

Cellulose

Synthesis, characterization and Ampyrone drug release behavior of Magnetite nanoparticles/2,3-dialdehyde Cellulose-6-Phosphate Composite --Manuscript Draft--

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Synthesis, characterization and Ampyrone drug release behavior of Magnetite nanoparticles/2,3-dialdehyde Cellulose-6-Phosphate Composite

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Abstract

Drug delivery system with magnetically enhanced properties was synthesized by co-precipitation of magnetite nanoparticles within DACP, characterized and studied for ampyrone drug loading and controlled delivery. The magnetic nanocomposite magnetite/2,3-dialdehyde cellulose-6-phosphate (DACP) were characterized using FT-IR, SEM-EDX, and XRD. The magnetic core contained as Fe_3O_4 was synthesized through an intramolecular Cannizzaro reaction during in situ preparation of magnetic nanoparticles (MNPs) in the presence of sodium hydroxide solution producing hydroxyl acid cellulose phosphate (HACP). The release profiles of the loaded ampyrone on DACP and MNPs/HACP showed continuous release from MNPs/HACP with more than 95 % after 50 h, while with respect to DACP, 60 % of the loaded ampyrone was released after 50 h proving an enhanced loading-release system of MNPs/HACP with potential application as a magnetically enhanced drug delivery system.

Key words: 2,3-dialdehyde cellulose-6-phosphate, magnetite, ampyrone, drug carrier

Introduction

Pharmaceutical industry has elevated the interest in designing and modifying polymers with improved drug loading-release properties. Characteristics of the cellulose can be transformed by physical and chemical modification methods reliant on the attributes needed for the product. These methods aim to break the hydrogen bonds between cellulose chains or replace a hydroxyl group as well as mostly to replace the hydrogen with a functional group in order to obtain the favorite properties (Keshk et al., 2019^a & ^b). Cellulose and its derivatives are employed in different medical applications, as either unmodified biopolymer or as esters and ethers of cellulose as well as either crosslinked or grafted copolymers (Keshk & Gouda, 2017). In the pharmaceutical industry, different forms of pure cellulose (powdered cellulose, low crystallinity cellulose, and microcrystalline cellulose) or cellulose derivatives are used as an excipient to control and/or sustain the drug release, to coat tablets (osmotic and enteric coating), to increase the muco-adhesiveness of the formulation and to enhance the compressibility of the powder mixture (Liechty et al., 2010; Shokri et al., 2013). Even though there are many excipients derived from cellulose used in drug preparations, to improve manufacturing processes, decrease the costs, and improve the performance of medicine by investigating and developing different modification methods to create favorite cellulose-based excipients (Dias et al., 2013). Different polymers used to provide controlled release of active pharmaceutical ingredients (API) in constant doses over long periods, increase the stability of the API by entrapping it within the matrix of the polymer, tune release of both hydrophilic and hydrophobic drugs by the swelling, and eroding nature of the polymers (Godwin et al., 2001; Kim et al., 2009). Cellulose acetate, cellulose acetate phthalate, cellulose acetate butyrate, cellulose acetate tri-melitate and hydroxypropyl methyl cellulose phthalate is commonly used cellulose esters in the pharmaceutical industry (Heinze et al., 2003; Edgar, 2004 & 2007; Volkert et al., 2009). Whereas cellulose

phosphate (CP) has the potential for use as an important implantable biomaterial in orthopedic applications (Fricain et al., 2001; Keshk et al., 2019_{a, b}). The phosphate functionalities could be applied to bind different biologically active species to get precisely active surfaces, on one hand (Leone et al., 2008). On the other hand, magnetic Fe₃O₄-based particles play a major role in magnetic solid phase extraction owing to their high magnetic saturation values, large surface areas, abundant adsorption capacities, and ease of operation and flexibility for modification (Zhang et al., 2016). However, the disadvantages of easy aggregation or oxidation, instability in acidic conditions, and low extraction efficiency are limit their use. Owing to its instability under acidic conditions, it will be advance in using it in drug delivery. Hence, recently magnetic particles are carried the drugs to the essential location in the body, typically cancer tissues. The strategy for utilizing magnetic nanoparticles has become much consideration from the exploration network with two main objectives: one to narrow the delivery of drugs in the body for reducing the side effects and other to reduce the amount of drug consumption. The biocompatible magnetic nanoparticles are compressed with drugs. They work as drug delivery carriers and control the drug release procedure. Therefore, the application of magnetic iron oxide nanoparticles in diagnosis and therapeutics has gained various promising achievements (Pham et al., 2016). Different scientists have studied improved magnetic nanoparticles. Magnetic Fe₃O₄/SiO₂-GO core/shell nanoparticles were prepared by means of covalent and used as adsorbent. The results show that this composite has a relatively high adsorption ability (Yao et al., 2012). Further, magnetic iron oxide (Fe₃O₄) nanoparticles were modified by chitosan (CS) using reverse micro-emulsion (water-in-oil) method. This composite showed relatively small size, good magnetic and high adsorption ability (Pham et al., 2016). Recently, 2,3-dialdehyde cellulose (DAC) and 2,3-dialdehyde cellulose-6-phosphate (DACP) experienced an intramolecular Cannizzaro reaction during the *in situ* reaction

with MNPs and give hydroxy acid, on one hand (Keshk et al., 2019_{a, b, c}). On the other hand, 4-
ampyrone (4-AA) is a metabolite of aminopyrine with analgesic, anti-inflammatory, and
antipyretic properties. It is used as a reagent for biochemical reactions producing peroxides or
phenols (Alam et al., 2012). 4-AA is not genotoxic and mutagenic *in vivo*, it can interfere with
DNA damaging agents' biological activities and may reduce the effectiveness of DNA damage-
based chemotherapy (Radi et al., 2012). In this study, Fe₃O₄ magnetite nanoparticles could react
with DACP to form MNPs/hydroxy acid cellulose phosphate (HACP) composite. The composite
efficiency toward 4-AA entrapping and release was studied for the first-time using UV-
spectrophotometer.

Materials and methods

Chemicals

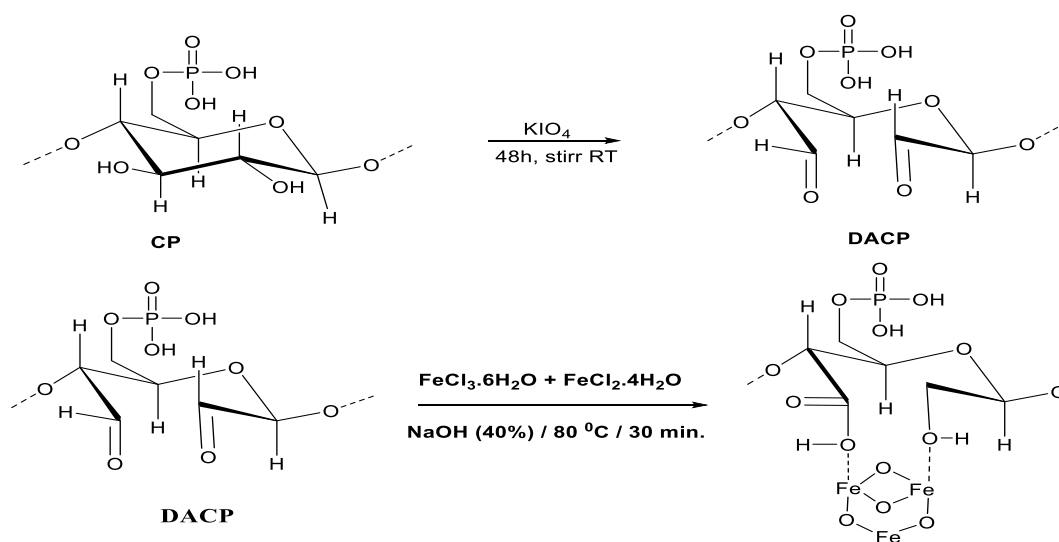
All chemicals and cellulose-6-phosphate were purchased from Sigma and Aldrich Chemical Co
and were used as received. The phosphorus content of cellulose 6-phosphate was found to be 12.25
% (Keshk et al., 2019_a).

Preparation of 2,3-dialdehyde cellulose-6-phosphate (DACP)

Cellulose-6-phosphate (CP, 0.68 g, 0.003 mole) was suspended in 50 ml water for 2 h, potassium
periodate (1.4 g, 0.006 mole) was added portion-wise gradually and the mixture was heated to 60
°C for 2 h. After cooling, the mixture was maintained in dark at room temperature for 48 h. The
product (DACP) was washed well with distilled water. The experimental yield of DACP was found
to be 96%.

Preparation of MNPs/HACP composite

An *in-situ* precipitation method was used for preparation of DACP magnetic nanoparticles composite (MNPs/ HACP) as in the previous work (Keshk et al., 2019_b). Briefly, 3.0 g DACP was suspended in 100 mL deionized water and mixed with 100 mL aqueous solution of ferrous sulfate heptahydrate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$) and ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) with stoichiometric ratio of 1:2.



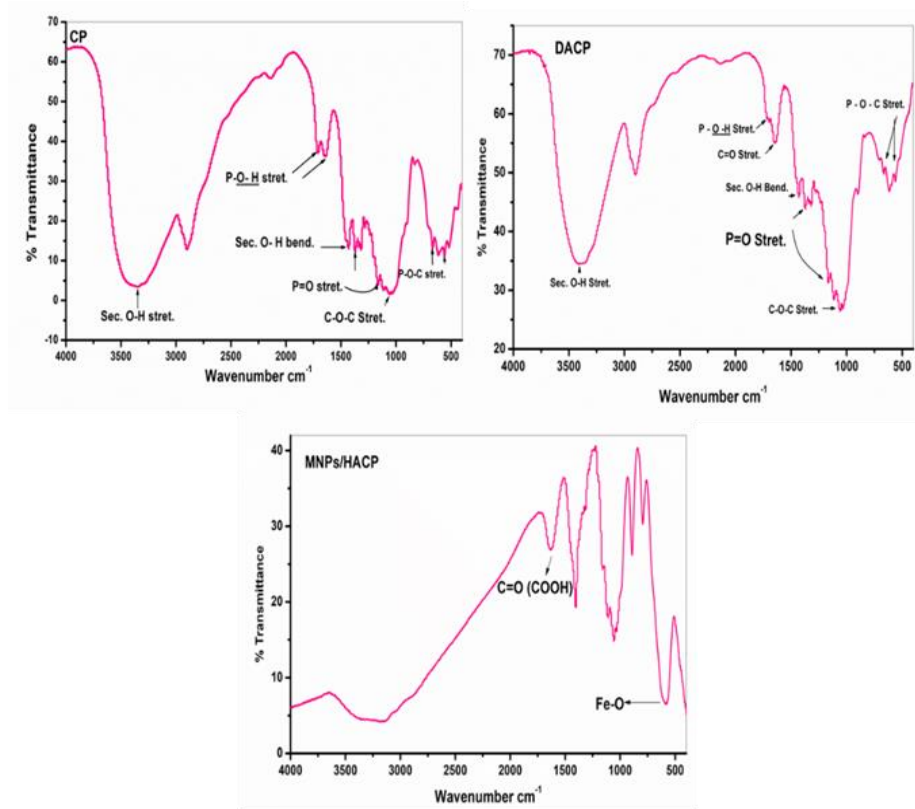
Scheme 1: Synthesis of DACP and MNPs/HACP

Characterization of MNPs/HACP composite

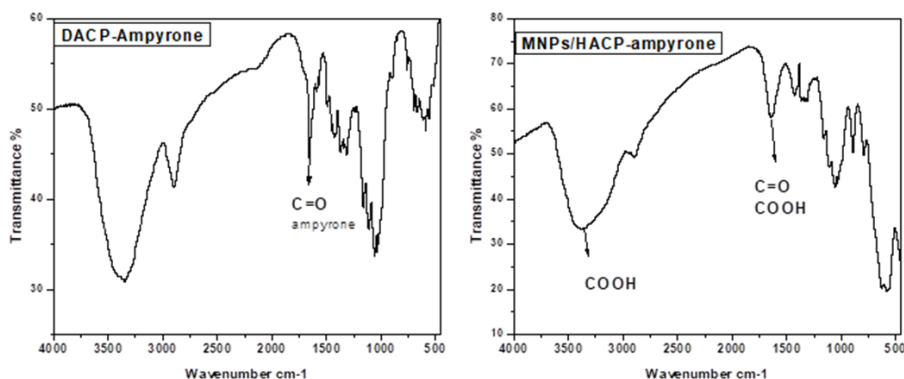
A Bruker FT-IR IFS 66 spectrophotometer was used for FT-IR analysis. The morphology of the composite samples was analyzed using field emission scanning electron microscopy (FESEM) of

FESEM JEOL 6340 type with an energy-dispersive X-ray instrument (EDX) for elemental composition assaying of the composite.	142 143
In vitro 4-ampyrone drug loading-release experiments	144
4-Ampyrone (4-AA) drug loading on DACP and MNPs/ HACP was performed by mixing 0.3 g of either DACP or MNPs/HACP with 0.1% 4-AA dissolved in of water-ethanol mixture (30:70) and stirred for 3 h to obtain a considerable uptake of 4-AA. After fixed periods, the composite (MNPs/HACP) was separated from the mixture by using a magnet. The residual 4-AA concentration in the supernatant was measured by UV–Vis spectrophotometer and the loading percentage was determined at different time interval. The release profile of the drug was studied in phosphate buffered saline (PBS) at pH value of 7.4. Either 4-AA-DACP or 4-AA-MNPs/HACP (0.3 g) was dispersed in PBS at 37 °C with slight shaking at 150 rpm. After different time intervals, the released 4-AA concentration in the PBS was analyzed by UV–Vis spectroscopy. The absorption spectra were assayed within the wavelength range 200-350 nm, and the concentration was calculated depending on the absorption peak at 240-245 nm.	145 146 147 148 149 150 151 152 153 154 155
Computational investigations	156
Various DFT functional were studied and it was concluded that B3LYP (Irfan et 2017) provides an exact and reliable description of small molecules. Moreover, B3LYP functional was successfully accepted to reproduce the experimental data and to predict numerous properties of interests. In the present study, the ground state geometries and frequency calculations were performed by B3LYP hybrid functional along with the 6–31G** basis set for H, C, N, O and K while taking LANL2DZ for the I atom. All the calculations were performed by using Gaussian09 package (Frisch et al., 2009).	157 158 159 160 161 162 163

Results and discussion	165
Characterization of the prepared magnetic composite:	166
FTIR spectroscopic analysis	167
Figure 1 displays the FTIR spectra of cellulose phosphate (CP), dialdehyde cellulose phosphate (DACP) and the composite (MNPs/HACP) with/without ampyrone. In the FTIR spectrum of DACP, the band that recorded at 1640 cm^{-1} was assigned to the carbonyl group associated with hydrogen bonding (Keshk et. al., 2019a). The broadness and intensity of the DACP bands most likely occur because of the smaller crystalline size or orientation effect. Moreover, the absorption bands at 3388 cm^{-1} and 1645 cm^{-1} in MNPs/HACP spectrum were assigned to OH as well as C=O stretching of carboxyl group in hydroxy acid cellulose phosphate (HACP) (Keshk et al., 2019 _b). Therefore, these results prove the disproportionation reaction (intramolecular Cannizzaro reaction) of DACP, yielding alcohol and carboxylic acid (Scheme 1) (Keshk et al., 2019 _{b, c}). The presence of Fe_3O_4 core was confirmed by a strong bending vibration band at 752 cm^{-1} , which corresponds to the Fe–O stretching (Chan et al., 2005).	168 169 170 171 172 173 174 175 176 177 178



179



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Figure 1. FT-IR spectra of cellulose phosphate (CP), dialdehyde cellulose phosphate (DACP) and its magnetic nanocomposite (MNPs/HACP), DACP-4-ampyrone and MNPs/HACP-4-Ampyrone

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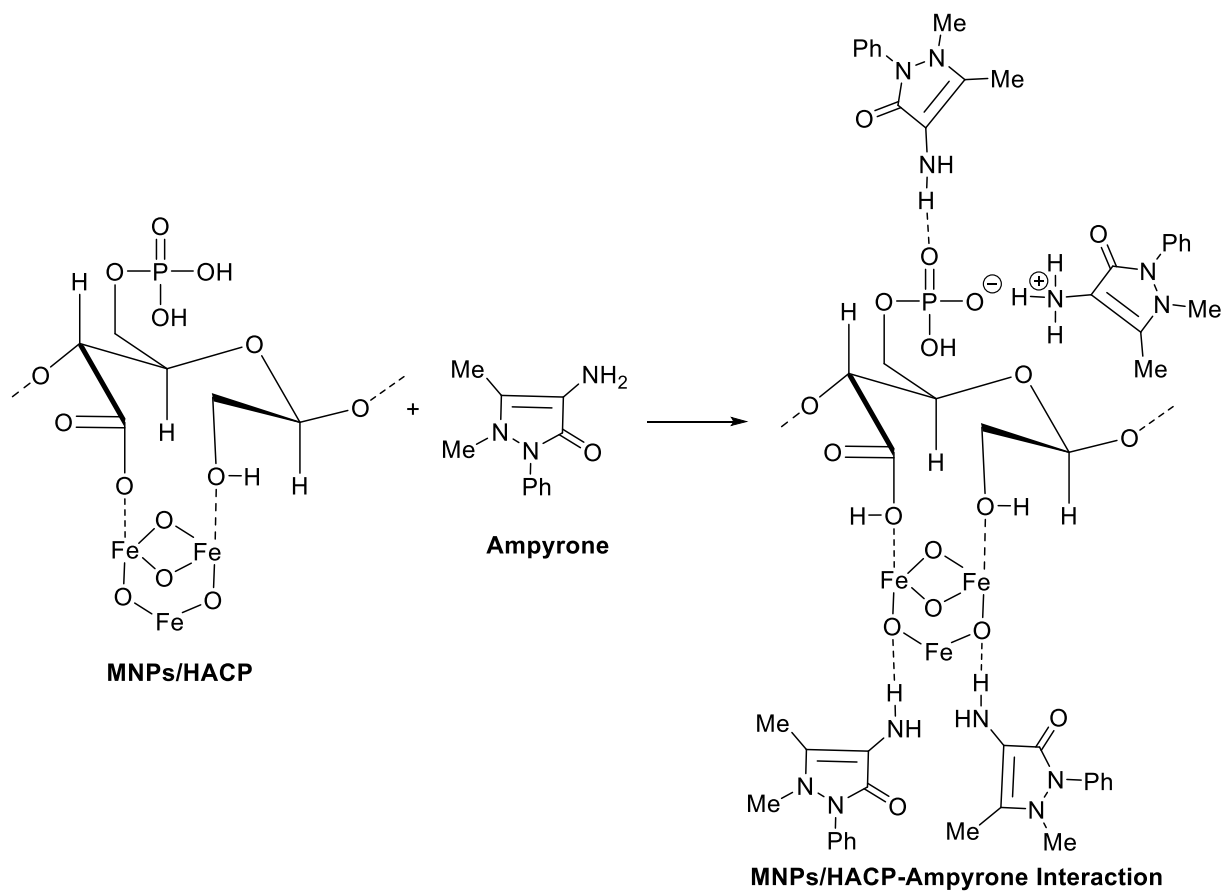
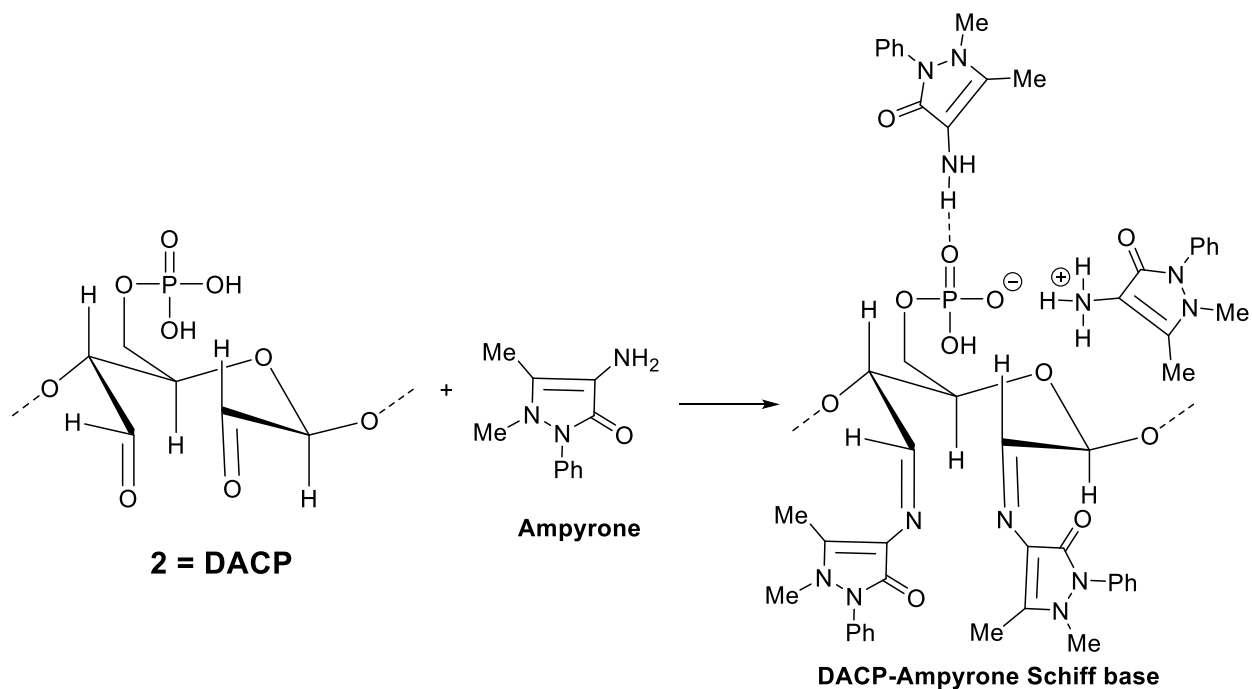
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Furthermore, the redshifts occurring in the carbonyl group in MNPs/HACP could be due to the interactions between the carboxyl group and Fe_3O_4 (Keshk et al., 2019_b). The comparison of the

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186

spectra of DACP/4-AA and magnetic nanocomposite/4-AA showed a new peak at 1653 cm⁻¹ and 1563 cm⁻¹ corresponding to carbonyl group of 4-AA and azomethine group (C=N), respectively. The absorption band of azomethine group could not be recognized in the spectrum of MNPs/HACP-4-AA. The stretching vibrational of CH₃ of 4-AA and CH₂ of glucan are recorded at 2929 cm⁻¹ and 2885 cm⁻¹, respectively. These results support the interaction between 4-AA and DACP to form Schiff's bases, on one hand. On the other hand, 4-AA is attracted by MNPs/HACP via formation of Zwitter ions as verified by the appearance of narrow broadened absorption band at 3388 cm⁻¹ depicted in Scheme 2. Furthermore, the shoulder band at 1485 cm⁻¹ is attributed to the C=C stretching vibration of the aromatic ring of 4-AA (Figure 1). In addition, the peak at 1059 cm⁻¹ appeared for C-O-C vibrational of glucan unit.



Scheme 2. Loading mechanism of 4-ampyrone on DACP and MNPs/HACP.

From the previous study, the Mulliken charges were determined to know the favorite site for hydroxyl and carboxyl groups in HACP (Keshk et al., 2019). It was confirmed that the favorite places for OH and COOH are C-2 and C-3, respectively. On the other hand, DACP reacted with 4-ampyrone via two carbonyl groups on C-2 and C-3. Computational calculations showed that carbonyl group on C-3 in DACP form Schiff's base through more stable transition state (Figure 2a) rather than carbonyl group on C-2 (Figure 2b). Furthermore, the dipole derivative charges were studied, also called the atomic polar tensor (APT)-derived charges that can be defined by equation (1) as follows:

$$qi = \frac{1}{3} \left(\frac{\partial \mu_x}{\partial x_i} + \frac{\partial \mu_y}{\partial y_i} + \frac{\partial \mu_z}{\partial z_i} \right) \quad \text{Eq.1}$$

Here, μ is the dipole moment of a DACP, and x_i, y_i, z_i are the positions of atom i . Although the components of dipole moment change with the choice of coordinate system, the defined APT charge for each atom is invariant under rotation and translation of the molecule and sum up to the total charge of molecule correctly. The estimated dipole moment for the Schiff's base that form between ampyrone and DACP on C3 is 4.14 whereas, on C2 is 8.72 in transition state (Table 1).

Table 1. Total energies of the DACP-C3=O and DACP-C2=O at B3LYP/6-31G* level of theory.

Parameter	DACP-C3=O	DACP-C2=O
ΔG (kJ/mol.)	0.0	12.02
ΔH (kJ/mol.)	0.0	9.67
Dipole moment	4.14	8.72

According to the charge analysis, both the carbonyl groups in DACP could show non-equal opportunities for nucleophilic addition. In the first step, the C-3 atom of the carbonyl group was substituted, and geometrical optimization and frequency calculations were performed. In the second step, the carbonyl group was substituted at C-2 and geometrical optimization and frequency computation were performed (Figure 2). It was remarked that C-3 stabilizes the Schiff's base almost by 12.02 kJ/mol. Thus, C-3 carbonyl in DACP is more reactive than C-2 toward formation of Schiff's base with 4-AA.

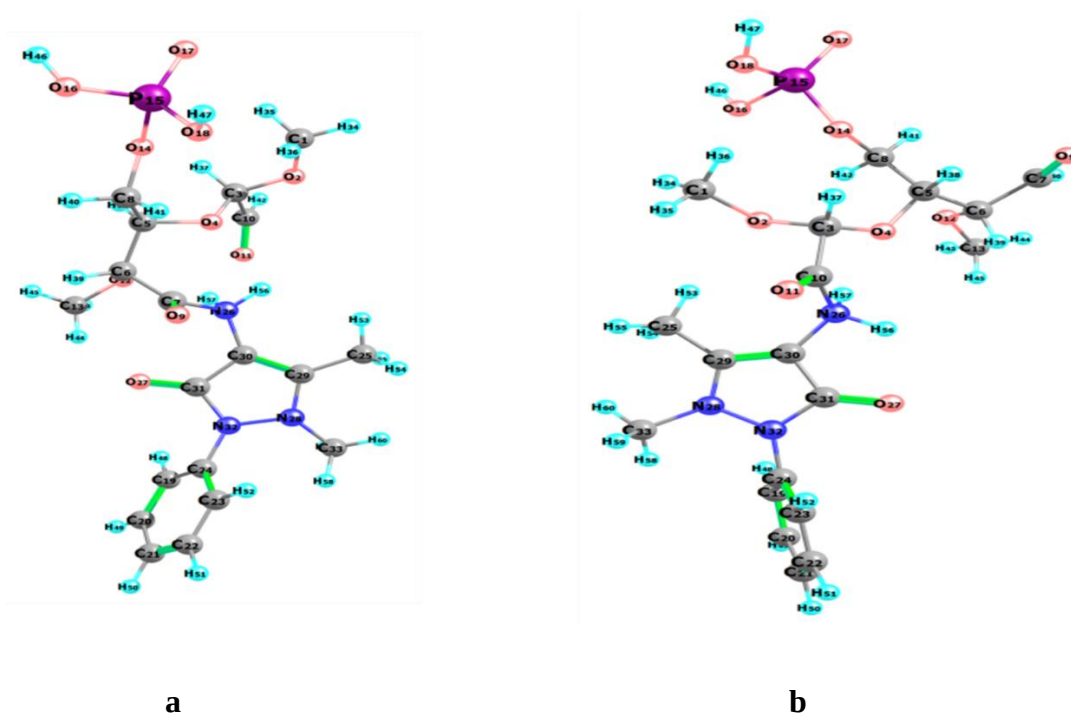


Figure 2. Optimized geometry for (a) DACP-C3=O (b) and DACP-C2=O in transition state

The CP sample had a greater and smoother morphological structure with fibrous appearance and a rough surface. DACP manifested a typical core-rood structure, which was changed to an elongated oval structure with more agglomerations in composite; therefore, the interactions between Fe_3O_4 and DACP occurred due to physical bonding (Figure 3). The average diameter of DACP increased from 58 nm to 90 nm, thus it confirms the effective crosslinking of Fe_3O_4 nanoparticles with DACP.

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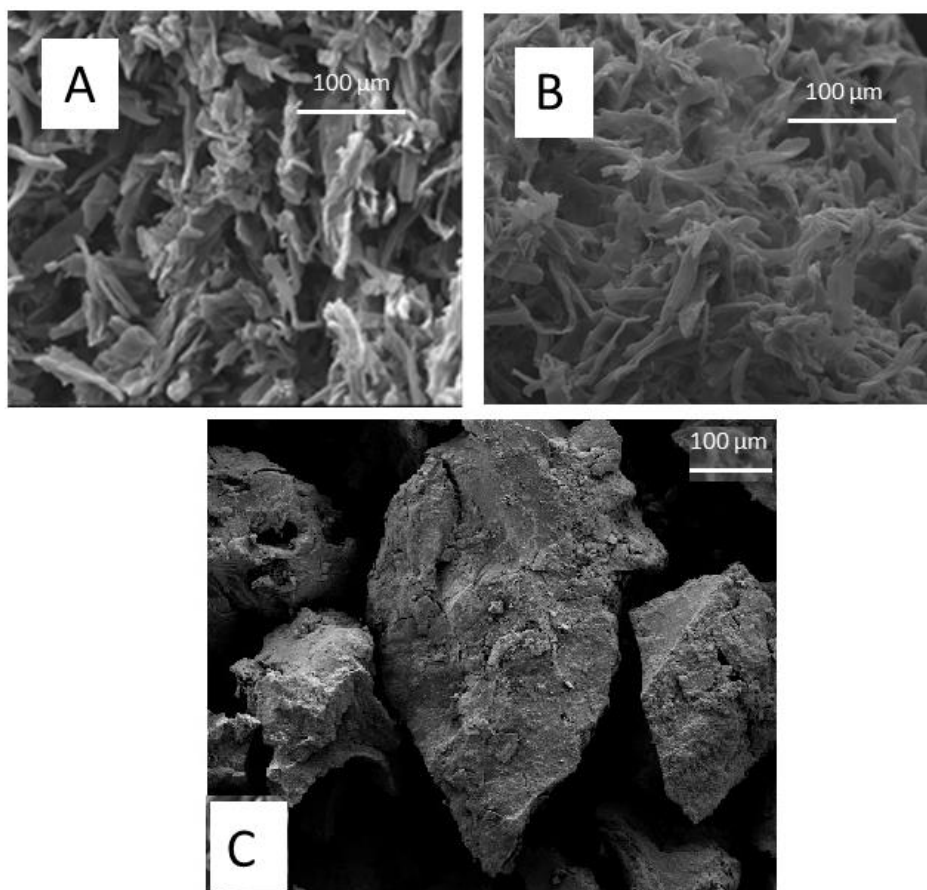
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Figure 3. SEM micrographs of CP (A), DACP (B), and MNPs/HACP (C)

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The elemental analysis conducted by EDX confirmed the presence of phosphorous and magnetic nanoparticles (Figure 4).

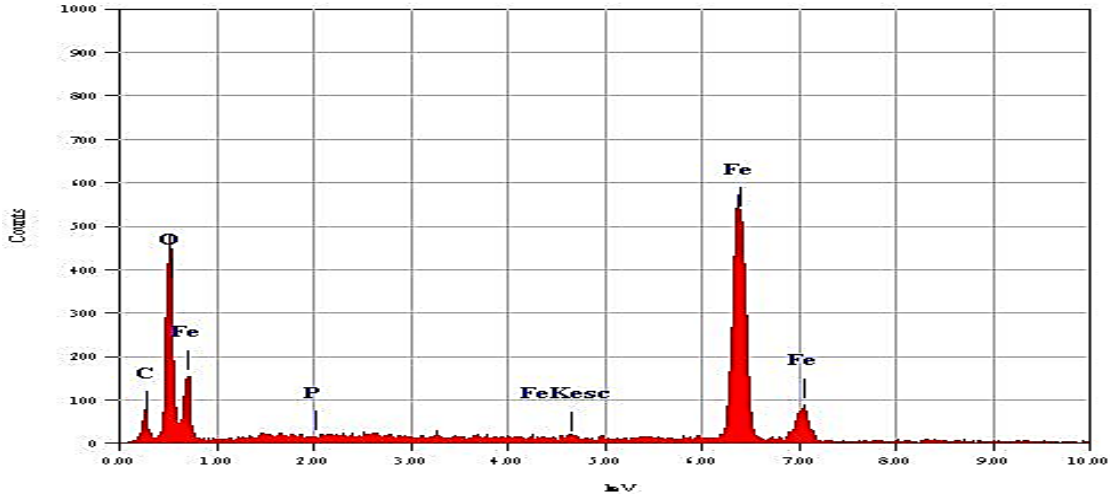


Figure 4. EDX spectrum of MNPs/HACP composite

X-ray diffraction (XRD)

X-ray diffraction pattern (Figure 5), showed two distinct peaks at $2\theta = 15.97^\circ$ and 22.74° for CP, corresponding to the merged peaks involving both the (1-10) and (110) reflections and (200) planes of CP, in addition to the phosphorous plane (211) that interfered with cellulose plane (004) at $2\theta = 34.76^\circ$ (Keshk & Omar, 2014; Keshk et al., 2019a). The XRD pattern of MNPs/HACP nanocomposites is different from that of DACP (Figure 5), which indicates that the significant change process results in the phase of DACP. The characteristic peaks of Fe_3O_4 at $2\theta = 30.1^\circ$, 35.5° , 43.1° , 53.4° , 57.0° , and 62.6° can be assigned to the (220), (311), (400), (422), (511), and (440) crystal planes, respectively; therefore, it is confirmed that Fe_3O_4 nanoparticles possessed a cubic phase in the composite (JCPDS No. 19-629).

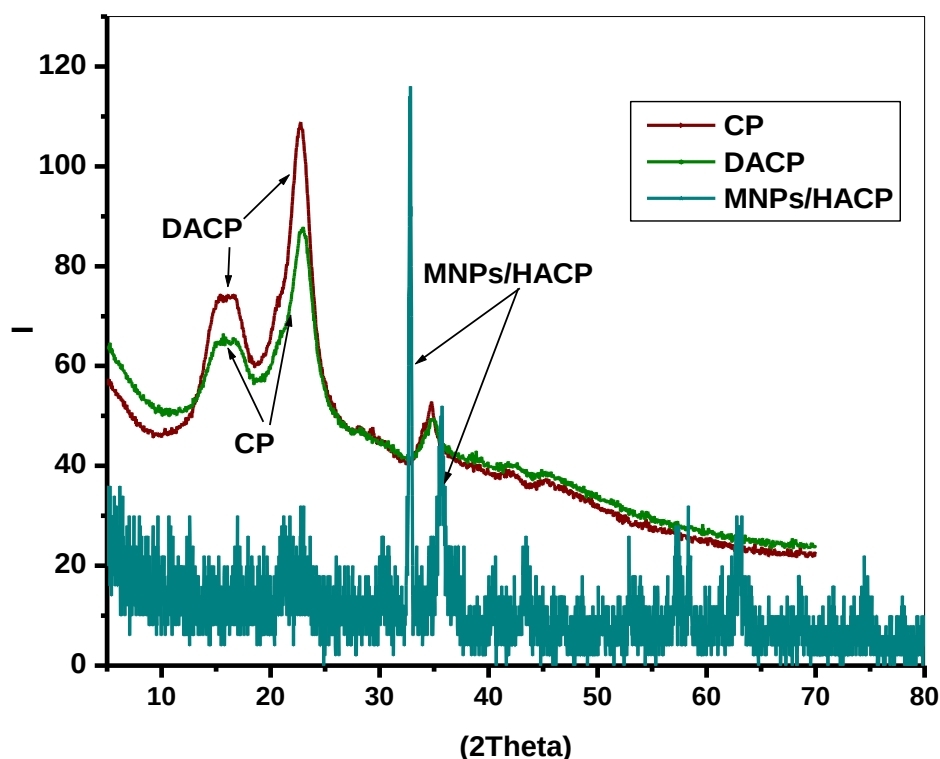


Figure 5. XRD of CP, DACP, and MNPs/HACP

In vitro loading investigation of 4-ampyrone

Most commonly used method for 4-ampyrone loading is impregnation in drug solution. 4-AA is soluble in water. The aim of the experimental efforts is to optimize satisfactory the drug adsorption onto the composite. The UV-absorption were assayed within the wavelength range 200-350 nm (Figure 6). The concentration was calculated from the absorption peak at 240-245 nm. The concentration-absorption relation was investigated to verify the concentration range to validate Lambert-Beer's law. The *in vitro* drug loading and release profile of 4-AA with DACP and MNPs/HACP was represented against time. The loading profile shows the rapid adsorption of 4-

AA in presence of MNPs in case of MNPs/HACP (abs.1.30) rather than DACP (abs 1.35) in the initial stages. The absorption rate slowed down after 45 min in MNPs/HACP and 65 min in DACP indicating the good incorporated MNPs with 4-AA. In addition, the absorption at 180 min was 0.7 for MNPs/HACP and 1.0 for DACP indicating that the presence of MNPs accelerates the absorption of drug.

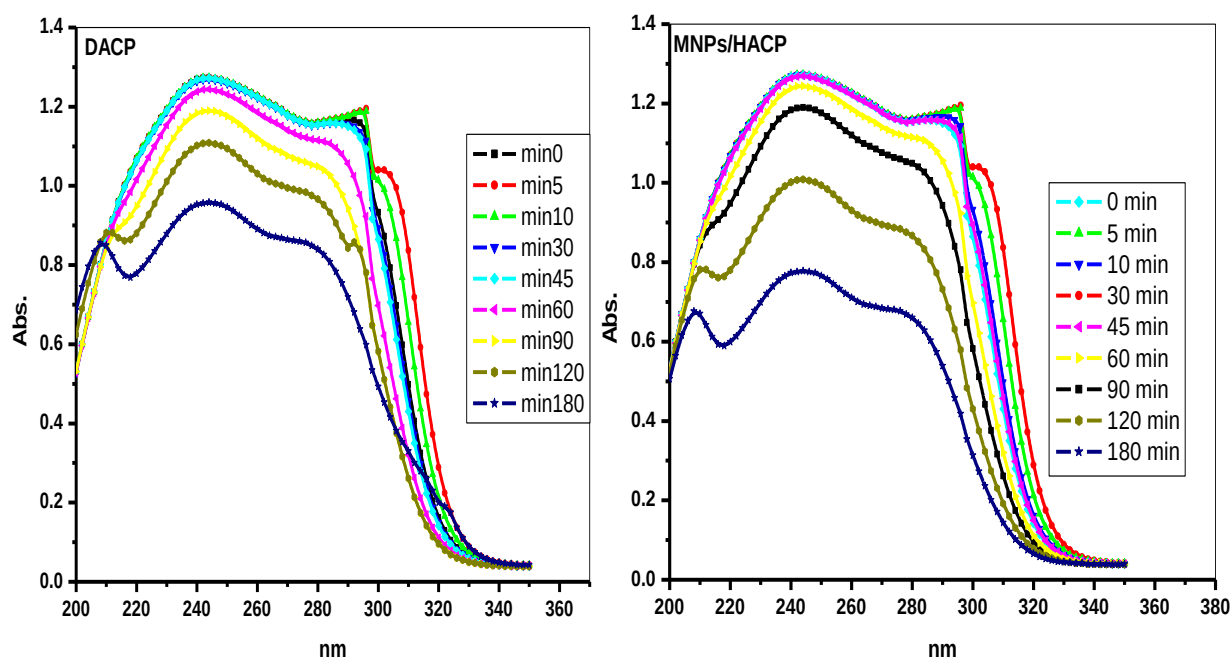


Figure 6. Loading spectra of 4-ampyrone on DACP and MNPs/HACP

The loading profile shows rapid adsorption of 4-ampyrone onto MNPs/HACP and the maximum loading was obtained in the first 60 min, followed by slowing down owing to surface saturation of the particles (Figure 7). With respect to DACP, the loading behavior is slightly different from that of MNPs/HACP, where the maximum loading was delayed, and drug amount loaded is lower.

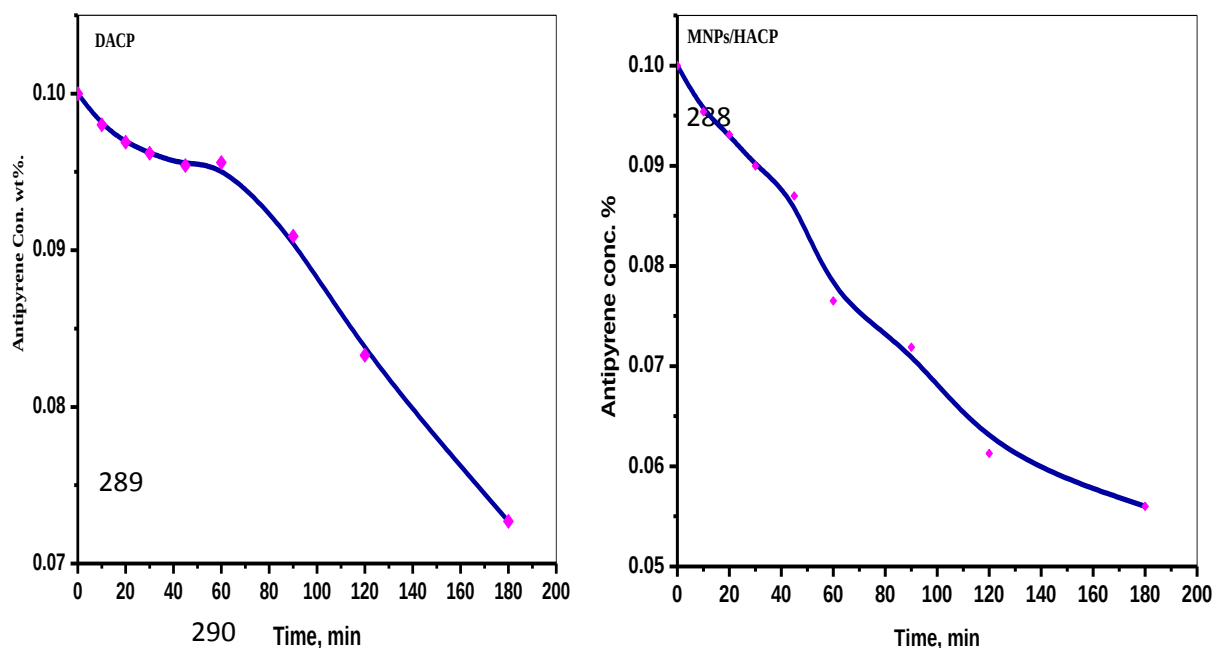


Figure 7. Loading profile of 4-ampyrone on DACP and MNPs/HACP

Incorporation of 4-AA onto the MNPs/HACP at different dosages will change the structure and morphology of the composite, subsequently controlling their diffusion properties. The presence of MNPs in the DACP contributes enhancing the pore sizes due to breaking the intramolecular hydrogen bond between glucan chains.

In vitro studies of release of ampyrone in phosphate buffer

The *in vitro* release test of 4-AA was performed by placing a pre-weighed, drug loaded samples in phosphate buffer (pH value of 7.5). At varied time intervals, aliquots were removed and analyzed for concentration of 4-AA as described before. The dissolution medium was reserved in

thermostatically controlled water bath, maintained at $37 \pm 0.5^\circ\text{C}$. The removed samples were replaced with equal volumes of fresh solution, to retain the volume of release media constant. The higher density and the homogeneous, smaller pores in the DACP allow a slower release rate. The *in vitro* release of 4-AA from the loaded DACP and MNPs/HACP nanocrystals is shown in Figures 8 and 9.

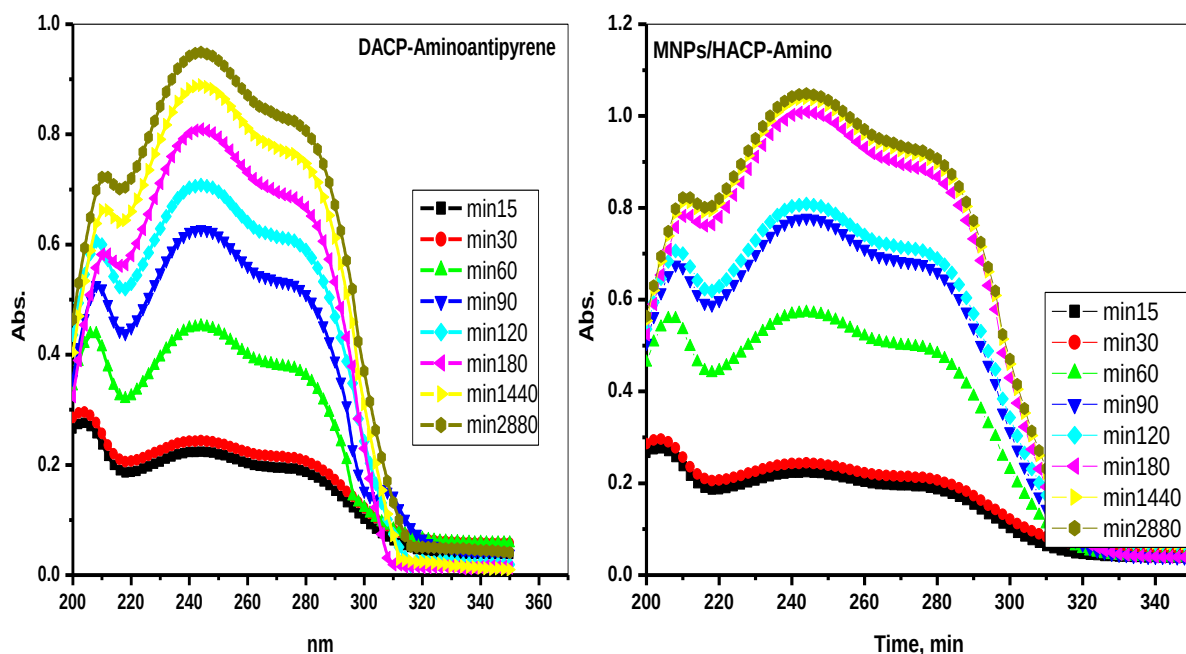


Figure 8. Release spectra of 4-ampyrone from DACP and MNPs/ HACP

The profile of 4-AA released from MNPs/HACP indicates two different steps of release in phosphate buffer at pH value of 7.4 (Figure 8). Firstly, a continuous release of 75 % of the 4-ampyrone within 250 min and secondly a slow sustained released of 4-AA for 3000 min where nearly 100 % of the drug was released. The rate of 4-ampyrone released in phosphate buffer at pH 7.4 is notably continuous. The cumulative percentage of 4-AA released at pH value of 7.4 was

approximately 100% within 3000 min. The release profile of 4-ampyrone from DACP was found to be clearly different from the release profile from MNPs/HACP (Figure 9).

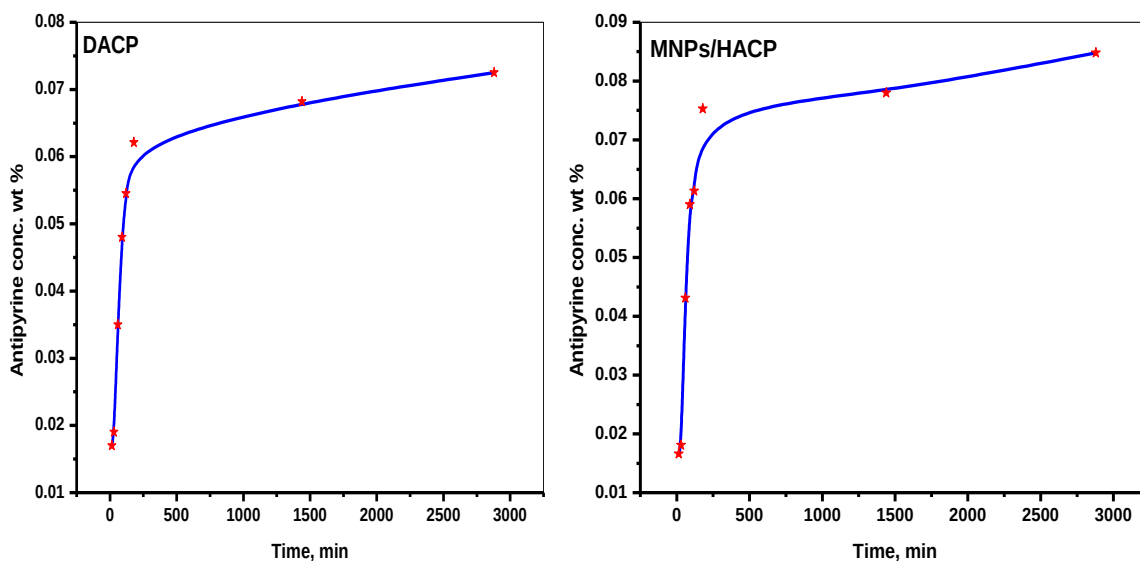


Figure 9. Release profile of 4-ampyrone from DACP and MNPs/ HACP

The release of 4-AA from DACP in phosphate buffer at pH value of 7.4 shows also two steps, where 60 % of the loaded drug was released within 195 min in continuous release behavior. In the second step, an extra 10% was released up to 3000 min. These results indicate that the bonding behavior in 4-AA -MNPs/HACP system is clearly different from that of 4-AA-HACP at the same conditions. Moreover, MNPs/HACP shows nearly complete release compared to DACP. These observations reflect the role of MNPs within the composite. This fact implies that the drug delivery within the nanoparticles influences the release pattern because with a higher amount of drug close to the surface or adsorbed to the surface, the initial burst effect is increased. In contrast, if the drug is more regularly distributed or a higher amount is captured inside the nanoparticles compared to

the amount close to the surface, the initial rapid release rate is reduced. The eruption release is an important subject that must be considered for drug delivery on nanoscale owing to the high surface to volume ratio. Furthermore, the release profile depends on the method of drug loading because the particle production method influences the drug delivery (Francesca et al., 2006). The release profile shows that the release rate is relatively slow when the time was prolonged (Figure 9). The drug release rapidly occurs for the first 180 min. It may be attributed to the excess of 4-AA molecules dispersed from matrix of the magnetic nanoparticles into buffer solutions, leading to the drug deliver at a faster rate (Longzhang et al., 2009). This observation may be attributed to the inter-molecular hydrogen bonding of 4-AA with magnetic nanocomposite (MNPs/HACP), which delay the release of the drug. These results agreed with the previously reported studies (Kayal & Ramanujan, 2010). The results show that MNPs/HACP are promising magnetic drug carrier's systems to be applied in proposed drug delivery.

Conclusion

In this study, a novel biocompatible polymer was designed and fabricated by the reaction of DACP and MNPs/HACP with 4-AA as drug model by forming Schiff's base linkage and hydrogen bond, respectively. Furthermore, the DACP with loaded MNPs could be easily synthesized using co-precipitation technique. DACP and MNPs/HACP showed excellent pH-regulated drug release behaviours. The *in vitro* release profile suggested that MNPs/HACP is promising in drug delivery carriers.

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