Preparation and Drug-Delivery Properties of Metal-Organic Framework HKUST-1

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ABSTRACT

In this research, the metal-organic framework of HKUST-1 (Hong Koung University of Science and Technology) was synthesized for use in modern drug delivery systems by the thermal solvent method. It was activated in two conditions: under vacuum pressure and by a freeze-drying method. The synthesized HKUST-1 Metal-Organic Framework was analyzed by IR, XRD, BET, and SEM. In order to examine and compare the results, the IR sample was synthesized using the sample before and after the activation of the sample. Regarding the XRD pattern, the peak area of $2\theta = 11.760$ showed the highest intensity. The SEM images showed an octagonal morphology in which the particle size was in the range of 5-65 µm. Furthermore, by using the BET method, the surface area of 1306 m^2/g was calculated.

1. Introduction

The usage of some Active Pharmaceutical Ingredients (APIs) like lipids and polymers, which have the most applications as drug carriers, is limited due to their deficiency such as persistence in the biological environment, low solubility or lack of ability to cross the biological barriers and side effects such as API toxicity and API protection against biological degradation. An alternative method for releasing and transferring drugs is to design a biologically active drug-based Metal-Organic Framework (MOF) because of its high porosity, controllable volume, and the simplicity of operating to other porous solids (for example, zeolites and Silica) such that the drug is a ligand, released along with degradation of the structure, or from a bioactive metal such as silver and zinc, which has antibacterial properties or application in medical imaging. MOFs are a branch of hybrid materials made by self-assembly of polydendate ligands and metal ions that are designed on a nano scale and one of their uses is in biomedical applications. The main target of MOFs for drug delivery is to design carriers that have low toxicity to the body [1]. The first report of using these structures as drug carriers was back in 2006 by Ferey et al. for using a drug model (anti-inflammatory ibuprofen); by using a medically transmitted drug carrier, MOFs were presented based on chromium hydrochloride (MIL- 100 (Cr) and MIL-101 (Cr)) [2]. The physiochemical

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properties of MOF can be well adapted for specific applications due to unlimited mixing of metals and ligands, and various structures can be provided with different compositions, sizes, morphologies, and properties. These structures have several benefits including biodegradable, high loading capacity, structural variation, and chemical properties than conventional structures used in nanomaterials. In 2017, San et al. synthesized the metal-organic frameworks of MOF-1 (Cu-BTC), MOF-2 (40 % H3BT and 60 % IPA), MOF-3 (70 % H3BT and 30 % IPA), and MOF-4 (Cu-IPA) that detected the pore size of each of these frameworks as 14.67, 2.12, 2.09, and 2.28 nm, respectively. They compared the loading and release rates of Ibuprofen drugs in the framework. The highest drug loading time was obtained in MOF-2 after 72 hours followed by MOF-3, MOF-1, and MOF-4 [3]. MOFs are divided into hard and flexible categories in the hard form. The hard MOF is characterized by permanent porosity and a tight frame similar to that of porous mineral material, but flexible MOFs are dynamic and responsive to external factors such as guest molecules, temperature, and pressure. They change the porosity depending on the type of molecule [4]. In 2008, the approach of using flexible MOF was developed [5]. In 2008, Lin et al. used nanoprecipitation to make NMOFs composed of Tb^{3+}; in this structure, 75 wt % cisplatin was loaded [6]. In the Solvothermal method, NMOFS can be heated by a conventional method or using a microwave, which results in quicker and homogeneous nucleation than the growth of crystals [7] or Sonochemical method which is fast, easy, and environmentally friendly was synthesized [8]. Qiu et al. succeeded in producing nanoparticles with high efficiency by using the sonochemical method at low temperatures and atmospheric pressure [9]. In this method, more precursor materials turn into NMOF due to the rise in temperature. Because of conventional solvents used for the synthesis of MOFs which are toxic, it is better to use the solvothermal method.

Direct biomedical mixing can be used as metal connection points for the loading of appropriate biomedical agents within the NMOFs [10], ligand bridges [11], or post-loading biomedical synthesis methods. In 2015, Lee et al. synthesized a new three-dimensional structure of an organic metal framework using tetracarboxylate and zinc salts. Then, they loaded it with 5-fluorouracil drug. Drug adsorption was 22.5 % Wt in this framework. Also, drug release was at the vicinity of phosphate buffer solution at 37 ℃ and after a week, was reported 92 % [12]. Noncovalent drug loading was performed first in a mass MOF and by ibuprofen loading of 1.4 g per 1 g of MOF [13]. The drug release in this structure was very slow, continuous and controlled and with the least destructive effect of its sudden release [14]. Additional processes can delay the onset of drug release from the structure due to the irreversibility of drug loading by the noncovalent procedure. For this reason, the loading can be done by connecting the covalent after the synthesis of the agent. In this method, drug release occurred only when Nano MOFs were destroyed. To connect the covalent factors to the nano MOF structure, nano MOF can be modified using appropriate functional groups [6].

The important reason for the use of porous solids in medicine is the use of their porosity to accommodate active molecules and transfer them through host-guest/penetration/ degradation considerations. Therefore, the

pore size and volume should be fit to optimize the carrier for the desired biomolecule, encapsulate the carrier in the drug solution, and rinse. An easy way to control solubility kinetics in solution is designing structures including effective drugs and low toxic metals, which can connect the active connector directly to the metal that can be activated [15]. Also, it is possible to affect the solubility of the metal-effective metal complex by modifying the ligands and improving the hydrophobic properties. In this study, we first synthesized the metal-organic framework, HKUST-1, as a porous solid for transferring the drug by solvothermal method. The HKUST-1 metal-organic framework was analyzed by IR, XRD, BET, and SEM.

2. Experimental
2.1. Materials
For the synthesis of the metal-organic framework HKUST-1, benzene-1, 3, 5-tricarboxylic acid with purity of 95 % and copper (II) salts of 5, 2 % water with purity of 99.99 % were provided by Sigma-Adrich Company and 99.5 % ethanol from Merck company. Also, the chemicals were purchased and used in this work as a steel autoclave with a container and teflon cap 30 ml. Excitation Furnace model EX.1200-2L equipped with temperature monitoring, vacuum oven, and freezer dryer was used.

2.2. Synthesis of metal-organic framework HKUST-1
To prepare the metal-organic framework HKUST-1 ($[Cu_3(TMA)_2(H_2O)_3]_n$) by solvothermal method, first, 0.42g of benzene-1, 3, and 5-carboxylic acid (H_3BTC) was dissolved in 12 ml of ethanol and 0.837 g of copper (II) nitrate 2.5 water in 12 ml of deionized water and mixed together and

stirred for 30 minutes. Then, the solution obtained in turquoise blue was placed in a teflon autoclave and placed in an oven at 120 ℃ for 12 hours. At the last stage, the sinter was washed with ethanol. Next, it dried at ambient temperature.

2.3. Activating the metal-organic framework HKUST-1
Following the synthesis of metal-organic framework HKUST-1, including vacuum oven and freeze-drying were used for activating and discharging the porous areas of the material. In a vacuum oven method, the HKUST-1 powder was placed in a Chinese crucible in a vacuum oven at a temperature of 120 ℃. The generated vacuum evaporates the guest molecule by heat and discharge from the pores. By the freeze-drying method, the biological materials removed through freezing and evaporating. In order to activate the pores, the MOF was placed in a vacuum oven and finally freeze-dried, without any change in its general and biological properties. To activate HKUST-1, the powder was heated to -70 ℃ and the temperature was slowly increased to -40 ℃. Finally, after two hours, the ambient temperature was reached.

3. Results and discussion
After the synthesis of metal organic framework HKUST-1, samples with different chemical and physical methods were identified. The IR spectrum of the synthesized sample represents the successful synthesis of HKUST-1 (Fig. 1). The index peaks of this sample are listed in Table 1. IR spectra were recorded by the KBr tablet and the ABB Bomem spectrometer of the FTLA 200-100 model. Furthermore, activation of the synthesized sample was carried out at 120 ℃ to achieve the proper porosity using two

methods of vacuum oven and freeze drying. In order to observe any change in the structure of HKUST-1, its IR spectrum was

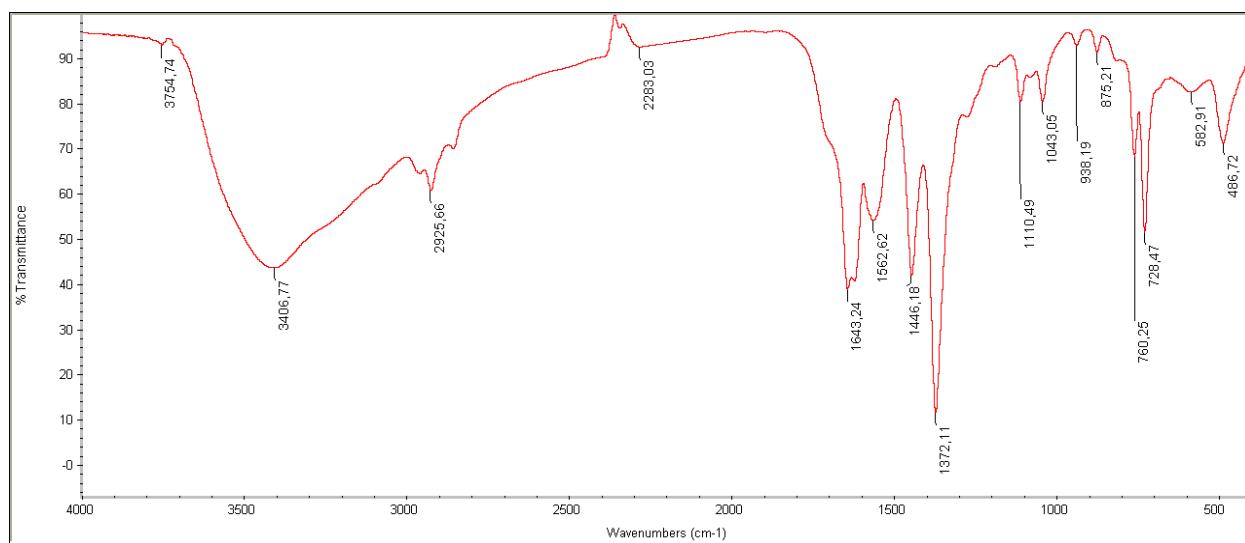examined which is quite similar to the sample before activation (Fig. 2).

Figure 1. The IR spectrum of the metal organic frame HKUST-1.

Table 1

HKUST-1 IR Spectrum Index Pixels.

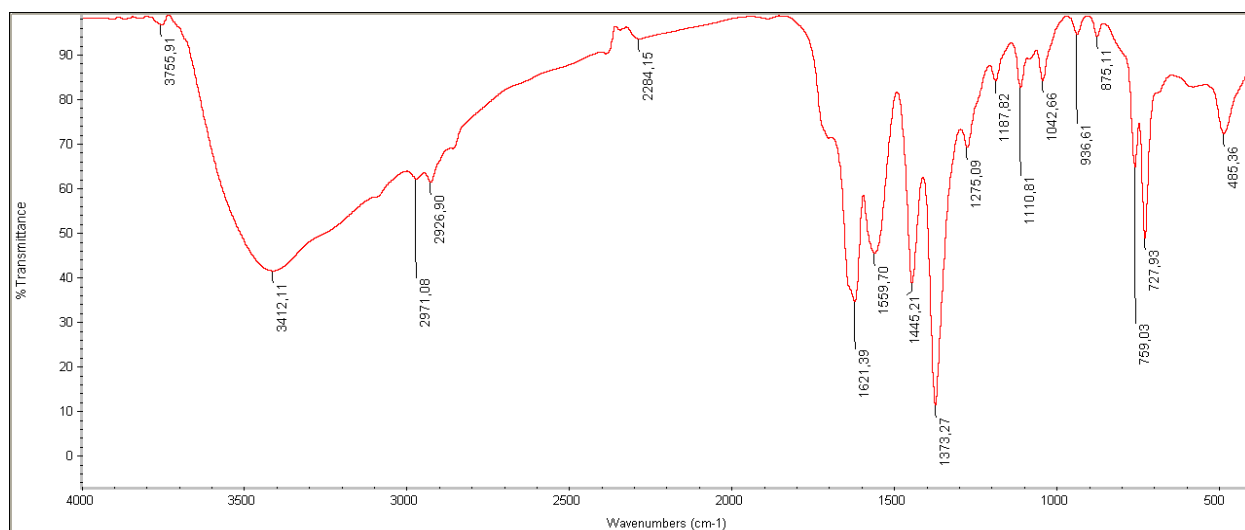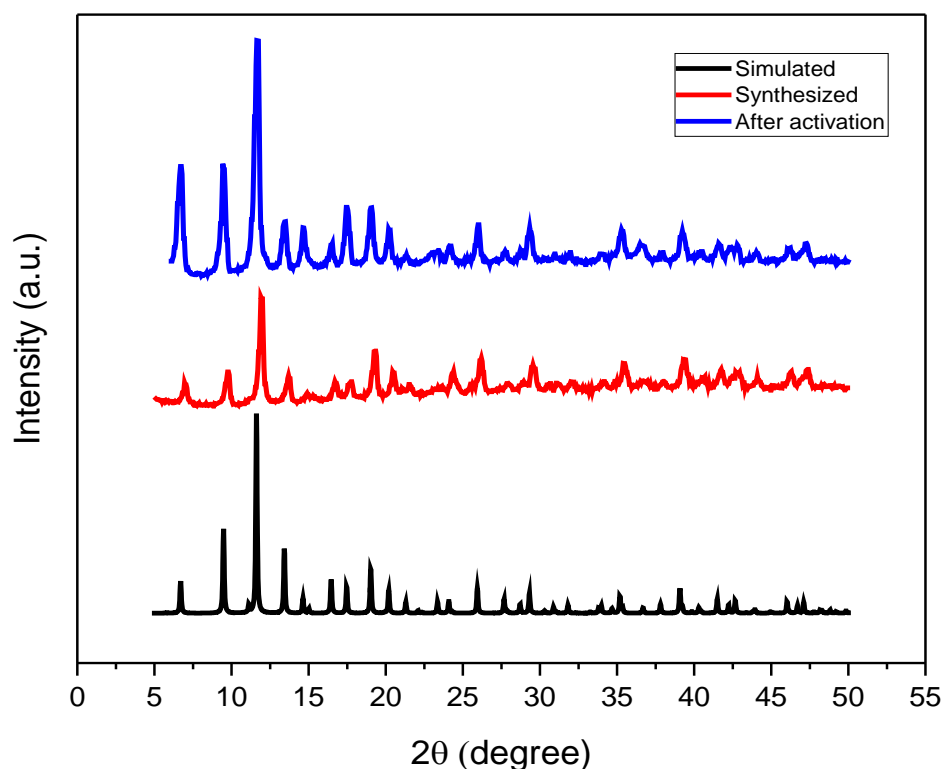| Vibration type	Type of link	Wave number (cm^{-1})
Aromatic symmetrical stretch	C-H	2925
Symmetric stretching of carbonyl	C=O	1643
Symmetrical stretch	CU-O	1372
Aromatic symmetrical bending	C-H	760-728

Figure 2. The IR spectrum for the activation method in one graph.

To check the repeatability of HKUST-1 synthesis, the samples prepared before and

after activation were analyzed by X-ray diffraction (XPERT MPD model with copper

anode) (Fig. 3). Comparison between the single-crystal XRD patterns and the synthesized sample shows that the structure is quite similar to the prototype and after activation, ir is still stable. Regarding the XRD pattern, the peak area of $2\theta = 11.760$ has the highest intensity, which is for page (222). Other index peaks at 2θ below 10 degrees are respectively related to the page (200) at $2\theta = 6.816$ and the page (220) at $2\theta = 9.54$.
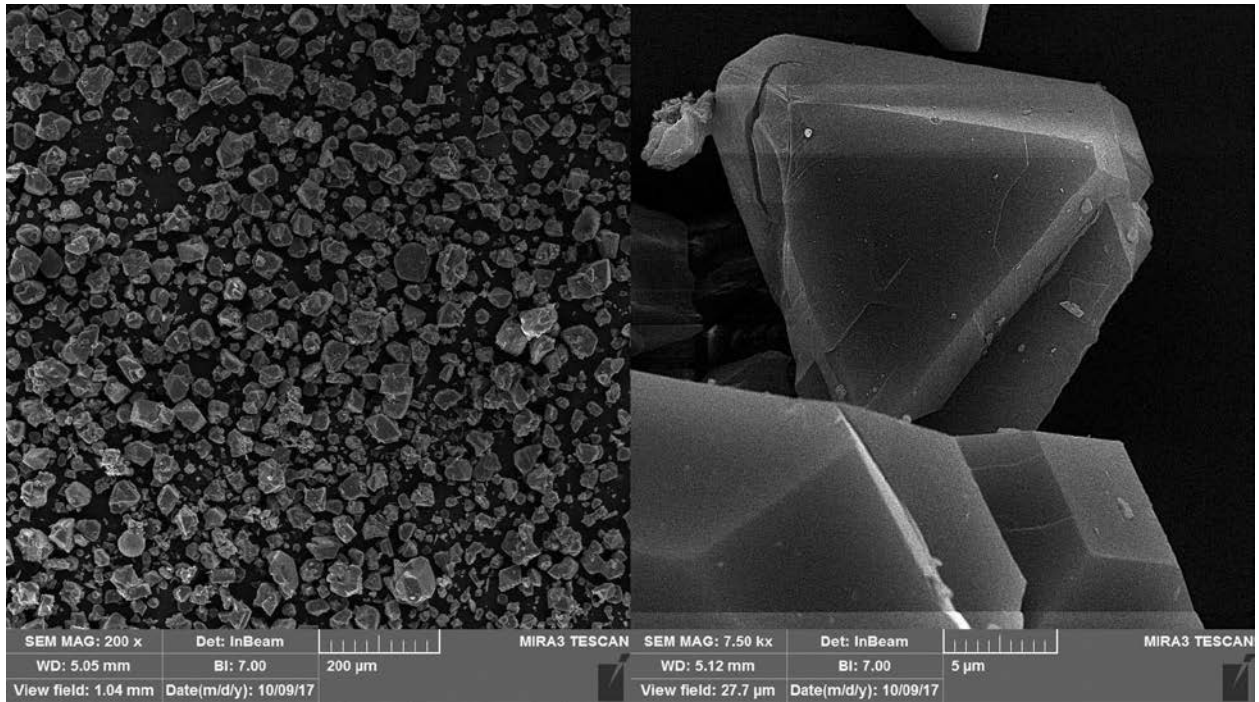

Figure 3. XRD pattern of HKUST-1 structure, simulated sample (Black), synthesized sample (Red), and active sample (Blue).
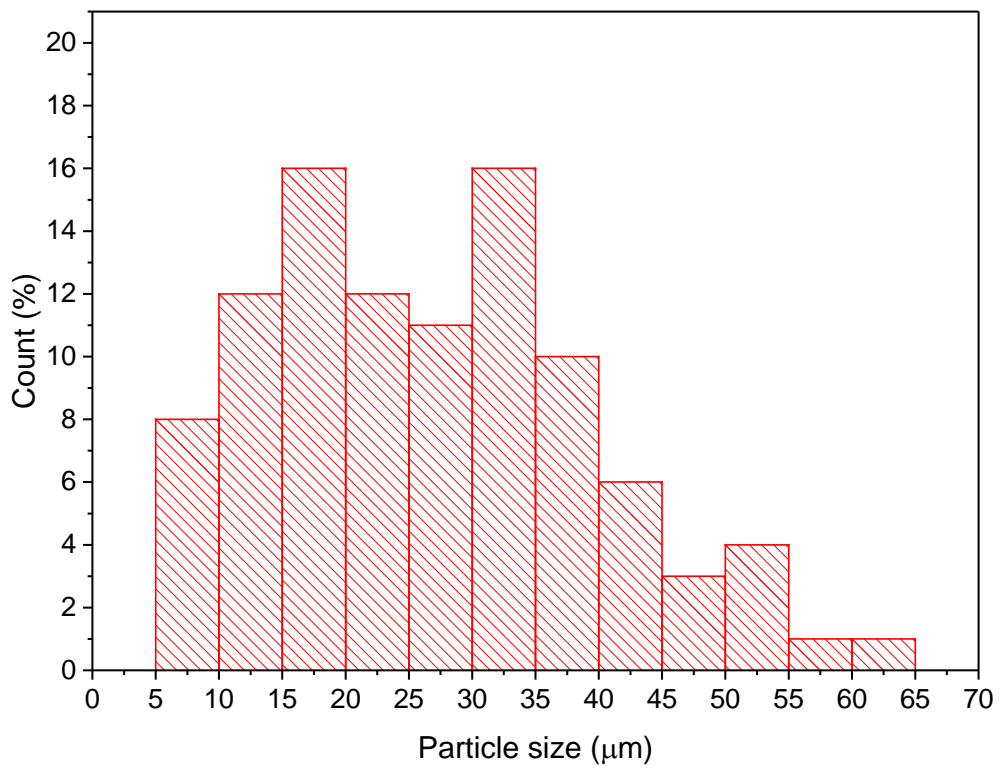
To study the surface morphology and particle size of synthesized HKUST-1, Scanning Electron Microscopy (SEM) images were prepared by a 1460 model with an accelerating voltage of 15 kV. According to Fig. 4, the morphology of the particles is octagonal and the particle sizes range from several micrometers to several ten micrometers. Regular and octagonal growth of particles occurred over a reasonable amount of time in the thermal solvent synthesis method. By analyzing the particle size and plotting the chart of frequency shown in Fig. 5, particle size was obtained from 5-65 μm, which has the largest particle size of 15-35 μm particles.
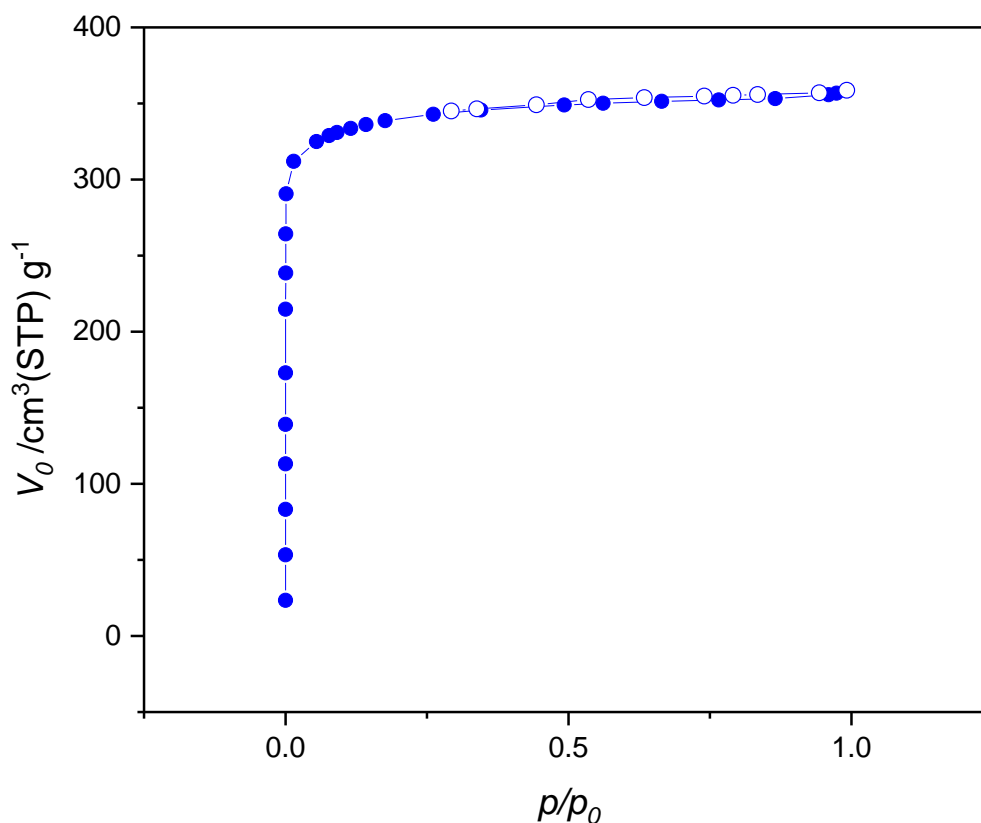
After activation, the porosity was measured by absorbing nitrogen gas at 77 K. To analyze the nitrogen gas adsorption, system of Micromeritics ASAP 2030 Surface area analyzer was used. According to Fig. 6, the surface area of the calculated BET for the metal-organic framework HKUST-1 was 1306 m^2/g, which introduced this structure as a suitable option for loading drug agents.

Figure 4. SEM image of HKUST-1 particles with a magnification of 200 μm (left) and a magnification of 5 μm (right).

Figure 5. Frequency chart of HKUST-1 particles.

Figure 6. Analysis of nitrogen gas adsorption at 77 °C.

4. Conclusions

Metal Organic Frameworks are significantly advantageous for absorption process and release of biomolecules due to the porosity size, the controllable volume, simplicity of the functionalization, flexibility of the network, and availability of metal sites. Required time for biodegradation also varies from a few minutes to a few days through the use of different types of metals and organic compounds. The metal-organic framework HKUST-1 is characterized by a range of particle sizes between 15-35 μm and a specific surface of 1306 m^2/g. It has good biodegradability for the absorption and release of drugs. This MOF can also be used to load Phenelzine and Sertraline antidepressants and Methotrexate and Chlormethine anticancer drugs. Despite numerous advantages, a number of modifications need to be made to these structures so that they can be used in medicine. Firstly, the degradation mechanism of these structures as well as the kinetics of transport must be examined for a drug sample and a carrier sample. Secondly, because of their degradable properties, the production of sustainable nanoparticles is a fundamental issue. The issue of functionalization of these structures should also be considered.

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