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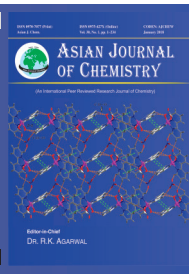

in vitro Controlled Drug Release of Antidiabetic Metformin HCl from Citric Acid Activated Natural Montmorillonite

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In this work, metformin HCl was encapsulated on citric acid activated montmorillonite as drug delivery system. The as-synthetized drug delivery systems were characterized by using FTIR and X-ray diffraction. FTIR spectra showed the presence of bending vibration of N-H from primary amines group and streching vibration of C=N at 1635.64 and 1506.41 cm^{-1}, respectively. X-ray diffraction pattern also showed a widening of the diffraction peaks of montmorillonite after encapsulated by metformin HCl. *In vitro* drug release results showed that the release of metformin HCl from the drug delivery system in simulated intestinal fluid (pH 7.4) higher than that in simulatied gastric fluid (pH 1.2) with a value of drug release of 61.44 % and 39.41 %. Metformin HCl release kinetics at each pH follow the zero-order model (pH 1.2 with R = 0.9924; pH 7.4 with R = 0.9972) suggested diffusion-controlled release mechanism.

Keywords: Drug delivery system, Encapsulation, Montmorillonite, Metformin HCl, Controlled release.

INTRODUCTION

Metformin HCl is the most frequently drug used to treat type 2 diabetes mellitus. This drug has been established as first line drug since it is low-cost, did not cause hypoglycemia and weight increment. It has also been shown to be effective in regulating blood sugar levels of type 2 diabetes mellitus patients with obesity. In addition, metformin HCl can protect the cardiovascular system, stabilize weight and improve the patient's survival rate better than sulfonylurea or insulin therapy [1,2]. However, high daily dose of metformin HCl (1.5-3 g/day) must be administrated to the patients because of its low oral bioavaliability (50-60 %) with a half-life of 1.5-1.6 h [3,4]. Incorporation of metformin HCl into new materials (organic or inorganic) to form drug delivery system should be the way to overcome this drawback.

Montmorillonite has received much attention from researchers due to its unique characteristics. Various studies have shown that montmorillonite is one of the inorganic materials that provides promising opportunities in biomedical applications [5-8]. Since the knowledge of their physical and chemical properties, the applications of montmorillonites were primarily focused on drug delivery systems [9]. The use of montmorillonite as a carrier of drugs has been reported by some researchers such as chlorhexidine acetate [10], platinum anticancer complex [11], gallic acid [12] and gentamycin [13]. Among the numerous studies, the use of montmorillonite as carrier of metformin HCl has not been reported. In this study, we synthesized drug delivery systems by encapsulating metformin HCl (MH) on natural montmorillonite (MMT). Montmorillonite was activated with citric acid to increase specific surface area and acid sites prior to synthesis. The drug release pattern of metformin HCl from montmorillonite was studied in simulated gastric fluid (pH 1.2) and simulated simulated intestinal fluid (pH 7.4).

EXPERIMENTAL

Activation of natural montmorillonite (MMT_0) with citric acid was based on method described by Khan *et al.* [14] with few modification. Encapsulation of metformin HCl on activated montmorillonite (MMT_1) was conducted by mixing 100 g of activated montmorillonite with 100 mL metformin HCl solution 500 mg/L. The mixture was stirred at optimum pH for 24 h. The residue of this mixture was then collected by filtration and heated at 105 °C for 6 h. The as-synthesized drug delivery system (denoted MMT_2) was analyzed by FTIR spectrometer and X-ray diffractometer. The amount of metformin HCl encapsulated on activated montmorillonitewas calculated using UV-visible spectrophotometric method [15]. *In vitro* drug release evaluation was conducted by mixing 1 g of MMT_2

with 100 mL of simulated gastric solution (buffer pH 1.2). The mixture was stirred with continously stirring. Every 1 h, an aliqoute of buffer solution (5 mL) was collected and replaced with the same amount of fresh buffer solution [16]. The concentration of metformin HCl in sample aliquote was measured by UV-visible spectrometer at 232 nm. This procedure was conducted for 12 h. The same prosedure was done with simulated intestine solution (buffer pH of 7.4).

RESULTS AND DISCUSSION

Fourier transform infrared (FTIR) spectrometer has been the most useful tool in functional groups characterization of the materials. It is also widely used to confirm an attachment of different functional groups in encapsulation process. Fig. 1 shows FTIR spectra of montmorillonite (MMT_0), citric acid activated montmorillonite (MMT_1) and drug delivery system metformin HCl/montmorillonite (MMT_2). In the FTIR spectrum of montmorillonite (MMT_0), absorption bands at 3626.17 and 3695.61 cm^{-1} indicate the stretching vibration of the -OH group (Al–OH and Si–OH of octahedral and tetrahedral layers) on the montmorillonite framework [12]. The absorption band at 1631.78 cm^{-1} indicates the H–O–H bending mode of adsorbed water [17,18]. The appearance of two bands at 1165 cm^{-1} and 796.6 cm^{-1} are attributed to asymmetrical stretching vibration and symmetrical stretching vibration of TO_4 (T = Si or Al), respectively [19]. The presence of bending vibration of Al-OH-Al appears at 921.97 cm^{-1}, whereas the bending vibration of the Si-O-Si and Si-O-Al appears at 457.13 and 489.92 cm^{-1} [20]. In the FTIR spectrum of drug delivery system metformin HCl/montmorillonite (MMT_2), a new peak appears at 1635.64 cm^{-1}, indicating the presence of N-H bending vibration associated with the primary amine group. This finding was supported by Nayak *et al.* [4] who stated that the absorption peak appearing at 1584 cm^{-1} was attributted to N-H bending vibration of the primary amino group of metformin HCl. Furthermore, the new band at 1560.41 and 1506.41 cm^{-1} are characteristics of stretching vibration of C=N in metformin HCl.

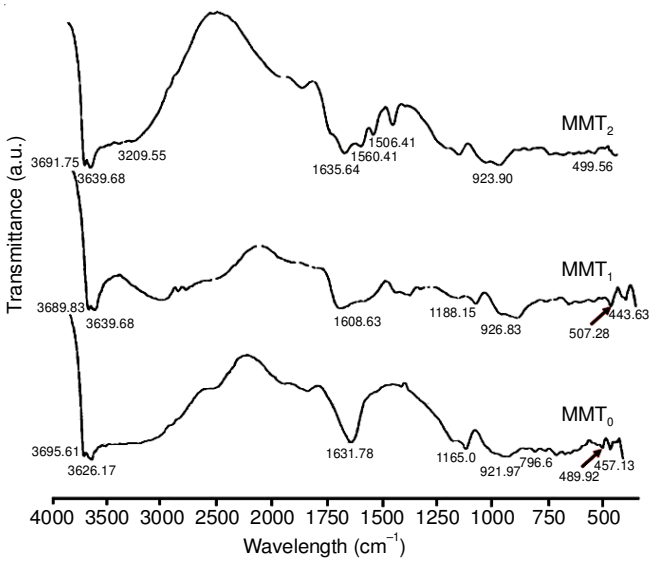

Fig. 1. FTIR spectra of montmorillonite (MMT_0), citric acid activated montmorillonite (MMT_1) and drug delivery system metformin HCl/montmorillonite (MMT_2)

X-ray diffraction (XRD) study was conducted to confirm the mineral characteristics of parent montmorillonite (MMT_0), activated montmorillonite (MMT_1) and drug encapsulated montmorillonite (MMT_2). The pattern is depicted in Fig. 2. The XRD pattern of MMT_0 shows some peaks, where the highest peak is appeared at 2θ = 19.86° (d = 4.46 Å). This peak is the characteristic of montmorillonite mineral (JCPDS,29-1498). The other peaks appearing at 2θ = 12.17° (d = 7.27 Å), 2θ = 20.77° (d = 4.27 Å), 2θ = 26.61° (d = 3.35 Å) and 2θ = 35.58° (d = 2.521 Å) are attributted to montmorillonite, illite, quartz and montmorillonite, respectively. The XRD pattern of MMT_1 reveals that the activation of montmorillonite using citric acid did not significantly affect the mineral crystallinity. This indicates that citric acid washed out the contaminants from montmorillonite.The XRD pattern of MMT_2 represents the widening on some diffraction peaks. This indicates that metformin HCl was successfully encapsulated on montmorillonite. This result was supported by Zheng *et al.* [21], who stated that the loading of metformin HCl on montmorillonite interlayer was denoted by peak widening in the XRD pattern.

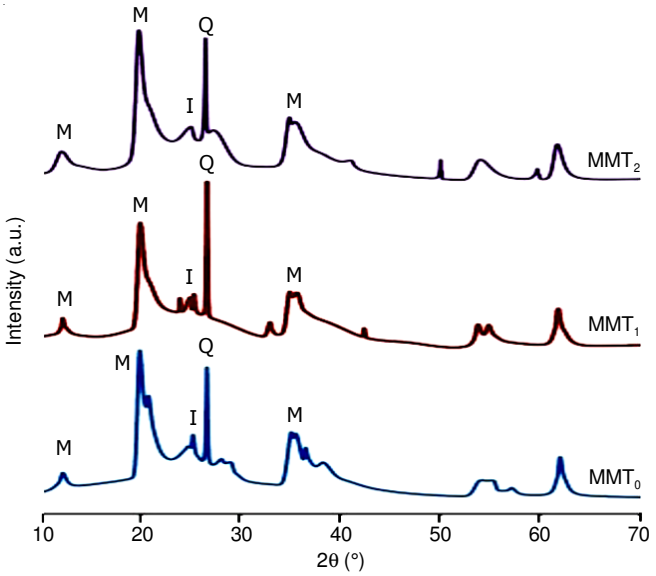

Fig. 2. X-ray diffraction pattern of montmorillonite (MMT_0), citric acid activated montmorillonite (MMT_1) and drug delivery system metformin HCl/montmorillonite (MMT_2)

The drug release study of MMT_2 was performed in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4). Fig. 3 shows the release pattern of metformin HCl from activated montmorillonite. It is clear that the amount of drug released from activated montmorillonite was influenced by pH. In simulated gastric fluid, MMT_2 shows an ordered release of 61.44 % of the drug within 12. The slow ordered release is also observed in simulated intestinal fluid, which 39.41 % of drug released within 12 h. The drug release in simulated gastric fluid is much lower than that in simulated intestinal fluid, indicates that drug release properties of MMT_2 are affected by pH [22]. Rapid initial burst release is not observed in this study as the other researchers observed [23-25], since the strong hydrophilic interaction between metformin HCl and montmorillonite occurred. At low pH, the positively charged protons (H^+) tend to urge the drugs and replace them *via* cation exchange [15]. The replacement of

TABLE-1
RELEASE KINETICS DATA OF METFORMIN HCl

Release media	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	k_0	R^2	k_1	R^2	k_H	R^2	k_{KP}
Buffer pH 1.2	0.9924	0.0512	0.9492	-0.00052	0.9794	1.821	0.9920	6.502
Buffer pH 7.4	0.9972	0.0866	0.9540	-0.00069	0.9794	3.042	0.9931	11.678

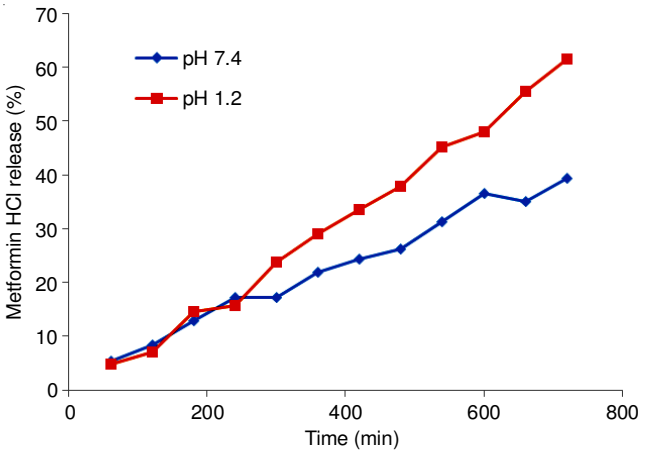

Fig. 3. *in vitro* release profile of metformin HCl from activated montmorillonite

the drugs *via* cation exchange may be more difficult in higher value of pH, since the concentration of H^+ is diminished.

The release mechanism of MMT_2 drug delivery system (DDS) can be evaluated by fitting the release data of drug delivery system with zero order, first-order, Higuchi and Korsmeyer-Peppas models of kinetic models [24]. The results are shown in Table-1. The release kinetic data of metformin HCl from activated montmorillonite was best fitted by zero order model. This is demonstrated by the highest value of R^2 which are 0.9924 in simulated gastric fluid (buffer pH 1.2) and 0.9972 in simulated intestinal fluid (buffer pH 7.4). The release mechanism of metformin HCl from activated montmorillonite in both the buffer solution follows controlled release mechanism [4].

Conclusion

The MMT_2 drug delivery system was successfully synthesized using simple encapsulation method at room temperature. Characterization MMT drug delivery system using spectrophotometer FTIR showed the presence of bending vibration of N-H from primary amines group and streching vibration of C=N at wavenumbers of 1635.64 and 1506.41 cm^{-1}, respectively. This result was also supported by X-ray diffraction pattern which showed a widening of the diffraction peaks of montmorillonite after encapsulated by metformin HCl. The slow ordered release of 61.44 and 39.41 % was observed in simulated gastric fluid (pH = 1.2) and simulated intestinal fluid (pH = 7.4) respectively within 12 h. The release kinetic data of metformin HCl from activated montmorillonite was best fitted by zero order model in both the buffer solution which indicated controlled release mechanism.

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