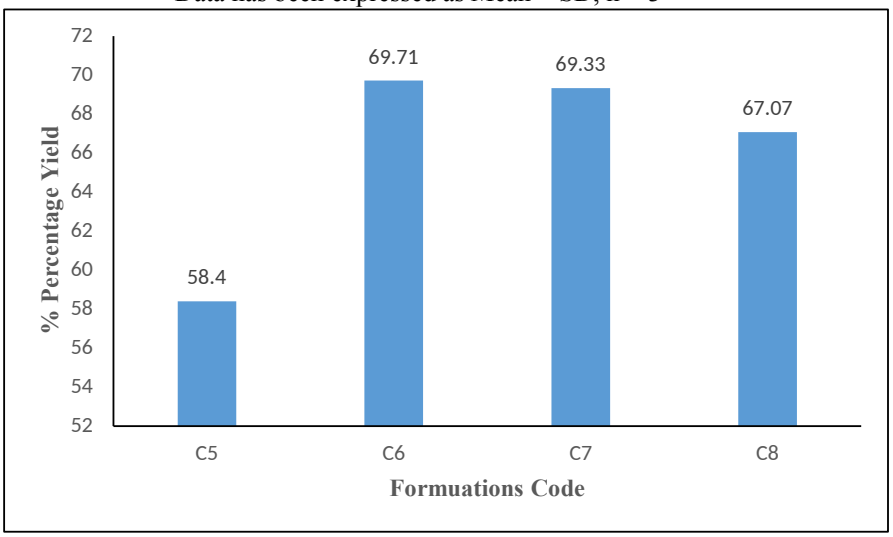

Figure 5.: Percentage Yield of Clonidine Hydrochloride-Loaded MOF Formulations (C5–C8)

Percentage Entrapment Efficiency: The entrapment efficiencies of the optimized MOF formulations (C5–C8), prepared using succinic acid as the organic linker, are presented in **Table 6**. Among these, formulation C7 exhibited the highest entrapment efficiency at 68.08 ± 0.08%, followed by C5 (30.34 ± 0.07%) and C8 (28.00 ± 0.70%). Formulation C6 showed a slightly lower efficiency of 23.57 ± 0.06%, which was still significantly higher than those observed in the screening phase. These results suggest that succinic acid contributed to more effective coordination with zinc ions and improved framework formation, thereby enhancing drug loading capacity.

The findings support the selection of succinic acid-based MOFs for further optimization and characterization (**Figure 6)**

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Table 6: Optimization phase: Entrapment efficiency of MOFs formulated using succinic acid

Formulation	Entrapment Efficiency (%)
C5	30.34 ± 0.07
C6	23.57 ± 0.06
C7	68.00 ± 0.08
C8	28.77 ± 0.70

* Data has been expressed as Mean ± SD, n = 3

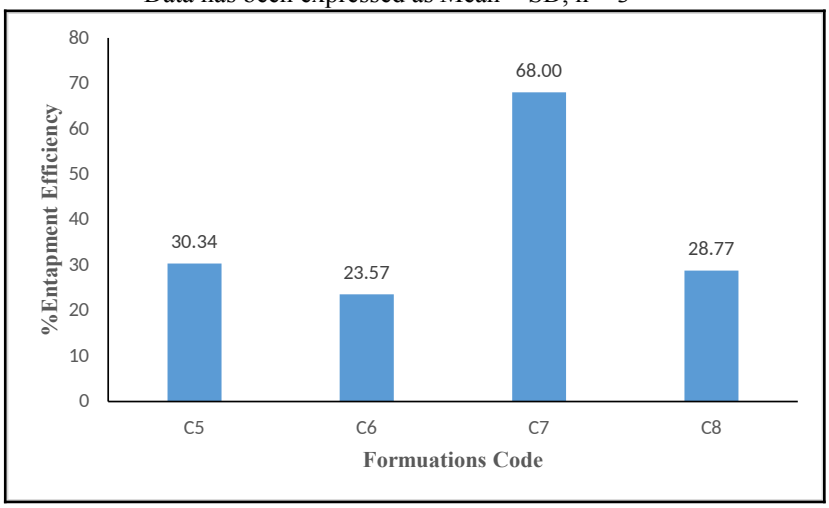

Figure 6: Percentage entrapment efficiency of different formulations (C5-C8)

Powder X-ray Diffraction (PXRD): X-ray diffraction (XRD) studies were conducted to evaluate the crystallinity, structural integrity, and drug loading characteristics of the synthesized zinc-based metal-organic framework (MOF) using succinic acid. Comparative XRD analyses were performed for both the unloaded and clonidine hydrochloride-loaded MOFs.

4.2.1 XRD of Unloaded MOF

The XRD pattern of the synthesized MOF was observed with very sharp and intense peaks at different 2θ values, suggesting its high crystallinity. The major diffraction peaks were located at about 15.58°, 18.67°, 22.73°, 25.30°, 27.73°, 30.93° and 33.12°. The calculated crystallinity was 79.2%, indicating well-ordered crystalline Framework. It demonstrates that during coordination process between Zn(II) ions and succinic acid, a stable and highly porous networks are obtained for drug loading. The lack of significant amorphous humps also supports that the sample is phase pure (**Figure 7, Table 7)**

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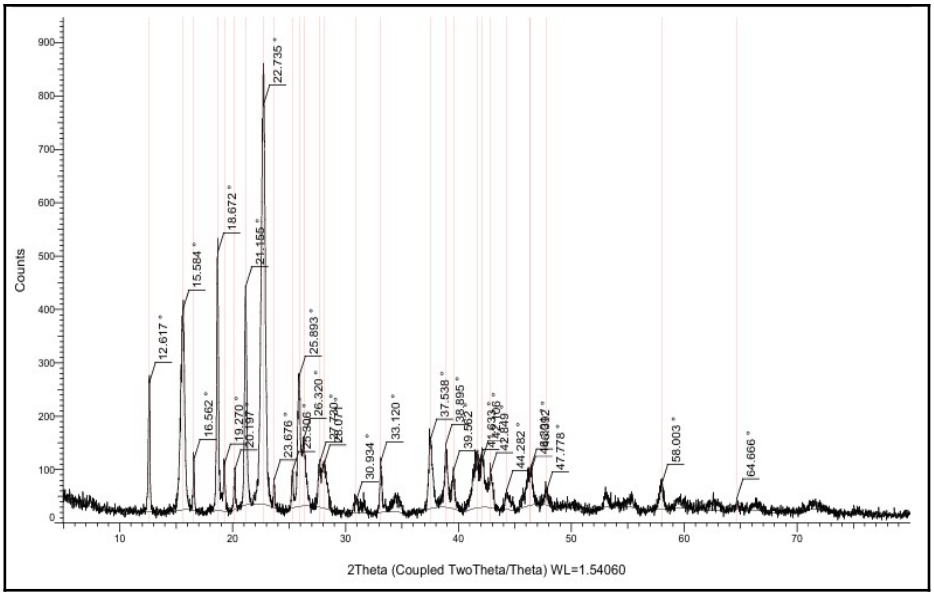

Figure 7.: XRD pattern of unloaded Zn-based MOF

Table 7.: Major diffraction peaks and crystallinity of unloaded MOF

2θ (°)	Relative Intensity (%)	Crystallinity (%)
15.584	12.8	79.2%
18.672	64.6	
22.735	100.0	
25.306	9.2	
27.730	17.0	
30.934	2.9	
33.120	12.7	

4.2.2. XRD of Drug-Loaded MOF

In the synthesis process, Clonidine hydrochloride was loaded in the MOF framework. The obtained XRD pattern showed typical characteristic peaks of the MOF and only small movements for the peaks and subtle decreases of peak intensity, which indicated that the framework of the MOF did not collapse after drug loading. Prominent diffraction peaks were detected at 15.37°, 18.65°, 22.51°, 25.84°, 27.73°, 30.90°, and 33.09°. The drug loaded MOF was found to be 77.1% crystalline. A small reduction in crystallinity (~2%) is acceptable and indicates that Clonidine hydrochloride has been incorporated into the MOF pores during formation without significant damage to the crystalline structure (**Figure 8, Table 8)**

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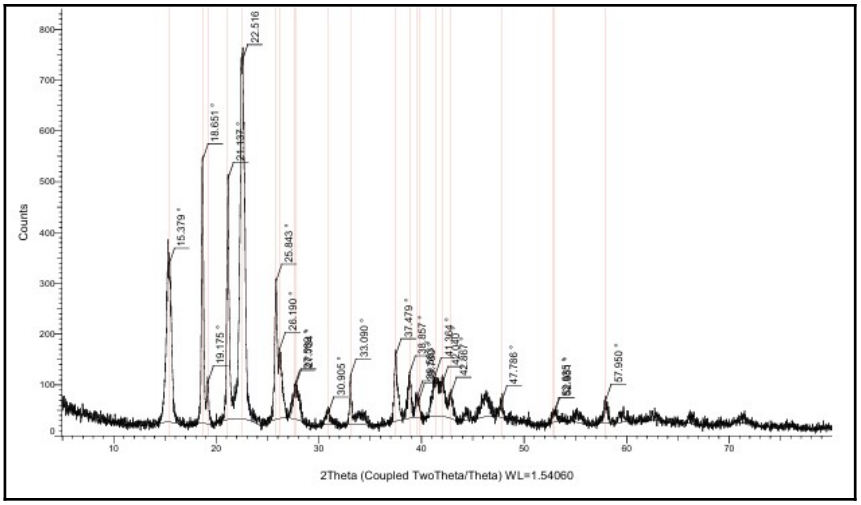

Figure 8.: XRD pattern of drug-loaded Zn-MOF

Table 8.: Major diffraction peaks and crystallinity of drug-loaded MOF

2θ (°)	Relative Intensity (%)	Crystallinity (%)
15.379	44.0	77.1%
18.651	73.6	
22.516	100.0	
25.843	38.7	
27.734	8.9	
30.905	3.0	
33.090	13.6	

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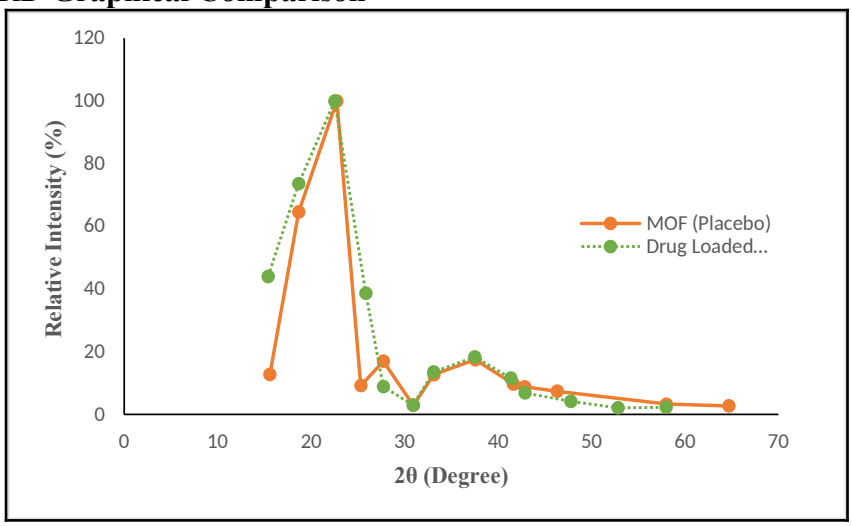
Figure 9: XRD Graphical Comparison



Scanning Electron Microscopy (SEM): The SEM image shows crystalline, rod-like particles with agglomerated morphology. The particles are in the nanometer range (~200 nm scale), confirming nanoscale formation. The sample was imaged at 15.0 kV, 11.0 mm WD, and 27,000× magnification. The well-defined structure suggests good crystallinity and potential for efficient drug loading in the delivery system as shown in **Figure 10**

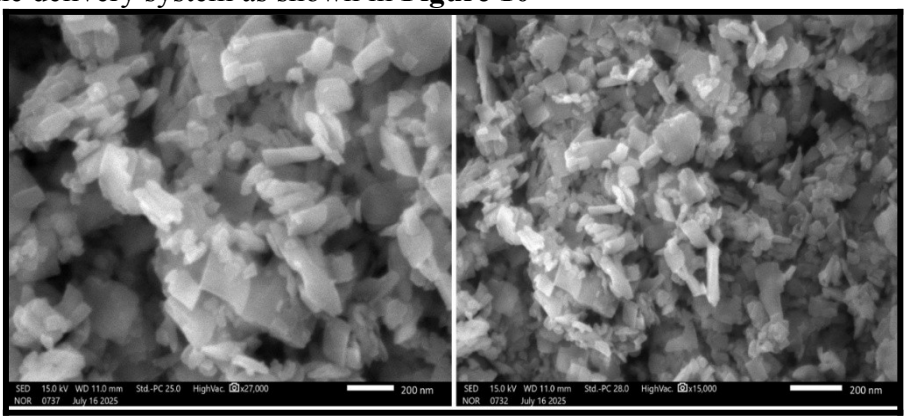


Figure 10.: Scanning Electron Microscopy of Clonidine Hydrochloride Loaded MOF

Particle Size Analysis: The particle size and distribution of MOF (Formulation C7)-loaded with Clonidine HCl were investigated to comprehend the impact on drug loading, release kinetics and formulation performance

The obtained results (Fig 1 and Table 3) showed that the Z-average particle size was 203.3 nm, indicating the nanoscale characteristics of the formulation that is favorable as mean for engineered-drug delivery system. The PDI value was 0.286, which suggested a relatively homogeneous size distribution. Moreover, the primary intensity peak observed at a peak position of 97.22 nm with the intercept value 0.967 indicated the measurement is reliable and accurate.

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These results suggest that the MOF particles have the intended nanoscale size and uniform size distribution, which is in favor of their desired drug delivery applications (**Figure 11, Table 9)**

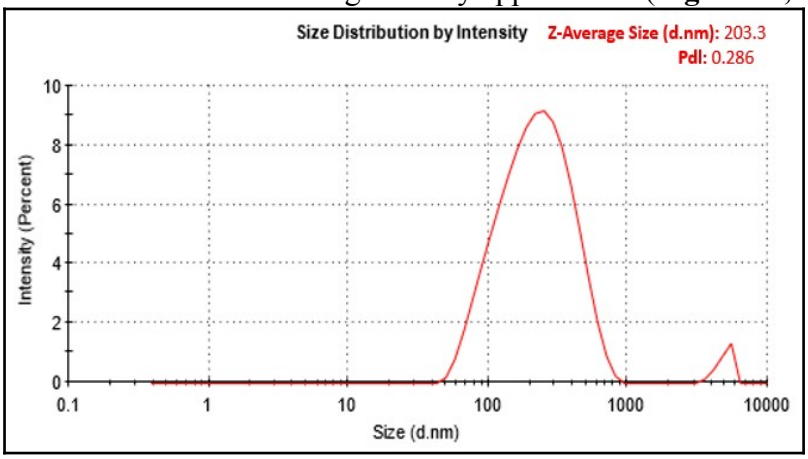

Figure 11.: Particle size analysis of Clonidine Hydrochloride loaded MOF (C7 Formulation)

Table 9.: Observed Value of Particle size analysis of Clonidine Hydrochloride loaded MOF

Parameter	Observed Value
Z-Average Size (d.nm)	203.3 nm
Polydispersity Index (PDI)	0.286
Major Peak (Intensity)	97.22 nm
Intercept	0.967
Result Quality	Good

4.2.3 Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetric analysis was performed to investigate the thermal properties, purity, and physical state of the pure Clonidine Hydrochloride and MOF-drug (C7) formulation. Around 2–5 mg each was taken in a sealed aluminium pan and measurement was taken in DSC instrument under nitrogen environment with the 10°C/min heating rate and temperature from 30°C to 300°C.

The identification of the drug was confirmed by determining the melting point of pure Clonidine HCl by using DSC where a sharp endothermic peak was obtained in the 244–251°C range and compared with literature value of the melting range between 240 and 310°C, indicating the drug purity and its good thermal stability.

The DSC thermogram of the MOF-loaded C7 formulation was also measured in order to detect potential shifts or alterations of the melting behavior that would be indicative of drug-matrix interactions or the amorphous dispersion of the API into the framework as shown in **Table 10, Figure 12-13**

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Table 10.: Meting point Analysis Data of Clonidine Hydrochloride and Clonidine Hydrochloride loaded MOF

Method Used	Experimental Value	Literature Value
Differential Scanning Calorimetry of Clonidine Hydrochloride	244 ˚C - 251 ˚C	240 ˚C –310 ˚C
Differential Scanning Calorimetry of Clonidine Hydrochloride loaded MOF	261 ˚C - 269 ˚C	200 ˚C - 300˚C

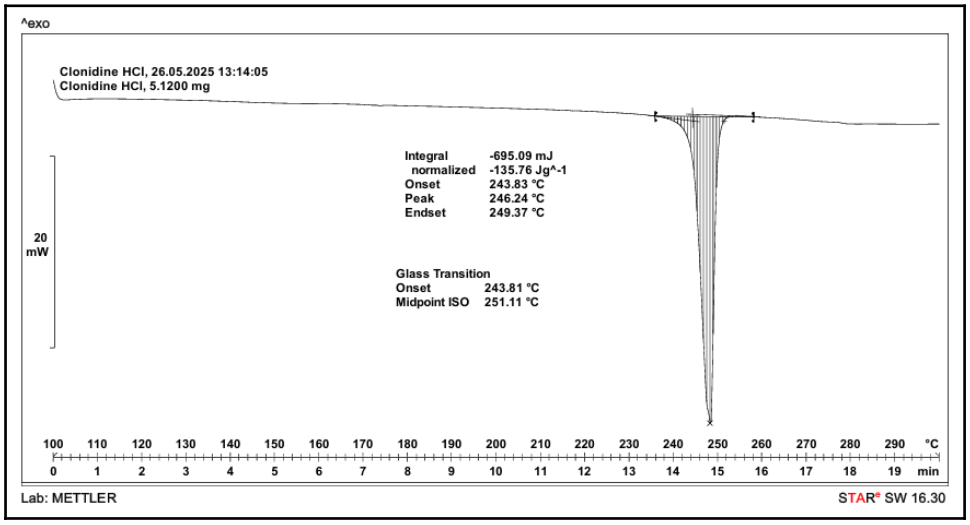

Figure 12.: Differential Scanning Calorimetry (DSC) of Clonidine Hydrochloride

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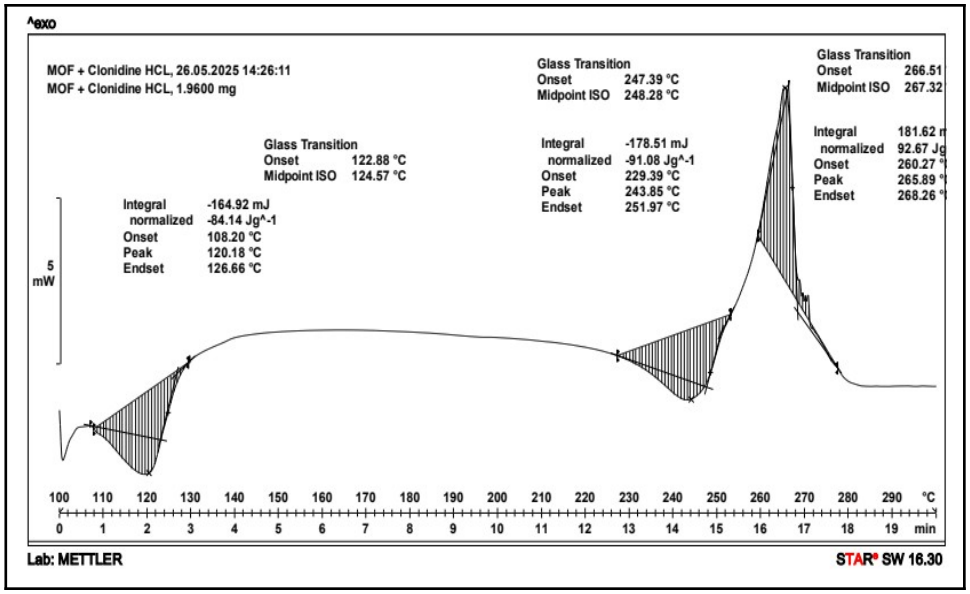

Figure 13.: Differential Scanning Calorimetry (DSC) of Clonidine Hydrochloride loaded MOF (C7 Formulation)

4.2.4. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy of the Clonidine HCl containing MOF (Formulation C7) was carried out to verify the functional group interactions and encapsulation. The spectrum (Fig 4) exhibited a band located in the range of 3300–3400 cm−1 with a broad shape related to the O–H and N–H stretching, which indicated a contribution of succinic acid as well as of clonidine. Changes of the C=O (1710 cm^{-1}) and C=N (1620 cm^{-1}) bands indicated a coordination or hydrogen bonding. A bands at 1585 cm^{-1} and 1385–1400 cm^{-1} were observed due to asymmetry and symmetry stretching COO^- of the Zn^{2+}–carboxylate bonds, respectively. A stretching Zn−O vibration near 600 cm^{-1}, which could be observed, confirmed the MOF formation, while bands at about 1265 cm^{-1} (C–N) and aromatic C–H bending provided additional evidence of Clonidine HCl dispersion. These results verify the achievement of proper framework synthesis and drug encapsulation (**Figure 14, Table 11)**

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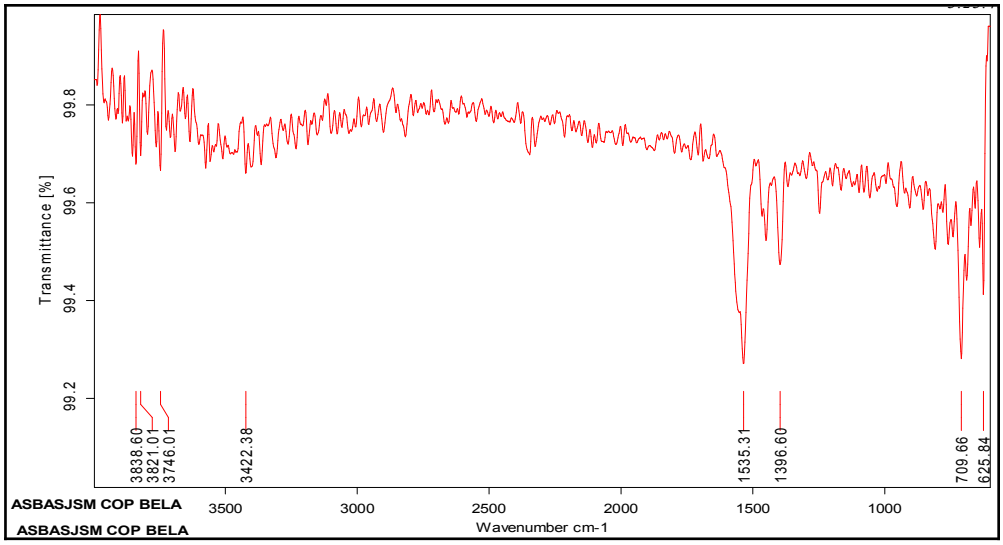

Figure 14.: Fourier transform infrared (FT-IR) of Clonidine Hydrochloride loaded MOF (C7 Formulation)

Table 11.: FTIR Range and functional groups present in C7 Formulation

Functional Group / Bond	**Typical Range (cm^{-1})**	**Observed (cm^{-1})**	**Interpretation**
Broad O–H / N–H stretching	3200–3500	~3300–3400	Broad peak indicates presence of both succinic acid (O–H) and clonidine (N–H)
C=O (acid stretch)	1700–1725	~1710	Retained; slightly shifted, suggests interaction with Zn^{2+}
C=N (imidazoline ring)	1610–1640	~1620	Present, slight shift suggests coordination or hydrogen bonding
COO^- asymmetric stretching	1550–1610	~1585	Confirms coordination of succinate with Zn^{2+}
COO^- symmetric stretching	1300–1440	~1385–1400	Slight shift confirms metal–carboxylate bonding
C–N stretching	1250–1300	~1265	Present, indicating presence of clonidine
Zn–O / Zn–O–C	500–700	~600	Confirms MOF formation
Aromatic C–H bending	700–900	Present	Confirms clonidine aromatic ring retained

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4.2.1. In-Vitro Drug Release Study:

The percent cumulative drug release up to 480 minutes for formulations C3 to C8 are shown in Table 8. The findings show significant heterogeneity in drug release that is dependent upon both synthesis route and organic linker. C7 exhibited the highest cumulative release (67.90 ± 0.03%) followed by C5 (30.00 ± 0.05%) and C8 (28.30 ± 0.02%) in tested formulations. On the other hand, C3 and C4 had the lowest release values (8.45 ± 0.02 and 11.70 ± 0.02%), which suggested the less migration from these matrices. C6 showed the moderate drug release (23.30 ± 0.03%). These findings highlight the significant impact of formulation parameters, particularly the choice of linker and synthesis method—on the drug release characteristics of clonidine-loaded MOFs.

Note: *In vitro* dissolution studies were not performed for formulations C1 and C2 due to the degradation of the MOF samples during storage, rendering them unsuitable for release testing.

Table 12, Figure 15

Table 12.: Percentage cumulative drug release vs Time intervals data of different formulations of Clonidine Hydrochloride- loaded metal - organic frameworks

Time (min)	C3	C4	C5	C6	C7	C8
0	0.00	0.00	0.00	0.00	0.00	0.00
15	0.99 ± 0.02	1.81 ± 0.03	9.25 ± 0.05	3.47 ± 0.02	24.93 ± 0.06	6.77 ± 0.02
30	2.63 ± 0.04	3.45 ± 0.05	11.72 ± 0.02	5.94 ± 0.04	33.19 ± 0.05	9.25 ± 0.05
45	3.45 ± 0.05	5.10 ± 0.05	15.85 ± 0.05	10.07 ± 0.02	43.09 ± 0.04	13.37 ± 0.02
60	5.10 ± 0.05	5.92 ± 0.07	19.15 ± 0.05	13.37 ± 0.02	49.70 ± 0.05	16.68 ± 0.02
90	5.92 ± 0.07	7.57 ± 0.03	22.46 ± 0.03	16.68 ± 0.02	54.65 ± 0.05	19.15 ± 0.04
120	7.57 ± 0.03	8.39 ± 0.03	24.93 ± 0.02	19.15 ± 0.04	60.43 ± 0.02	22.46 ± 0.03
240	8.39 ± 0.03	10.03 ± 0.03	27.41 ± 0.02	21.63 ± 0.02	62.91 ± 0.03	25.76 ± 0.03
360	8.39 ± 0.01	11.68 ± 0.02	29.89 ± 0.03	23.28 ± 0.02	67.86 ± 0.03	28.23 ± 0.02
480	8.45 ± 0.02	11.70 ± 0.02	30.00 ± 0.05	23.30 ± 0.03	67.90 ± 0.03	28.30 ± 0.02

* Data has been expressed as Mean ± SD, n = 3

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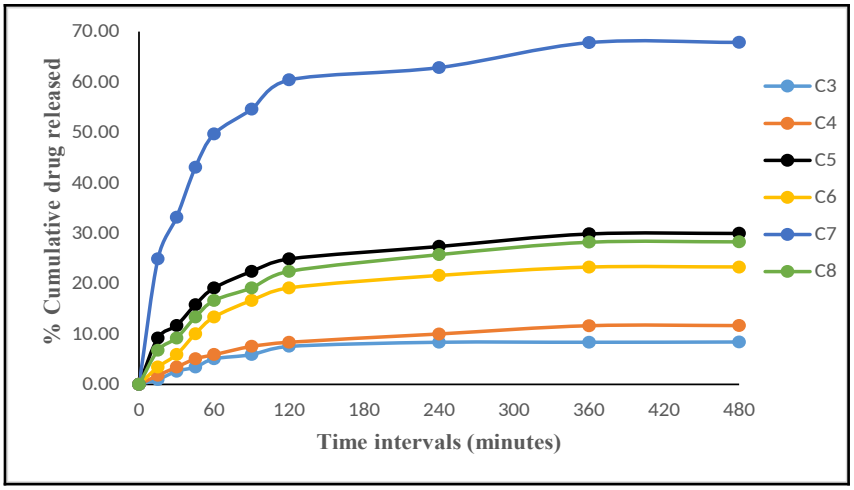

Figure 15.: Percentage cumulative drug release vs Time intervals profiles of prepared formulations

4.2.2. Release Kinetics Analysis

From *in vitro* release data of Clonidine HCl-loaded MOF tablet (Formulation C7), the release data was analyzed according to various models including Zero-order, First-order, Higuchi and Korsmeyer–Peppas to understand the release mechanism. From which, the Korsmeyer–Peppas model presented the highest correlation (R^2 = 0.8842) and followed after n = 0.34 (Fickian release mechanism). Higuchi model also fit very well (R^2 = 0.8020), thus confirming a diffusion controlled process. On the other hand, the Zero-order (R^2 = 0.6507) and First-order (R^2 = 0.6863) models exhibited less correlation demonstrating irregular and less concentration dependent release. These results confirm that in the MOF system the release of drug was mainly diffusion controlled as would be expected. **Figure 16-19, Table 13**

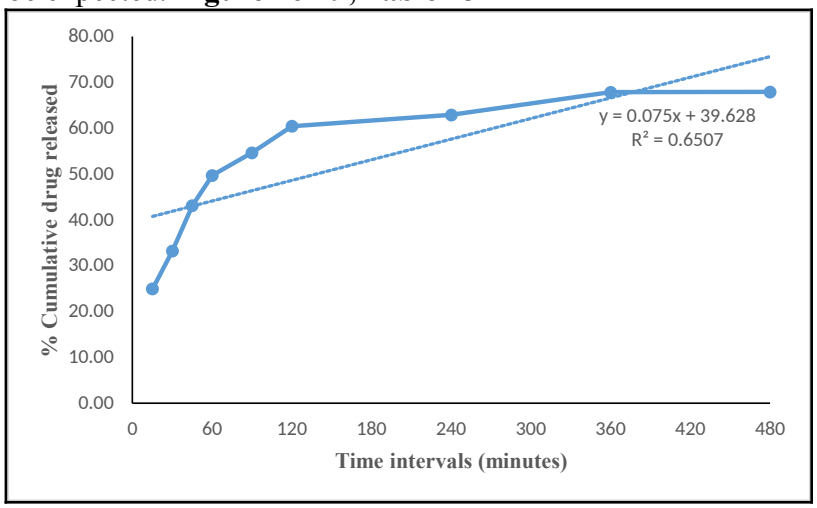

Figure 16.: Zero Order: Graph was plotted between % cumulative drug released Vs Time (mins)

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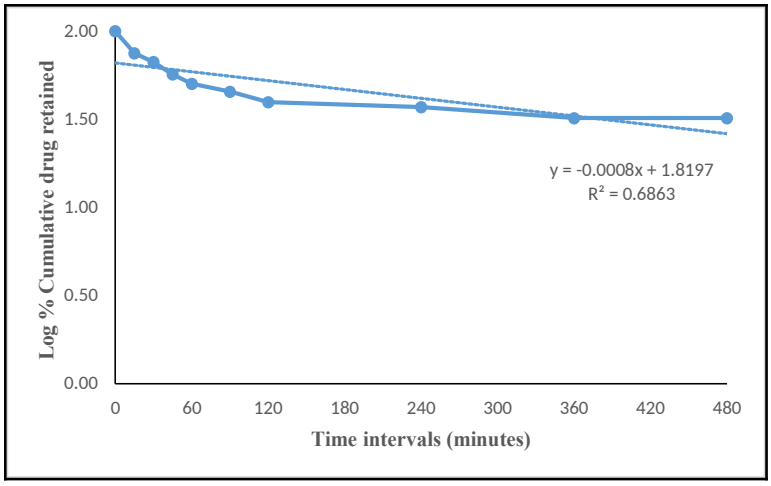

Figure 17.: First Order: Graph was plotted between % cumulative drug retained Vs Time (mins)

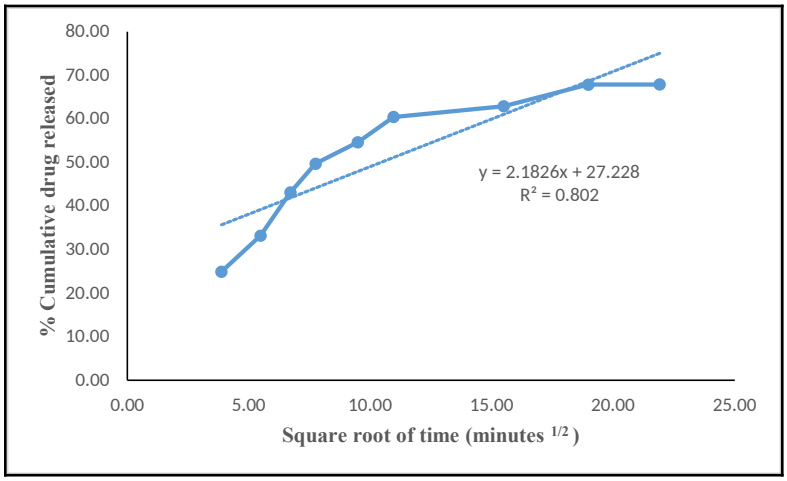

Figure 18.: Higuchi Model : Graph was plotted between % Cumulative drug released Vs square root time

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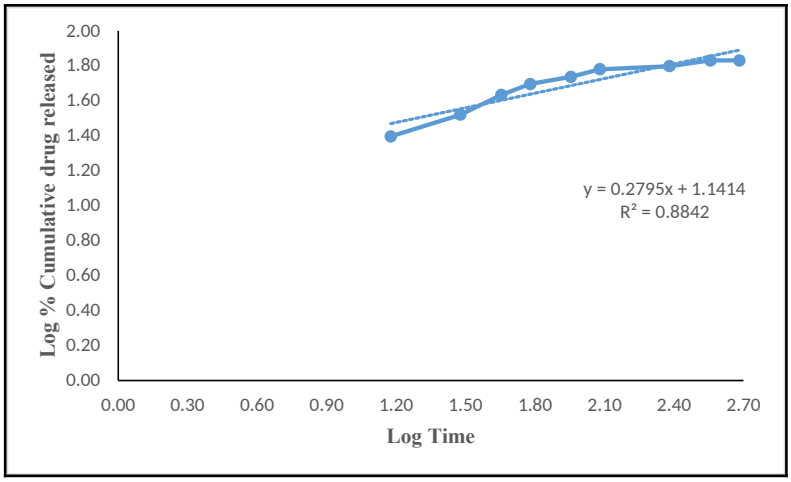

Figure 19.: Koresemeye peppas: Graph was plotted between Log % Cumulative drug released Vs Log Time

Table 13.: *In vitro* drug release kinetics studies data of Clonidine Hydrochloride- loaded metal - organic frameworks, C7

Model	Kinetics parameter	Observed values
Zero order Kinetics	**k_0 (% sec^{-1})**	0.075
	R^2	0.6507
First Order Kinetics	**k_1 (sec^{-1})**	-0.0008
	R^2	0.6863
Higuchi Model	**k_H (% cm^{-2} $sec^{-1/2}$)**	2.1826
	R^2	0.802
Korsmeyer-Peppas Model	**K(sec^{-n})**	0.2795
	R^2	0.8842
	n Value	0.34

4.2.5 Stability Study:

The Stability results demonstrate that under accelerated storage conditions (40 ± 2 °C / 75 ± 5% RH) for a period of 30 days, the C7 MOF formulation remained physically and chemically stable. No changes were observed in physical appearance at any time point, indicating preserved organoleptic properties throughout the study. The drug content showed only a slight decrease from 99.12 ± 0.41% at day 0 to 98.45 ± 0.37% at day 30, while entrapment efficiency marginally declined from 68.00 ± 0.70% to 67.35 ± 0.62%. Similarly, the *in vitro* drug release at 480 minutes exhibited minimal variation, decreasing from 67.90 ± 1.12% to 67.10 ± 1.09%. These minor changes were not significant and remained within acceptable limits, confirming the stability of the formulation over the study period as shown in Table 14

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Table 14: Evaluation data of C7 MOF Formulation during Storage period

S. No.	Parameter	0 Day	7 Days	14 Days	21 Days	30 Days
1	Physical Appearance	No change	No change	No change	No change	No change
2	Drug Content (% ± SD)	99.12 ± 0.41	98.97 ± 0.39	98.75 ± 0.38	98.60 ± 0.37	98.45 ± 0.37
3	Entrapment Efficiency (% ± SD)	68.00 ± 0.70	67.85 ± 0.68	67.65 ± 0.67	67.50 ± 0.64	67.35 ± 0.62
4	% Drug Release at 480 min	67.90 ± 1.12	67.60 ± 1.08	67.40 ± 1.07	67.20 ± 1.06	67.10 ± 1.09

* Data has been expressed as Mean ± SD, n = 3

Dissolution Profile Comparison Under Stability Conditions

The *in vitro* drug release profile of the optimized C7 MOF formulation before and after 30 days of accelerated storage (40 ± 2 °C / 75 ± 5% RH) showed only minimal variation, indicating consistent release behavior. Dissolution profile comparison using model-independent analysis yielded an f_1 value of 4 and an f_2 value of 74. These values fall within acceptable regulatory limits (f_1 < 15 and f_2 > 50), confirming the stability of the formulation's drug release characteristics during storage (**Table 15, Fig 20)**

Table 15.: *In Vitro* Drug Release Profile of C7 MOF at Accelerated conditions (40 °C ± 2 °C / 75 %RH ± 5 %RH)

% Cumulative drug released		
Time (min)	**0 Day (Before Storage)**	**30 Day (After Storage)**
0	0.00	0.00
15	28.61 ± 1.34	28.23 ± 1.26
30	36.14 ± 1.22	35.82 ± 1.19
45	43.76 ± 1.11	42.91 ± 1.17
60	49.70 ± 1.07	49.35 ± 1.03
90	54.86 ± 1.03	54.10 ± 0.97
120	57.68 ± 1.02	56.90 ± 1.00
240	60.43 ± 0.98	59.98 ± 1.02
360	65.50 ± 1.05	64.70 ± 1.01
480	67.90 ± 1.12	67.10 ± 1.09

* Data has been expressed as Mean ± SD, n = 3

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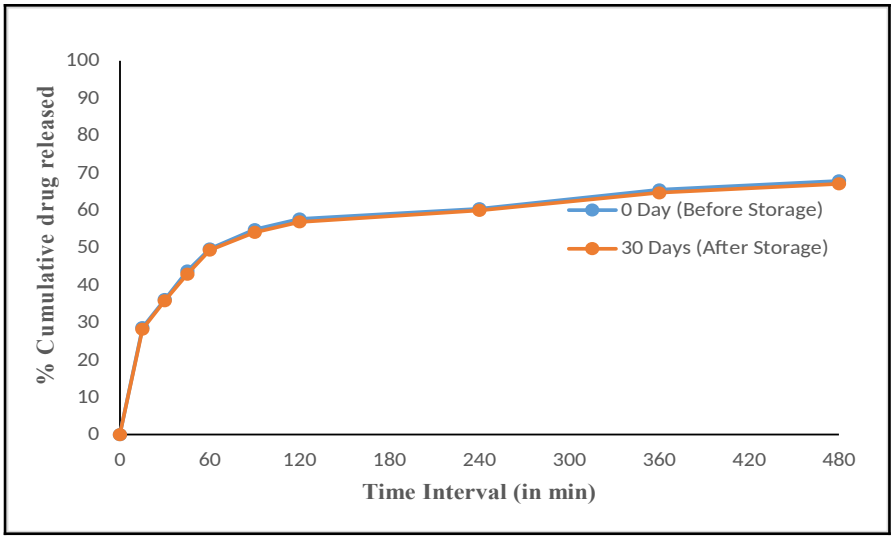

Figure 20.: Dissolution Profile Comparison of formulation C7 MOF at Accelerated conditions (40 °C ± 2 °C / 75 %RH ± 5 %RH) at t = 0 days (Before Storage) and 30 days (After Storage)

T_{90} (Shelf-Life Estimation):

The shelf life (T_{90}) of the optimized clonidine hydrochloride–loaded C7 MOF was estimated using first-order degradation kinetics. Based on the calculated degradation rate constant (k = 0.000575 day^{-1}), the T_{90} value was approximately 183 days, indicating that the formulation is expected to retain at least 90 % of its initial drug content under accelerated storage conditions.

5. Discussion:

This study employed a structured, two-phase formulation strategy to develop zinc-based metal-organic frameworks (MOFs) for the sustained oral delivery of Clonidine Hydrochloride. Two biocompatible dicarboxylic acids—fumaric acid and succinic acid—were investigated as organic linkers to evaluate their influence on MOF synthesis, drug loading efficiency, and overall formulation yield.

In the preliminary screening phase, fumaric acid-based formulations (C1–C4) demonstrated limited success, with low percentage yields ranging from 25.16 ± 0.21% to 36.48 ± 0.29% and entrapment efficiencies between 4.45 ± 0.05% and 12.35 ± 0.07%. These suboptimal results are attributed to poor solubility and less favorable coordination between fumaric acid and zinc ions, resulting in weak framework formation and minimal drug incorporation. Based on these findings, fumaric acid was excluded from further development.

The optimization phase focused on succinic acid as the linker, which significantly improved formulation outcomes. Succinic acid-based MOFs (C5–C8) exhibited higher yields (58.40 ± 0.03% to 69.71 ± 0.10%) and markedly improved entrapment efficiencies. Among these, formulation C7, synthesized via the precipitation method with post-synthetic drug loading, emerged as the optimized candidate, achieving the highest entrapment efficiency (68.00 ± 0.08%) and a yield of 69.33 ± 0.77%. Other formulations, such as C5 (30.34 ± 0.07%) and C8 (28.77 ± 0.70%), also demonstrated moderate drug encapsulation, underscoring the influence of formulation technique and loading method on MOF performance.

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Comprehensive physicochemical characterization confirmed successful MOF formation and drug incorporation: PXRD analysis showed retention of crystallinity with only a marginal reduction after drug loading, indicating preservation of framework integrity; SEM revealed crystalline, rod-shaped nanoparticles; particle size analysis confirmed nanoscale dimensions with a narrow size distribution; DSC thermograms demonstrated molecular dispersion of Clonidine Hydrochloride within the MOF matrix without evidence of degradation; and FTIR spectra confirmed Zn^{2+}–carboxylate coordination along with characteristic functional groups of Clonidine Hydrochloride, validating successful encapsulation. *In vitro* drug release studies in acidic media demonstrated a controlled release pattern over 8 hours, and kinetic modeling indicated a diffusion-controlled mechanism best described by the Korsmeyer–Peppas model. Accelerated stability studies showed excellent physical and chemical stability, with dissolution profile comparison yielding an acceptable similarity factor (f_2 = 74), indicating reproducible release behavior. Shelf-life estimation (T_{90}) based on first-order degradation kinetics revealed a degradation rate constant of 0.000575 day^{-1}, corresponding to a T_{90} of approximately 183 days, indicating that the optimized C7 MOF is expected to retain at least 90 % of its initial drug content under accelerated storage conditions.

Although in vivo evaluations were not part of the current study, the use of FDA-approved or GRAS-listed components—zinc acetate, succinic acid, and Clonidine Hydrochloride—supports the potential clinical applicability of the developed system. These findings highlight succinic acid-based MOFs, particularly formulation C7, as a promising platform for sustained oral drug delivery. Future research should focus on in vivo pharmacokinetic and biosafety assessments to establish therapeutic relevance.

6. Conclusion:

The present investigation successfully formulated and evaluated zinc-based metal-organic frameworks (MOFs) for the controlled delivery of Clonidine Hydrochloride using biocompatible linkers. A two-phase development strategy was employed, starting with fumaric acid-based MOFs, which exhibited poor drug loading and low yields, followed by optimization of succinic acid-based MOFs. Among these, formulation C7, prepared via the precipitation method with post-synthetic drug loading, demonstrated the most promising characteristics, including an entrapment efficiency of 68.00 ± 0.70%, a yield of 69.33 ± 0.77%, nanoscale particle size (Z-average 203.3 nm, PDI 0.286), and a controlled release profile over 8 hours governed by Fickian diffusion. Comprehensive characterization using PXRD, SEM, DSC, and FTIR confirmed successful drug incorporation, structural integrity, and framework stability. Accelerated stability studies indicated excellent chemical and physical stability, with a similarity factor (f_2 = 74) and a shelf-life (T_{90}) of approximately 183 days, confirming that the formulation retains at least 90% of its drug content under stress conditions.

The use of GRAS and FDA-approved materials further supports the pharmaceutical relevance of the formulation. While in vivo studies were not included, these findings provide a solid foundation for future research to evaluate the biological safety and therapeutic efficacy of succinic acid-based MOFs as a novel oral controlled-release drug delivery system for Clonidine Hydrochloride.

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