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Original Article

Design of Lamivudine Loaded Metal Organic Frameworks MIL 100 (Fe) by Microwave Assisted Chemistry

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ABSTRACT

Background: Lamivudine is an Anti-Viral Drug belongs to BCS Class II Drug which exhibits limited solubility and high permeability through oral route. **Aim:** The study was designed to predict the solubility potential of Lamivudine loaded Metal Organic Framework complexed with MIL 100 by using microwave assisted chemistry through topical route. **Materials and Methods:** In combination of MIL 100 (Fe) we utilize Ferric chloride hexahydrate as metal particle and benzene 1,3,5-carboxyl corrosive as natural linker. The anti-viral drug Lamivudine was used to load in the MIL 100 (Fe). The specific proportion of $FeCl_3.6H_2O$ and benzene 1,3,5-carboxylic acid was weakened with deionized water. Above combination is put in microwave at 130°C for 6 min which prompts development of complex called MIL 100 (Fe). Various proportions of Lamivudine medication and MIL 100 (Fe) were taken to prepare the formulations and the effect of drug loading with various ratios were interpreted. Evaluation of MOF was done for drug-excipient compatibly studies and surface morphology for structural analysis. **Results and Discussion:** Spectral studies conforms the purity of the sample and from drug-excipient compatibility studies no interactions were noticed. Microwave Assisted Technology can be proven as a best fit model for synthesis of advanced 2D Materials called MOF and drug loading was found to be high at a ratio of Lamivudine: MIL (1:0.5). The particulate studies conform the nanonisation of drug which results in enhanced solubility due to increased surface area of drugs. **Conclusion:** Lamivudine loaded Metal Organic Frameworks (MOF) with MIL 100 (Fe) was successfully fabricated with high loading and decreased particle size authenticates the utilization of microwave assisted technology as a promising tool for MOF and with the result of increase in solubility, Lamivudine can be used in a best way as an anti-viral drug in the form of MOF through topical route.

Keywords: Metal Organic Frameworks, Ferric chloride hexahydrate, Benzene 1,3,5-tricarboxylic acid, Microwave assisted chemistry.

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INTRODUCTION

Metal Organic Frameworks (MOFs) are a novel family of chemicals composed of metal clusters coordinated to organic ligands to create 1-D, 2-D and 3-D structures. Metal organic frameworks are hybrid crystalline porous materials made up of a regular array of positively charged metal ions connected by organic linkers. Metal organic frameworks offer unique features that allow them to be employed in a variety of applications such as medication delivery systems, gas purification, gas separation, water remediation and super capacitors.

Metal organic frameworks are utilised in the pharmaceutical sector as drug delivery vehicles and biosensors to safeguard delicate pharmaceuticals, as well as photodynamic cancer therapy, among other applications. MOFs have been studied as a promising drug delivery mechanism for a wide range of disorders, including bacterial infections, lung disease, diabetic mellitus, ophthalmic disease, antiviral infections, wound healing and cancer treatment. This metal organic framework use in the pharmaceutical business is gaining popularity, since it is a cutting-edge method for treating, diagnosing and delivering drugs.

Metal-Organic Frameworks (MOFs) are new hybrid crystalline materials composed of inorganic foundations such as metal or metal-oxide ions or clusters that are connected by organic linkers known as ligands to produce three-dimensional porous structures. Their high porosity (up to 90% free volume) results in a specific surface area greater than 6,000 m^2/g. Because of these properties, MOFs are appealing for applications in a variety of sectors, including drug delivery, medicine, gas storage and separation, photocatalysis and catalysis. Furthermore, the

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potential of MOFs to segregate, store and adsorb gases opens up new opportunities for their usage in food preservation methods.

MOFs have drawn a great deal of interest for imaging applications. By adding paramagnetic metal particles and radiance-based materials, MOFs could be used in optical and Magnetic reverberation imaging. For MOFs to be utilized as nanocarriers for drug conveyance and imaging, they should meet various necessities, including low poisonousness, biocompatibility and biodegradability.[1]

Lamivudine is an antiviral medication that anticipates Human Immunodeficiency Infection (HIV) or hepatitis B infection by preventing the replication of DNA. Lamivudine is most commonly used to treat Human Immunodeficiency Disease (HIV) or hepatitis B in combination with other antiviral medications. In this study, we identified the lamivudine-loaded MIL 100 (Fe), which can be used with almost no additional antiviral drugs. Furthermore, long-term concealment of viral replication and rebuilding of serum transaminase activities were obtained by lamivudine organisation before and after liver transplantation to prevent or treat unite reinfection with HBV. Lamivudine may potentially mark a shift in the management of HBV illness. According to recent research, the drug is effective even when chemotherapy-induced HBV illness recurrence occurs. The usefulness of lamivudine in these serious situations is unclear, however, because there have been few reports of SAE associated with the discontinuation of cytotoxic or immunosuppressive therapy for chronic HBV infection.[2]

There are several significant benefits to MOF amalgamation facilitated by microwaves. It most notably, provides a rapid warming rate, which takes into account much shorter mix times-here and there only a few minutes. This characteristic improves energy efficiency, resulting in significant reductions in energy use. Second, after the microwave power is turned off, it is simple to manage the manufacturing cycle. To summarise, this technique is environmentally friendly and reduces overall pollution.[3]

Because MW-assisted techniques use less energy and create more opportunities to complete, they have grown in popularity over time. This drop is due to MW dielectric warming, which is based on a material's ability to convert energy into heat. Throughout the cycle, a rotating electromagnetic field is provided and as it sways, the particle field or dipole in the example is forced to realign. The arrangement's overall intensity increases because to atomic grating and dielectric instability, which cause intensity to be lost to the surrounding medium. MW warming provides several benefits, including the ability to warm the entire arrangement instantaneously, to warm the instances without heating the compartment and to produce more homogeneous particles. The charge or extremity of reagents influences their capacity to convert electromagnetic radiation into heat. Dielectric materials are so ideal for MW methods.[4]

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Microwave-assisted MOF combinations have gained popularity as a new alternative to traditional solvothermal techniques. They consider faster reactions, increased proficiency, stage selection and less challenging morphological control.[6] Hence, in this research an attempt has been made to load the Lamivudine into MOF using microwave technique to predict the solubility augmentation through topical route.

MATERIALS AND METHODS

Materials

Lamivudine was procured from Yarrow Chem Pvt. Ltd., Mumbai. 1,3,5-Benzenetricarboxylic acid (BTC), Ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) was obtained from Carbino, Mumbai. The other chemicals were purchased from SD fine chemicals.

Methods

Preformulation Studies

Solubility Studies

Equilibrium solubility studies were carried out in different solvents like distilled water, ethanol, chloroform and phosphate buffer of pH 6.5. Excess amount of drug was added in to the different solvents and subjected to sonication for 2 hr at room temperature. Measured volume was withdrawn and diluted with respective solvents and drug concentrations were estimated spectrophotometrically by scanning from 400 nm to 200 nm.

FT-IR Spectrometer

Using a tiny spatula, remove approximately 0.1 mg of the sample and add the KBr. Crush with a pestle in a mortar until it is fully blended. Fill the pellet and press the material at 5000-10,000 psi. When done correctly, the crushed circle should be nearly transparent. The pellet was scanned in the region of 4000-400 cm^{-1} and the vibrational frequencies were recorded. FT-IR frequencies were recorded for pure drug and 1:1 mixture of drug and excipients. Spectral interpretation was done to check the compatibility of the selected ingredients for formulation of MOF.

Synthesis of MIL 100 (Fe)

Ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) (2.43 g) and 1,3,5-Benzenetricarboxylic acid (BTC) (0.84 g) were broken down in 30 mL of refined water to make MIL 100 (Fe) powder. In

Table 1: Formulation of Lamivudine loaded into MIL 100.

Sl. No.	Formulation	Weight of MIL 100 (Fe) in g	Weight of Lamivudine drug in g
1.	A	0.25 g	1 g
2.	B	0.5 g	1 g
3.	C	0.75 g	1 g
4.	D	1.0 g	1 g
5.	E	1.25 g	1 g
6.	F	1.5 g	1 g
7.	G	1.75 g	1 g
8.	H	2.0 g	1 g
9.	I	2.25 g	1 g
10.	J	2.5 g	1 g

a microwave, the response blend was warmed to 130°C for 6 min and it was then permitted to cool for room temperature. Utilizing centrifugation, the formulations was refined with purified water. The preparation was dried and an orange-hued item was framed that is MIL 100 (Fe). The schematic representation of the synthesis MIL 100 (Fe) is represented in Figure 1.[7]

Loading of lamivudine drug into MIL 100 (Fe)

The loading of Lamivudine into MOFs, namely MIL 100 (Fe) is an important cycle. The MIL 100 (Fe) was prepared by the aforesaid technique and the MOF and drug to be loaded were mixed in varied amounts in 10 mL of purified water. The mixture was mixed to ensure proper pharmaceutical loading and was subjected to ultrasonication for 15 min. Centrifuge the sample and collect the sediment after filtration. Medication-loaded MOF was obtained after subsequent drying for 20-30 min. The schematic representation of the loading of drug is presented in Figures 2 and 3.[8]

The drug loading was directed by the above cycle. The loading of drug was finished by various proportions of MIL 100 (Fe) and Lamivudine. The proportions of Lamivudine and MIL 100 (Fe) were in the range of 1:0.25 and 1:2.5. The drug loading capacity and drug loading efficacy was determined by utilizing UV visible spectrophotometry.

The formulation of drug loaded MOF is illustrated as, The formulations table is represented in Table 1.

Evaluation of Drug Loaded MOF

Characterization of sample

The powder was characterized using UV Visible spectrophotometer and FT-IR Spectrometer in the range of 4000-400cm^{-1}.

Table 2: Saturation Solubility of Drug in Various Solvents.

Sl. No.	Solvent	Saturation Solubility (mg/mL)
1	Distilled Water	9.8 mg/mL
2	Phosphate Buffer pH 6.0	6.2 mg/mL
3	Phosphate Buffer pH 6.5	6.0 mg/mL
4	Phosphate Buffer pH 7.2	4.5 mg/mL

Microscopical investigation

The item MIL 100 (Fe) development was distinguished by translucent design. The formulation of the MIL 100 (Fe) was seen fewer than 100X magnification. First take the powder of MIL 100 (Fe) and add some water blend it. Place the sample on the slide and cover with cover slip. Check the particle size under magnifying instrument.[9]

SEM Analysis

SEM imaging was completed for the MIL 100 (Fe) using scanning electron microscopy in order to detect the transparent design and evaluate the surface morphology of the MOF.

Drug Loading capacity and efficiency

Drug loading capacity and efficiency was determined by the accompanying equation;

$$\text{DLC (\%)} = (\text{weight of medication in MOF} / \text{weight of MOF}) \times 100\ \%$$

$$\text{DLE (\%)} = (\text{weight of medication in MOF} / \text{weight of medication in feed}) \times 100\ \%$$

The drug content in MIL 100 (Fe) was evaluated using UV-visible spectrophotometry. The drug loading in the excess addition after

the loading in the MIL 100 (Fe) was determined and reduced by the weight of medication fed into MIL 100 (Fe). The equation above allows us to calculate drug loading capacity and efficiency.

In vitro Drug Release Studies

In vitro drug release of drug loaded MOF gel (prepared by dissolving in 1:0.5 ratios of formulation and chitosan) and plain drug was carried out by using dialysis bag method. MOF containing an equivalent amount of 100 mg of drug were dropped in pre-soaked dialysis bag of molecular weight cut off 12-14 KDa, both ends were tied and immersed in the Phosphate buffer of pH 6.5 and volume 500 mL upto 24 hr at 37±0.1°C temperature. Agitate the system at 100 rpm and 5 mL of sample was withdrawn at regular time intervals of from receptor compartment and the same volume was replaced with fresh dissolution medium to maintain sink condition. Filter the samples by using 0.45 µ filters and dilute them to a pre-requisite concentration with phosphate buffer. Absorbance was measured by UV at 271 nm using placebo as blank. After cessation of drug release, cumulative amount of drug release was plotted against function of time. Experiments were repeated 3 times and the results were expressed as mean values±SD.[10]

Table 3: Interpretation of FTIR results of MIL 100 (Fe).

Sl. No.	Wave Number (cm^{-1})	Functional Group
1	354.38	N-H Stretching
2	2596.61	S-H Stretching
3	842.74	C=C Bending
4	757.88	C-H Bending

Table 4: Interpretation of FTIR results of Lamivudine Drug.

Sl. No.	Wave Number (cm^{-1})	Functional Group
1	3306	O-H Stretching
2	2971	CH_3 Stretching
3	1317.14	C-O Stretching
4	1076.08	C-OH Stretching

Stability Studies

The stability of the optimized formulation was tested in accordance with ICH guidelines. Each formulation was kept in an airtight glass jar at 40±2°C/75±5% RH for 45 days. After 45 days, the samples were analysed to determine the influence on particle characteristics and % of drug release. The results were compared to a pure drug. The results obatined were tabulated in Table 6.

RESULTS AND DISCUSSION

The MIL 100 (Fe) was synthesised and the drug was loaded using into MIL 100 (Fe). The prepared sample was characterized using various techniques, followed by drug release detailed below.

Solubility Studies

Solubility studies were carried out in the various solvents specified in the procedure and the results were tabulated in the Table 2.

UV-visible spectrophotometry

The UV-visible spectrophotometry of the drug Lamivudine was conducted and the standard curve for the lamivudine was used for the calculation of the drug loading capacity, drug loading efficacy and drug release study.

Fourier-transform infrared spectroscopy

The FTIR spectrum of MIL 100 (Fe), Lamivudine drug and drug loaded MIL 100 (Fe) was recorded. The results of the FTIR were represented in Figure 4 and Figure 5 and the interpretation of FTIR results of MIL 100 (Fe) and drug Lamivudine are represented in Tables 3 and 4. There were no deviations/shift observed in the vibrational frequencies of drug and mixture. Hence, the same was selected for further studies.

Table 5: DLC % and DLE % of the obtained drug loaded MIL 100 (Fe) with different ratios of MIL 100 (Fe) and Drug Lamivudine.

Sl. No.	Ratio of Drug / MIL 100 (Fe) (w/w)	Drug loading capacity (DLC %)	Drug loading efficacy (DLE %)
1.	1: 0.25	60%	40%
2.	1: 0.5	98.2%	49%
3.	1: 0.75	68.8%	46.8%
4.	1: 1	48.8%	48.8%
5.	1: 0.25	45.5%	47.4%
6.	1: 0.5	30.6%	46.6%
7.	1: 0.75	38.4%	30.8%
8.	1: 2	35.1%	28.7%
9.	1: 2.25	33.4%	24.5%
10.	1: 2.5	20.7%	22.9%

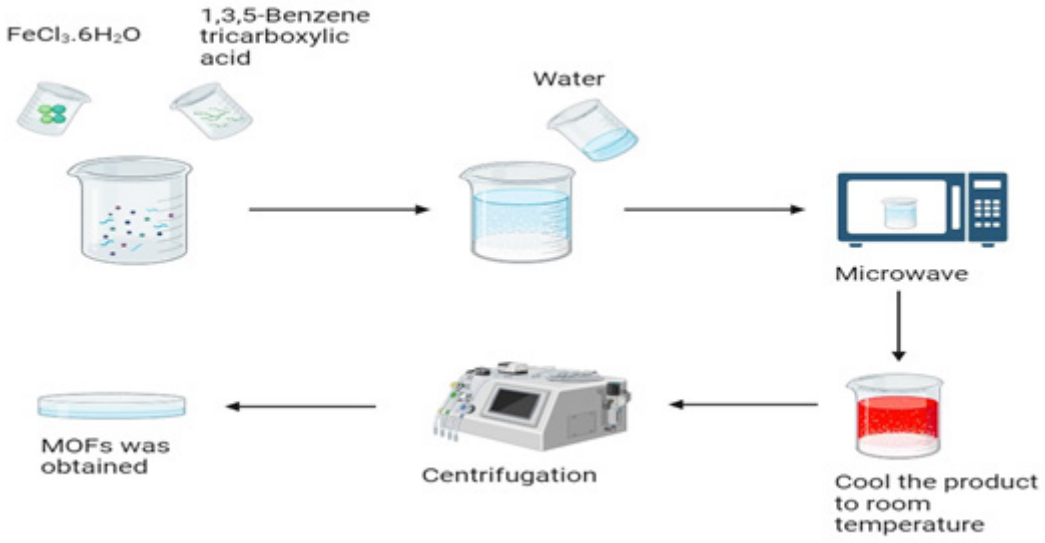

Figure 1: The synthesis of the MIL 100 (Fe) by two chemicals i.e., $FeCl_3.6H_2O$ and BTC through microwave assisted chemistry (Image was drafted by using Biorender.com).

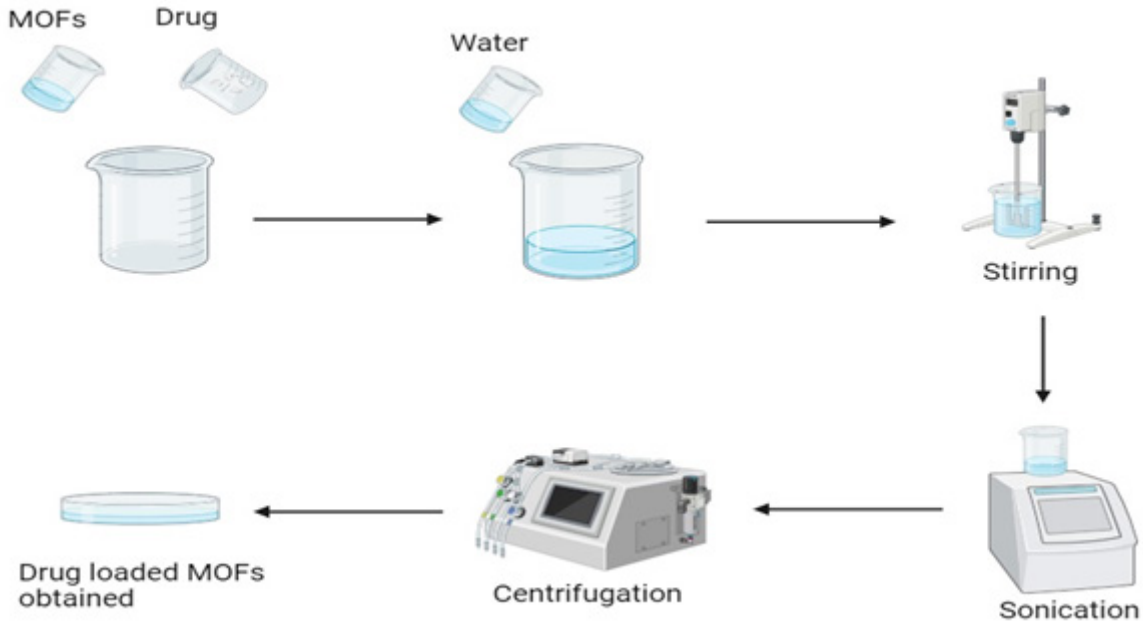

Figure 2: The loading of drug Lamivudine into the Metal organic frameworks MIL 100 (Fe) through continuous stirring followed by centrifugation. (Image was drafted by using Biorender.com).

Microscopical analysis

The MIL 100 (Fe) formation was confirmed by the formation of the crystalline structure. Basic identification of the MIL 100 (Fe) by the microscope can detect the formation of crystals. The formed crystals are represented in Figure 6.

Particulate Analysis by Zeta Sizer-Particle size analysis was depicted in the Figure 7.

Scanning Electron Microscopy Imaging

The SEM analysis of MIL 100 (Fe) was done and the particle size was observed in the range of 102 nm, 99.3 nm, 95.4 nm, 89.3 nm and 120 nm. The presence of smooth surface with spherical structure can be ideal for delivery of drugs through topical route and parenteral route as well. The SEM image was presented in Figure 8.

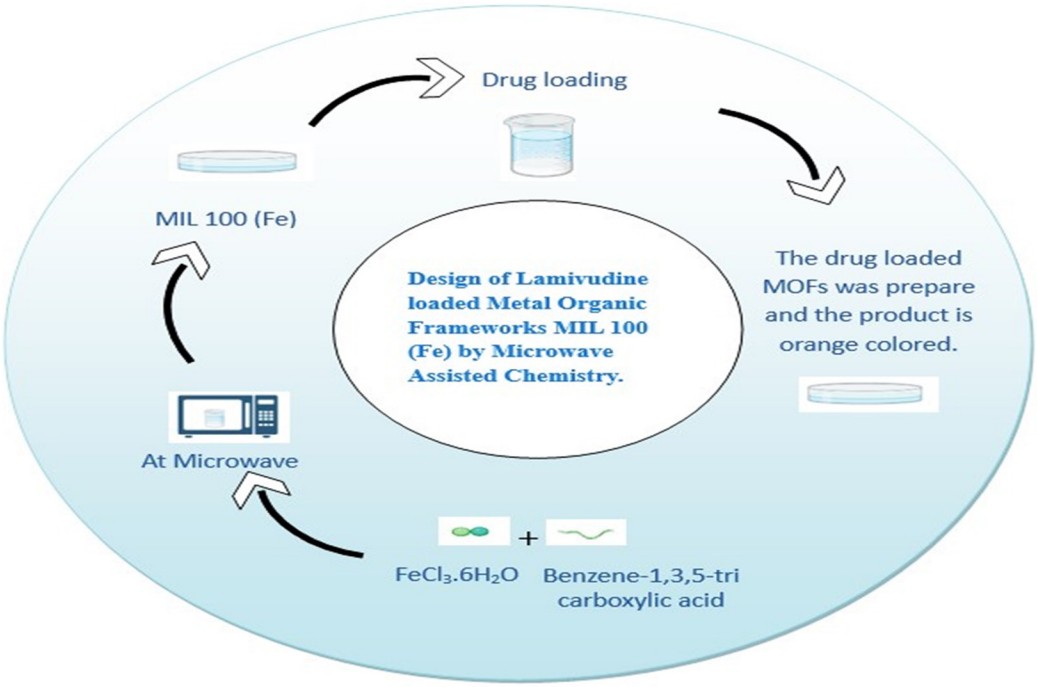

Figure 3: The complete process of the synthesis and drug loading of MIL 100 (Fe) by microwave assisted chemistry. (Image was drafted by using Biorender.com).

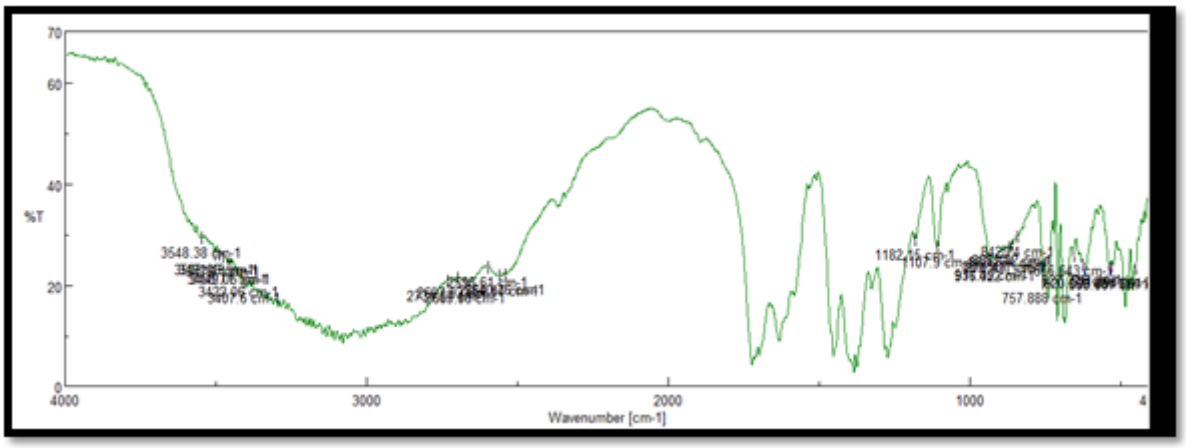

Figure 4: The FTIR spectrum of MIL 100 (Fe).

Drug Loading Capacity and Drug Loading Efficacy

The different proportions of the MIL 100 (Fe) and Lamivudine were examined using UV-Visible spectrophotometry and the drug loaded into the MIL 100 (Fe) was calculated. The 1:0.5 proportions resulted in a high DLC and DLE percentage which is attributed due to high concentration of drug and increased surface area. The following approach was the best method to fabricate MOF with BCS Class II Drug. Table 5 shows the computed values for Drug loading capacity and drug loading efficacy in %.

In vitro Drug Release Studies

In vitro drug release studies were mentioned in Figure 9 which depicts that Lamivudine MOF shows burst effect followed by prolonged effect for 24 hr and the % drug released was found to be 95%. The rate of drug release from dosage form met official standard limits i.e., USP <80% within 12 hr. Dissolution profiles were mentioned in Figure 9.

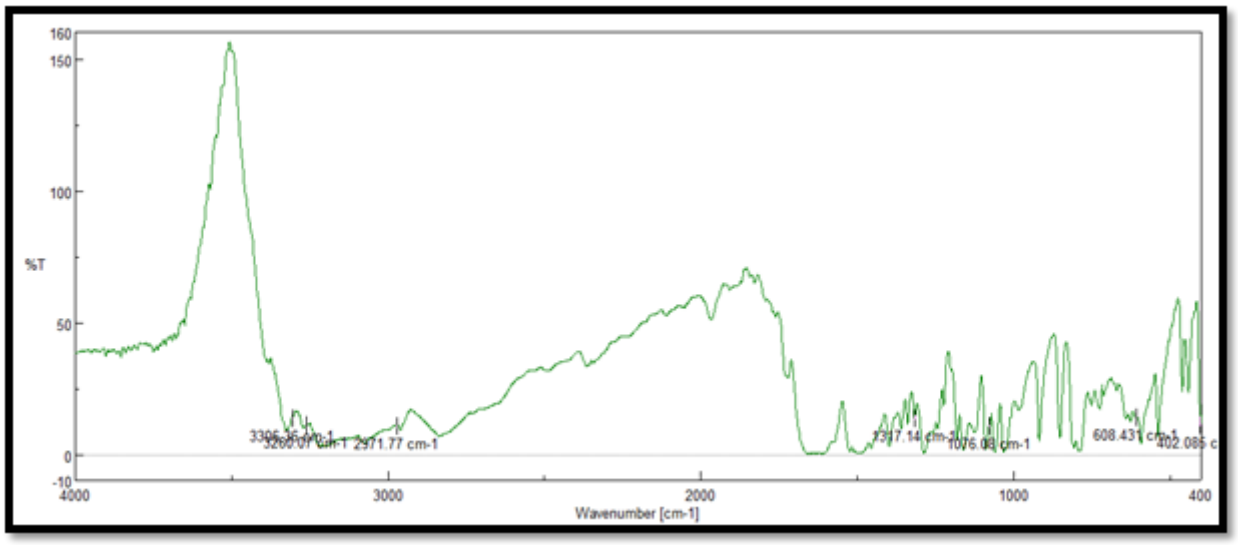

Figure 5: The FTIR spectrum of Drug lamivudine.

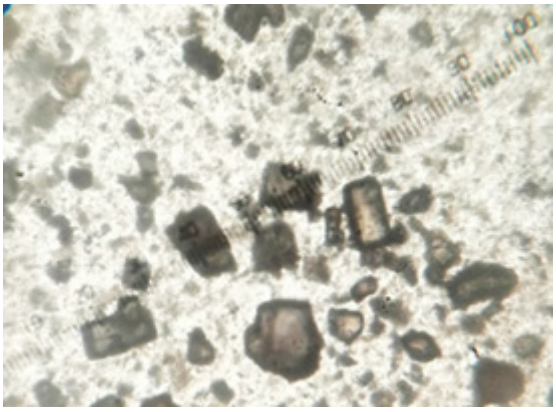

Figure 6: The Microscopic image of the MIL 100 (Fe).

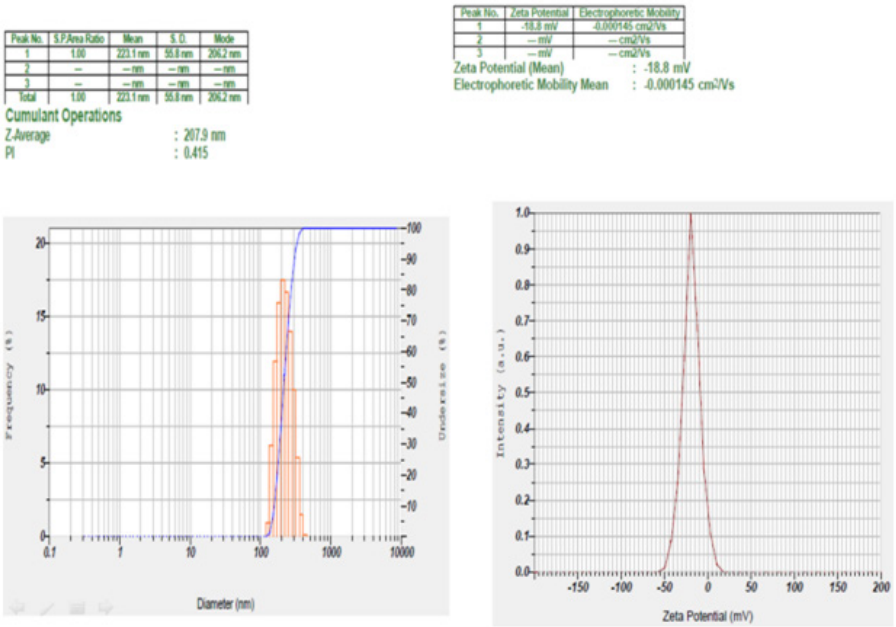

Figure 7: Particle Size and Zetapotential of Optimised formulation.

Stability Studies

Table 6: Stability studies of Drug Loaded MOF after 45 Days.

(MOF)	Initial	After 45 Days	Acceptance Criteria
Particle Size (nm)	204.5±2.66	189.7±2.66	10-500 nm
Zeta potential (mV)	-18.4±2.42	-17.4±2.42	±15 to 60 mV
PI	0.355±0.04	0.401±0.04	<0.5
Drug Loading %	83.42±3.54	81.90±2.68	> 75%

All values are expressed as mean±SD, *n*=3. Parameters were depicted in Figure 10.

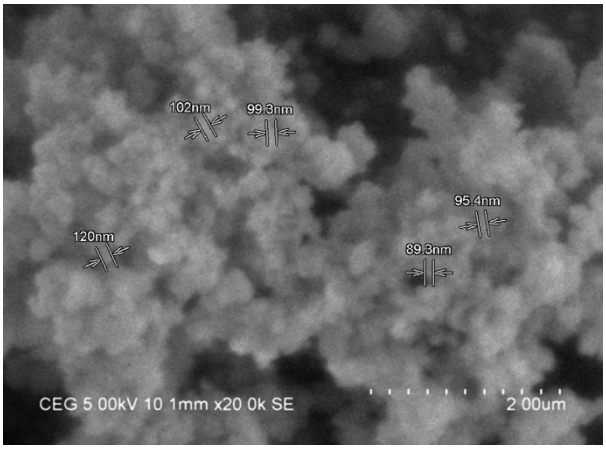

Figure 8: Scanning electron microscopy image of the MIL 100 (Fe).

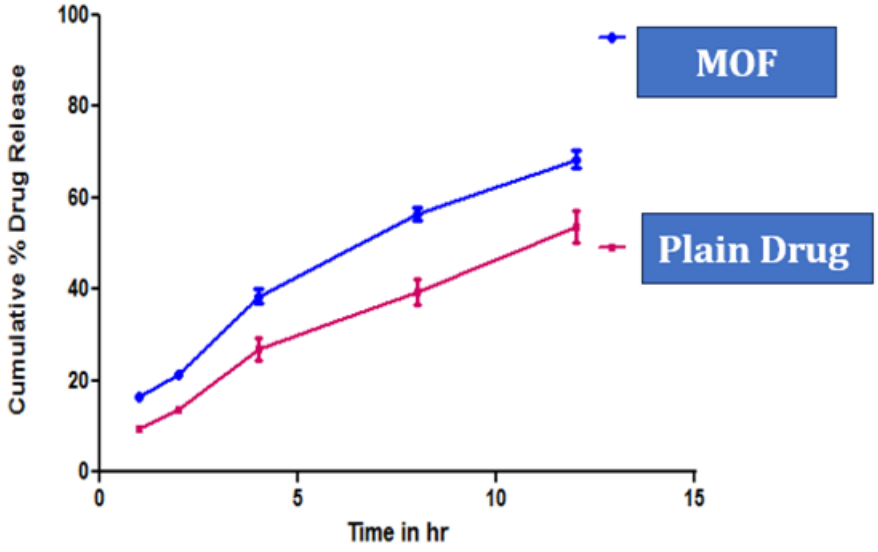

Figure 9: Comparative *in vitro* drug diffusion release studies between Lamivudine MOF in Phosphate buffer saline (pH 6.8) Values are expressed as mean±SD, *n*=3.

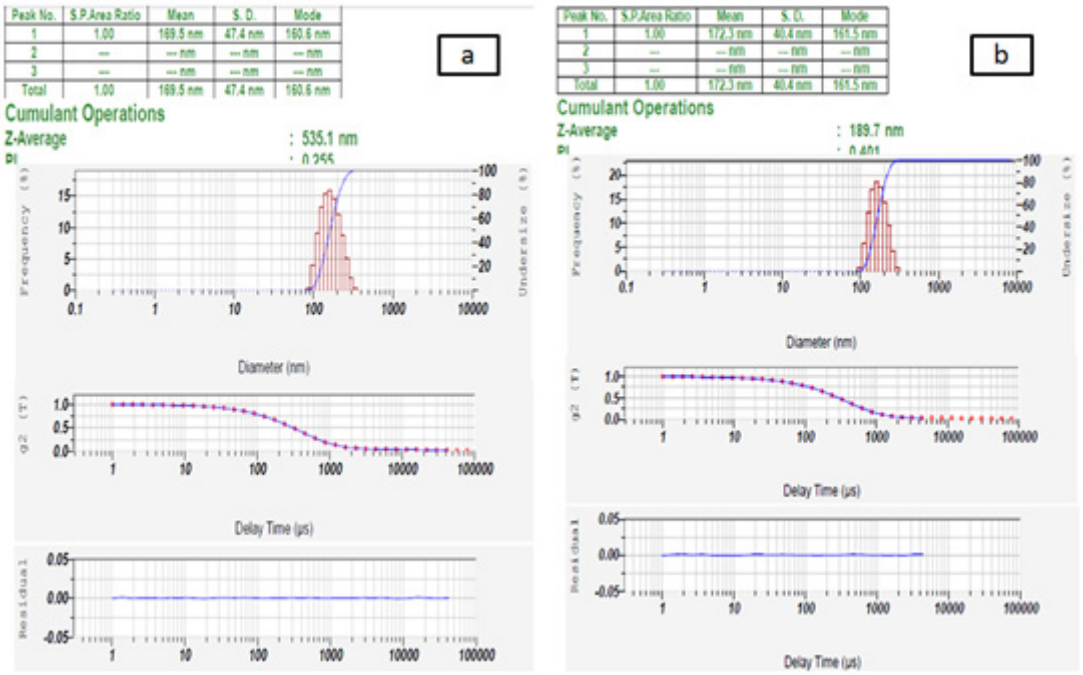

Figure 10: Stability Studies-PS reports of Drug Loaded MOF.

CONCLUSION

The present research is about the drug Lamivudine and in this investigation; we sort out the lamivudine-loaded MIL 100 (Fe), which can be employed with almost no other antiviral treatments. MIL 100 (Fe) is a subclass of MOFs that are widely used in several sectors. We designed the Lamivudine-loaded MOF with MIL 100 (Fe), which has more favorable activity for augmentation of solubility and attaining controlled release compared to plain Lamivudine. We structured MIL 100 (Fe) using microwave-assisted technology, which has a high return and adequacy. The resulting plan has a high DLC and DLE percentage. Thus, we assume that Lamivudine drug fabricated as MOF increase the drug's solubility and further bioavailability. This method can be a possible choice for the delivery of drugs through microwave assisted technology using advanced 2D materials called MOF using topical route.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MOF: Metal Organic Frameworks; **MIL 100 (Fe):** Material Institute Lavoisier 100 (Fe); **HBV:** Hepatitis B; **FTIR:** Fourier-transform Infrared Spectroscopy; **SEM:** Scanning Electron Microscope; **KBr:** Potassium Bromide; **DLC:** Drug Loading Capacity; **DLE:** Drug Loading Efficacy; **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **UV:** Ultra-Voilet.

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