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Delayed Drug Release Films Based on MIL-100(Fe) Metal-Organic Framework

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Abstract—Biocompatible metal-organic framework MIL-100(Fe) was used as a container for a model hydrophobic active pharmaceutical ingredient, ibuprofen, in composite films based on gelatin, pectin, and kappa-carrageenan. According to powder X-ray diffraction and scanning electron microscopy data, the metal-organic framework retained the crystal structure and its particles were uniformly distributed throughout the hydrocolloid matrix. Testing of the obtained film materials under simulated biological conditions using chromatography–mass spectrometry analysis showed that they are applicable as a dosage form for slow release of active pharmaceutical ingredients.

Keywords: targeted delivery, active pharmaceutical ingredients, biocompatible materials, hydrocolloids, metal-organic frameworks, films

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INTRODUCTION

Solid dosage forms, particularly tablets, dominate the current pharmaceutical market, owing to easy and convenient distribution and use as well as high productivity of the manufacturing process [1]. However, an important drawback of tablets is the lack of targeted action of the active pharmaceutical ingredient (API), which causes side effects and necessitates frequent administration of the drug [2]. Therefore, in recent years, special attention has been paid to the search for targeted drug delivery systems that would prevent drug degradation in the patient's gastrointestinal tract and make it possible to avoid first pass effects, overdose, or poisoning [3].

Among such systems, films are most efficient for treatment of various infectious diseases of skin and mucous membranes. Owing to the moist wound healing, films promote epithelialization, i.e., fast wound healing with reduced risk of infection, while controlled release of APIs solve problems of non-healing wounds [4]. As matrices for these films, synthetic or natural water-soluble polymers are used most often; the incorporation of hydrophobic APIs into such matrices is often accompanied by component separation during the production of films [5]. Previously [6–8], a similar problem was addressed by encapsulating hydrophobic compounds in the pores of metal-organic frameworks (MOFs), representatives of a unique class of porous crystalline materials [9].

In recent years, MOFs, consisting of metal nodes and organic linkers, have been actively used in various fields of science and technology [10], including targeted drug delivery [11], owing to very large specific surface area and controlled porosity specified by the nature of structure components [12]. A very popular biocompatible MOF is MIL-100(Fe), $Fe_3O(H_2O)_2OH(BTC)_2$ (H_3BTC is trimesic acid). Owing to low cytotoxicity [13], high hydrothermal stability [14], and very high specific surface area and porosity [15], this MOF is well suited for biomedical applications [13].

In this communication, we describe new composite film materials based on a hydrocolloid matrix consisting of a mixture of gelatin, pectin, and kappa-carrageenan for targeted delivery of the model drug ibuprofen. The obtained materials containing ibuprofen encapsulated into the pores of MIL-100(Fe) MOF were found to be applicable as dosage forms for slow release of APIs.

EXPERIMENTAL

All operations were performed in air using commercial solvents and chemicals. The following chemicals were used: gelatin, pectin, kappa-carrageenan, glycerol (edible grade), trimesic acid (H_3BTC, 95%), iron(II) chloride tetrahydrate (≥99.0%), sodium hydroxide (≥98%), sodium citrate (99%), and potas-

sium sorbate (99%) (Sigma Aldrich). Ibuprofen was prepared by recrystallization of ibuprofen-AKOS tablets (OJSC Sintez) from a mixture of ethanol and water (1 : 1). The phosphate-buffered saline (pH 7.4) was purchased from the research and production enterprise PanEco. Analysis for carbon and hydrogen was carried out on a CarloErba microanalyzer, model 1106.

MIL-100(Fe) (MOF) was synthesized by an adapted previously reported environmentally friendly protocol [16]. A solution of $FeCl_2 \cdot 4H_2O$ (11.4 mmol, 2.26 g) in distilled water (100 mL) was added dropwise with stirring to an aqueous solution (100 mL) of trimesic acid (7.6 mmol, 1.676 g) and sodium hydroxide (22.8 mmol, 23.72 g). The reaction mixture was stirred at room temperature for 24 h. The resulting precipitate was filtered off and washed by successive soaking in hot water (300 mL) and hot ethanol (300 mL). The sample was dried under reduced pressure at 120°C for 12 h.

For $C_{18}H_{11}O_{16}Fe_3$		
Anal. calcd., %	C, 33.22	H, 1.70
Found, %	C, 33.01	H, 1.88

Synthesis of MIL-100(Fe)_IBU. The active pharmaceutical ingredient was inserted into MIL-100(Fe) pores by keeping a dry MOF powder in an ethanol solution of ibuprofen, with MIL-100(Fe) to ibuprofen ratio of 1 : 2. Then the resulting MIL-100(Fe)_IBU powder was collected on a filter, washed three times with ethanol, and dried at room temperature.

Preparation of composite films. A mixture of gelatin (0.2 g), pectin (1.2 g), and kappa-carrageenan (0.6 g) was added with stirring to a solution of glycerol (1 g), sodium citrate (0.2 g), and potassium sorbate (0.02 g) in distilled water (25 mL) preheated to 80°C. To the obtained homogeneous solution was added an ethanol solution of ibuprofen or a suspension of MIL-100(Fe)_IBU (1, 3, and 5 wt % of the total weight of hydrocolloids) in distilled water (25 mL) prepared in advance in an ultrasonic bath for 3 min. The mixture thus obtained was poured onto a plastic Petri dish and left up to complete drying. After drying, the film was separated from the Petri dish and placed to a dry place for storage at room temperature.

Powder X-ray diffraction study was performed on a Proto AXRD diffractometer with a copper anode, nickel K_β-filter ($\lambda = 1.541874$ Å), and Dectris Mythen 1K 1D detector in the in Bragg–Brentano geometry in the 5°–60° range of angles with a 0.02° 2θ step.

Scanning electron microscopy (SEM). The SEM images for films placed on a 25-mm aluminum stage and secured with a conductive carbon tape were obtained in the secondary electron mode at an accelerating voltage of 5 kV in the medium vacuum range on a Hitachi TM4000Plus tabletop electron microscope.

The release of the active pharmaceutical ingredient was assessed using an LCMS-2020 liquid chromatography–mass spectrometry experiment (Shimadzu, Japan) with electrospray ionization and quadrupole detector (detection of both positive and negative ions with m/z in the 50–2000 range with additional monitoring of ions at 206.1). The samples were prepared by keeping MIL-100(Fe)_IBU films and powder in phosphate buffered saline (pH 7.4) with orbital stirring (80 rpm) at 37°C for 24 h. At specified time intervals, the mother liquor containing released ibuprofen was withdrawn and replaced with the same volume of fresh buffer. The percentage of released API was determined by the following relation:

$$\text{Percentage of release} = \frac{c_t}{c_0} \times 100\%. \quad (1)$$

The correction for dilution of the solution was made using the equation:

$$c_c = cC_t + \frac{V}{V}\sum_0^{t-1} c_t, \quad (2)$$

where c_c is the corrected API concentration at time point t, c_t is the measured ingredient concentration at time t, c_0 is the maximum calculated concentration, v is the sample volume, V is the total volume of the solution.

RESULTS AND DISCUSSION

The composite films for targeted drug delivery must possess a number of properties such as strength, elasticity, and resistance to dissolution throughout the time period needed for the release of the active pharmaceutical ingredient. According to published recommendations [17], we first used a mixture of pectin and gelatin in 4 : 1 ratio as a hydrocolloid matrix. Also, we added glycerol as a plasticizer to the film-forming mixture to increase the film flexibility and elasticity and potassium sorbate as a preserving agent to prevent the growth of pathogenic organisms during storage of composite materials. The initial components were dissolved in distilled water at 80°C and the solution was cast into Petri dishes on a smooth surface. The films were dried at room temperature; during drying, the matrix components separated into layers. For solving this problem, we decided to add kappa-carrageenan, which contains negatively charged sulfate groups capable of binding to protein polymer chains of gelatin. The resulting film, which consisted of pectin, gelatin, and kappa-carrageenan in 6 : 1 : 3 ratio and was dried to a constant weight at room temperature, was characterized by high transparency and elasticity (Fig. 1).

The stability of the resulting hydrocolloid material against dissolution under simulated biological conditions was assessed as follows. A film sample was placed into phosphate-buffered saline (pH 7.4) and kept

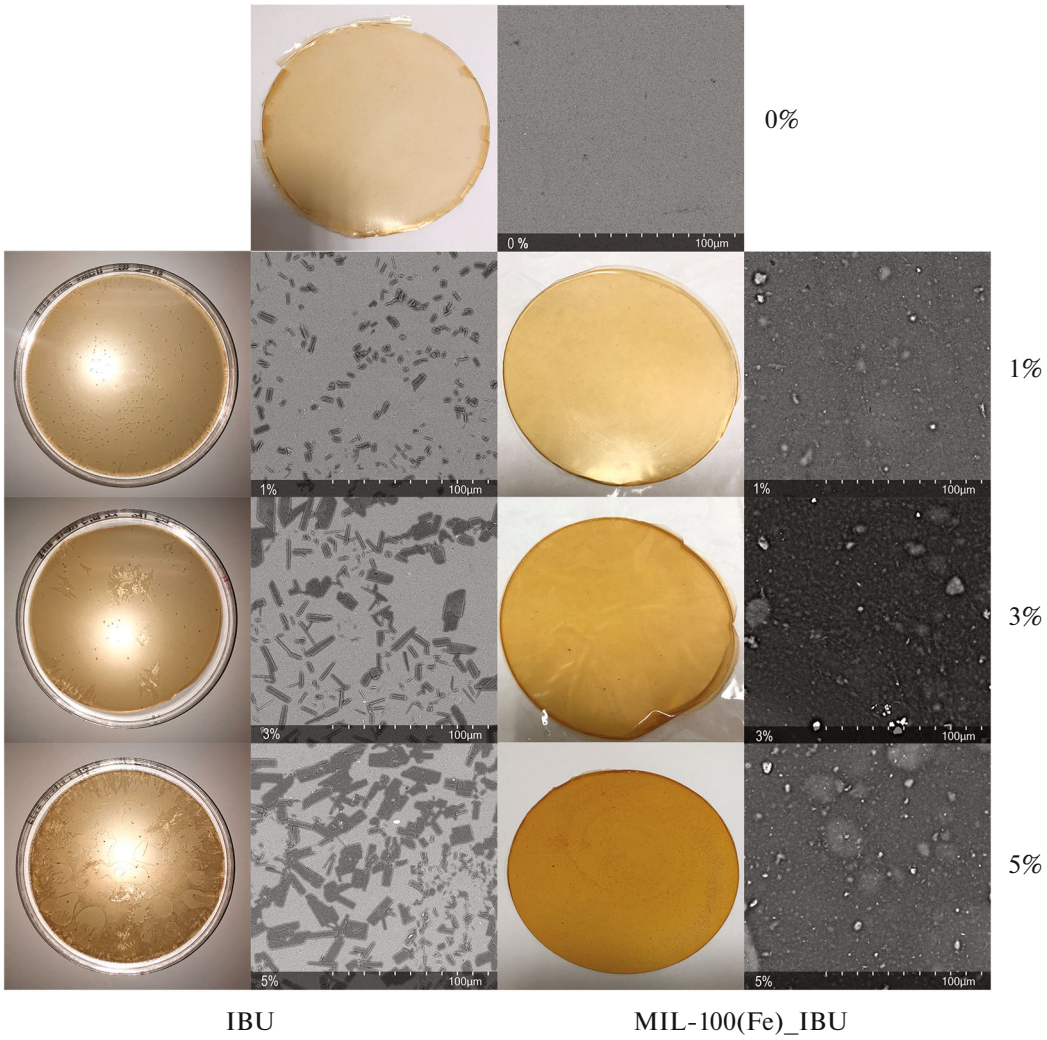

Fig. 1. Micrographs of composite films based on ibuprofen and MIL-100(Fe)_IBU of various compositions. SEM images of the surface fragments were obtained immediately after manufacturing of the films.

under orbital stirring (80 rpm) at a temperature of 37°C for 24 h. The most pronounced swelling of the material was observed after 3 h, while complete dissolution took place 5 h after the start of the experiment.

In order to increase the degree of cross-linking of polymer chains and thus reduce the solubility of the material, sodium citrate capable of binding to molecules of all used hydrocolloids via hydrogen and covalent bonds was added to the hydrocolloid composition in various amounts (5, 10, and 15% of the total hydrocolloid weight). A study of the swelling—dissolution properties of the resulting material showed that the composition containing 5% sodium citrate completely dissolved in 10 h, while increase in the concentration of the cross-linking agent to 10 and 15% increased the dissolution time to 24 and 26 h, respectively. Unfortunately, addition of the cross-linking agent deteriorated the mechanical characteristics of the material by increasing its brittleness; therefore, the concentration of sodium citrate in the composition was chosen to be 10% of the total hydrocolloid weight.

After determining the optimal hydrocolloid composition, films with ibuprofen were obtained by adding an ethanol solution of ibuprofen to the gelling solution in amounts of 1, 3, and 5% of the total hydrocolloid weight. These composite films had inclusions that disrupted the homogeneity of the hydrocolloid matrix (Fig. 1). This fact is attributable to the hydrophobic nature and low solubility of ibuprofen, which hence crystallizes on the surface of films as water evaporates during drying; this was confirmed by scanning electron microscopy data (Fig. 1).

Powder X-ray diffraction data for the composite films (Fig. 2) indicated the presence of a crystalline phase corresponding to ibuprofen. Crystallization of API on the film surface is inadmissible, because apart

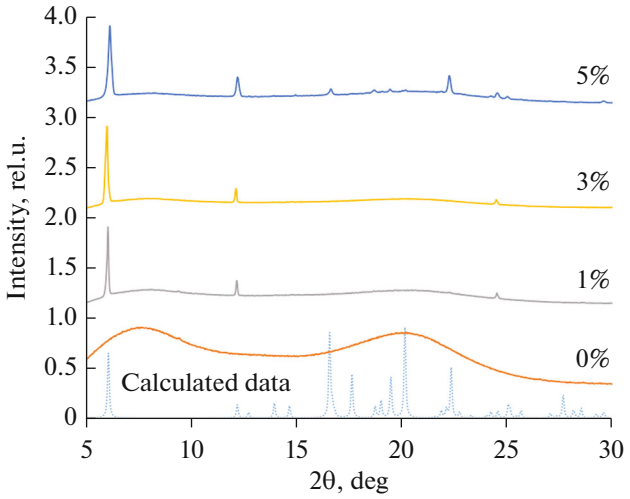

Fig. 2. Powder X-ray diffraction data for samples of composite films based on ibuprofen added in amounts of 1, 3, and 5% of the total weight of hydrocolloids in comparison with theoretically simulated X-ray diffraction pattern of ibuprofen.

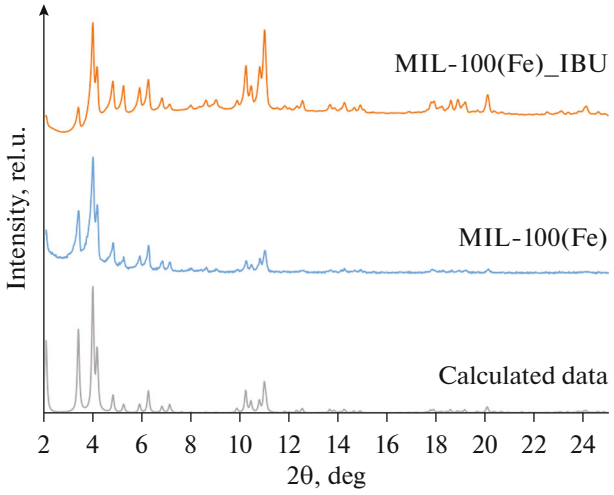

Fig. 3. Powder X-ray diffraction data for MIL-100(Fe) and MIL-100(Fe)_IBU samples in comparison with theoretically simulated X-ray diffraction pattern of MIL-100(Fe).

from the non-uniform distribution and disruption of matrix homogeneity, this can bring about undesirable effects for tissues occurring in long-term contact with a highly concentrated form of this substance.

In order to avoid crystallization of ibuprofen on the surface of composite films, we decided to use biocompatible MIL-100(Fe) MOF, which has a low toxicity and high porosity, as a container for targeted API delivery. Ibuprofen was encapsulated into the MOF pores by soaking a pre-activated MIL-100(Fe) powder at a MOF to API ratio of 1 : 2. The metal-organic framework retained the crystal structure, as indicated by powder X-ray diffraction data (Fig. 3) for MIL-100(Fe) and MIL100(Fe)_IBU powders, which coincided with the theoretically calculated data for pure MIL-100(Fe). The observed change in the intensity ratios of the X-ray diffraction peaks may be due to the slight changes in the interatomic distances and bond angles, which indirectly confirms the encapsulation of ibuprofen into the pores of chosen MOF.

The completeness of ibuprofen encapsulation was assessed by keeping a MIL-100(Fe)_IBU sample in excess hydrochloric acid until the MOF crystal structure was completely broken via acid hydrolysis. Then the aqueous fraction was extracted into dichloromethane. After removal of the organic solvent, the API weight was determined upon drying under reduced pressure to a constant weight. It is important that other products of MIL100(Fe) hydrolysis with HCl, that is, $FeCl_3$ and trimesic acid, are insoluble in dichloromethane. The content of the drug in MOF was 10 wt %.

The obtained composite films containing MIL-100(Fe)_IBU had high transparency, elasticity, and uniform distribution of MOF particles, which imparted a brown color to the films (Fig. 1). Powder X-ray diffraction data for film samples (Fig. 4) showed the presence of a crystalline phase corresponding to MIL-100(Fe). The low intensity of the crystalline phase peaks against an amorphous halo from the hydrocolloid matrix is presumably caused by low con-

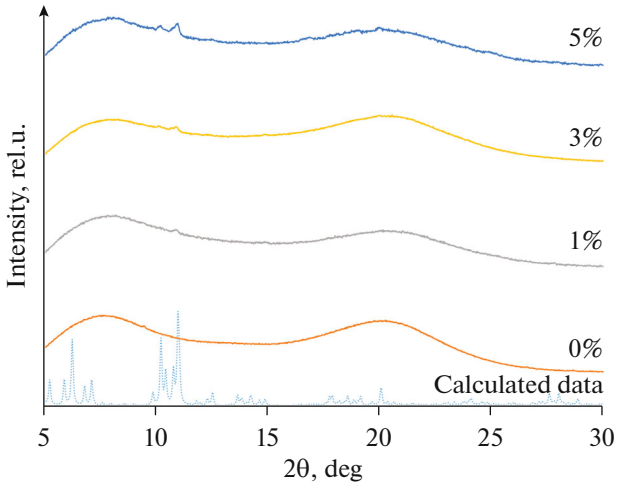

Fig. 4. Powder X-ray diffraction data for samples of composite films based on MIL-100(Fe)_IBU added in amounts of 1, 3, and 5% of the total weight of hydrocolloids in comparison with theoretically simulated X-ray diffraction pattern of MIL-100(Fe).

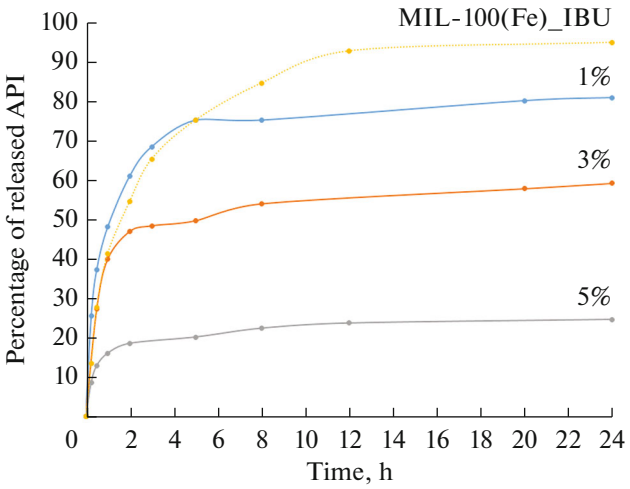

Fig. 5. Release profiles of ibuprofen from MIL100(Fe)_IBU powder samples and films containing MIL-100(Fe)_IBU.

centration of MOF particles distributed throughout the films.

For determination of the time needed for complete release of ibuprofen from MOF pores, a sample of the MIL-100(Fe)_IBU powder was placed into phosphate-buffered saline (pH 7.4) and kept under orbital stirring (80 rpm) at 37°C for 24 h. At specified time intervals, the mother liquor containing the released API molecules was withdrawn and replaced with the same volume of fresh buffer. The mass-spectrometric determination of the amount of ibuprofen in the samples was performed after separation of components of the mother liquor by high-performance liquid chromatography. The rate of ibuprofen release from the films containing MIL-100(Fe)_IBU was estimated in a similar way. Almost complete drug release from MOF pores took place after 24 h of the experiment; therefore, more than 50% of the active pharmaceutical ingredient dissolved in the first 2 h (Fig. 5).

The introduction of MIL-100(Fe)_IBU into composite films markedly decreased the efficiency of ibuprofen release to the solution owing to the decrease in the surface area of MOF particles in direct contact with the buffer. In this case, the API release rate was determined by two stages: diffusion of ibuprofen from the MOF pores into the gel and diffusion of ibuprofen from the gel into the bulk solution.

The ibuprofen dissolution profiles for film samples are similar and can be conventionally considered as consisting of two regions. The first (fast release) region apparently corresponds to the diffusion of the active pharmaceutical ingredient from the pores of MOF particles located on the surface of films, while slow increase in the ibuprofen concentration after 2–3 h is determined by diffusion of the active pharmaceutical ingredient from the gel.

Thus, we obtained biocompatible film materials based on a hydrocolloidal matrix composed of a mixture of gelatin, pectin, and kappa-carrageenan containing MIL-100(Fe) MOF particles bearing a model active pharmaceutical ingredient, ibuprofen, in the pores. The rate of ibuprofen release from the obtained films, assessed in model experiments under simulated biological conditions, was significantly lower than the release rate observed in the absence of MOF, indicating the applicability of the composite materials based on hydrocolloids and MOFs with encapsulated hydrophobic active pharmaceutical ingredients as dosage forms for delayed drug release.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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