Journal of Novel Applied Sciences
Available online at www.jnasci.org
©2013 JNAS Journal-2013-2-S/812-820
ISSN 2322-5149 ©2013 JNAS

Synthesis, Characterize and Study Controlled Release of Ibuprofen From the new PEG/NaY and PEG/MCM-41 nanocomposites

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ABSTRACT: Recently, hybrid material using poly ethylene glycol and porous nanocrystals have been developed for drug release. In this study, a series of poly ethylene glycol (PEG)/NaY zeolite and PEG/MCM-41 nanocomposites synthesized. These materials characterized by using FT-IR spectroscopy, XRD, TGA and SEM. After it ibuprofen loaded onto these nanocomposites. Ibuprofen was encapsulated into synthetic nanocomposites, then the release profile of these drug loaded nanocomposites was evaluated in different pH (1-12) and different temperatures (36-40°C) at certain time intervals by using a HPLC method. The results show the same profile similar to ibuprofen-only dissolution profile except to the drug release percent which is lower than ibuprofen-only profile. The effect of temperature on the release amount of loaded-ibuprofen shows an interesting result; the increasing the temperature, the decreasing the release amount of ibuprofen. Result show that these nanocomposites have further release related to NaY , MCM-41 and the orders of release in different pH were PEG/NaY> PEG/MCM-41> NaY> MCM-41.The behaviour of drug release for these nanocomposites is probably due hydrogen bonding interaction between drug and the hydroxyl group on the composite framework.

***Keywords*:** PEG/NaY, PEG/MCM-41, Controlled release, Ibuprofen

INTRODUCTION

Controlled release has been employed extensively in food, agriculture and pharmaceutical industries to deliver active substances such as drugs, pesticides, herbicides and fertilizers (Duncan et al., 1989). There are many groups of materials that have been used for controlled release system such as dendrimers (Kono, 2002), zeolites (Zhang 2006, Horcajada et al., 2006), polymers (Langer et al, 1981), MCM-41 (Vallet-Regi et al., 2001) and organic-inorganic composite material (Takahashi et al., 2005).

Nano sized particles with a well-defined morphology are receiving wide spread interest as advanced materials on the basis of a large surface area and unique physical and chemical properties which are different from bulk solids. Zeolites and mesoporous materials are crystalline aluminosilicates with a well defined nanoporous network that recently using for controlled release, for example surface modified zeolite can be used for control release of parquet (Zhang et al., 2006). In another work dealuminated faujasites used for in vitro drug delivery Ibuprofen (Duncan et al., 1989). In contrast inorganic materials have been less studied as carriers of drug compared with organic materials such as polymers.

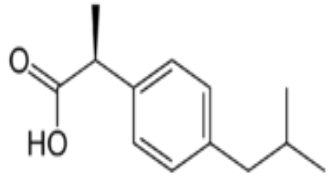
However inorganic materials (clay, zeolite and MCM-41) have important advantages such as high chemical and mechanical stability and low toxicity and porous structure that can in principle be tailored to control the diffusion rate of an adsorbed or encapsulated drug, but these materials have some problems for using in aqueous solution.

When we spontaneous these materials in aqueous solution in all of the application accumulated of its have seen under physiological conditions, porous material dispersion are unstable due to high salt concentration.

Literature review shows many works for modification of porous materials introduced for using of its in many systems. T. Takahashi and co-workers at 2005 showed that PEG can be increase dispersion stability of clay.

Recently Rivera et al. 2001 studied the possible interactions between natural zeolite and aspirin, also interaction between this zeolite and two drugs, metronidazole and sulfamethoxazole considered. In this contribution we have studied controlled release of Ibuprofen. In the first section we reported preparation and characterization of PEG/NaY zeolite and PEG/MCM-1 and the second section we used them for release of Ibuprofen.

Ibuprofen (IBP) is a nonsterodial anti-inflammatory drug (NSAID) derivative of propionic acid used widely as an analgesic an as an antipyretic.



Ibuprofen (IBP)

2. Experimental

2.1. Preparation of MCM-41and NaY

MCM-41 was prepared in our laboratory as follow by the before method:

A gel composite with molar composition: 1TEOS: 0.13 C_{19}TMABr: 5.4 HCl: 150 H_2O was prepared and stirred at room temperature for 7 days. After filtering and washing with water, the catalyst was characterized using XRD. The NaY zeolite was prepared and activated according to the procedure described based on Barrer and Breck works.

2.2. Preparation of PEG/NaY zeolite and PEG/MCM-41

The best PEG/porous ratio were obtained according to the before work. The solution of 0.25 g PEG and 0.025 g N, N- methylene bis acryl amide was prepared. Then, to this solution 0.35 g porous material (NaY zeolite or MCM-41) after dispersed by sonication was added and stirred for 30 min at room temperature. Ammonium persulfate (APS) for beginning the polymerization and N, N, N, N-tetra methyl ethylene diamine (TMED) as initiator was used.

2.3. Preparation of PEG/porous material/IBP

0.35 g porous material (NaY zeolite or MCM-41) was added to a solution of 0.30 g IBP drug and acetone then was stirred for 2 h *and* vaporized completely. After, porous material /IBP were added to 0.25 g PEG and 0.025 g N, N- methylene bis acryl amide. Polymerization process carried out with ammonium persulfate (APS) as accelerator and N, N, N, N-tetra methyl ethylene diamine (TMED) as initiator.

2.4. Ibuprofen release from PEG/porous material

The release of the IBP from NaY zeolite, MCM-41, PEG/NaY and PEG/MCM-41 were measured in a dissolution apparatus using the paddle method (USP II method). In each dissolution vessel quantities of drug-loaded zeolites equivalent to about 10 mg IBP were placed (Karavas et al., 2007). The dissolution medium was 500 ml of pH adjusted buffer (1 to 12). At predetermined time intervals, samples of 2 ml were withdrawn from the dissolution medium, filtered through 0.45 µm membranes and assayed by HPLC method.

HPLC method

For HPLC analysis, the stationary phase was a µBondapak C18 column (3.9*150mm) and a mobile phase of 65% acetonitrile and 35% phosphate buffer (adjusted to pH 3.2 using orthophosphoric acid). UV detection was employed at 225 nm and a flow rate of 1.0 ml/min (Watkinson et al., 2009).

2.5 Swelling Studies

Water diffuses into the hydrogel network when it is immersed into water. This diffusion is due to the osmotic pressure difference and water molecules enter into the empty space between the chains. In order to study the hydrogel swelling, the dried sample is weighted, immersed in 100 ml of distilled water in a 250 ml beaker. After a while, the sample is brought out, the excess water on its surface is dried with a tissue, and the sample is weighted again in particular time intervals. The final amount of swelling is obtained after 36 hours, when no significant weigh

difference was observed in two successive weighing. The result of swelling study is shown in Figure5. Water absorption kinetics is determined by weighing different amounts of absorbed water by gel in various time steps. Eq. (1) is used to calculate the swelling kinetics.

$M_t/M_\infty=kt^n$ (1)

Where k is the hydrogel swelling constant, n is the swelling ability, M_t is the amount of absorbed water at time t, and M_∞ is the amount of absorbed water by the network at equilibrium time. The slope of the line obtained by plotting ln(Mt/M∞) versus ln(t) shows the values of n and k (Buckley et al., 1962).

RESULTS AND DISCUSSION

XRD patterns of PEG/NaY nanocomposite before and after drug loading are presented in Figure.1a, b. In Figureure 1a the peaks related to NaY zeolite could be observed .Figure.1b shows that the intensity of peaks decreased after loading IBP. Powder X-ray patterns of PEG/MCM-41 nanocomposite before and after drug loading are shown in Figures.1c, d .In Figureure 1 c some diffraction peaks at 2θ: 1-5 are clearly seen and can be indexed as the MCM-41 peaks and these peaks decreased after loading mesoporous material. Decreasing the intensity corresponds to covering particles with composite [Xu et al].

Figures. 2a-d show TGA/DTA curves for PEG/NaY and PEG/MCM-41 nanocomposite before and after the absorption of IBP.Figure.2a shows three peaks related to PEG/NaY, the mass losses that take place at 0-250^o C is related to the desorption of water. The PEG decomposition can be occurred at 360^o C that is about 9.53%. The last step can be related to the decomposition of the structure of composite. Figure.2 b shows three steps for PEG/NaY/ IBP. The second steps at 390^o C can be assigned to the decomposition and oxidation process of the IBP, which evidences its presence in the composite (13.08%). The PEG/MCM-41 shows four peaks which the first and second (280^o C) steps are related to desorption of water and surfactant (8.49 and 17.54 %). The PEG decomposition can be occurred at 370^o C that is about 14.25%. The last step can be related to decomposition of structure of composite. Figure.2d shows four steps for PEG/MCM-41/drug. The step at 310^o C can be assigned to the decomposition and oxidation process of the Ibuprofen, which evidences its presence in the composite. Hence, decomposition of surfactant occurs in this temperature. We have seen a shift, which appears in all of the peaks, to higher temperature after adding of IBP. Thus, thermal stability the composite increases when the micelles host the IBP in their interior (Rivera et al., 2005; Lam, 2006). Figureure 3b-c shows FT-IR spectra in the range of 400 to 4000 cm^{-1} for PEG/NaY and PEG/MCM-41 nanocomposite after the absorption of IBP.Figure.3b shows three peaks related to hydroxyl groups of Al-OH and Si-OH in pore materials. In addition, we can see two bands at about 1070,743 cm^{-1} due to Si-O and 438 cm^{-1} related to Al-OH in the composites. The peaks of PEG around 1352 cm^{-1} and 3416cm^{-1} correspond to O-H bond and two peaks about 2876 and 1456 cm^{-1} related to C-H bonding are presented. Figure.3b shows three peaks related to MCM-41 about 462,554 and 1103 cm^{-1} .Also, the peaks related to PEG are presented around 1352 cm^{-1} , 3416cm^{-1} (O-H bond) and two peaks about 2876 and 1456 cm^{-1} (C-H bond). Ibuprofen has six major peaks about 1721, 1232, 779, 1185, 1273, 870 cm^{-1}, which are present in the drug-loaded NaY and MCM-41 spectra.

SEM images of the NaY zeolite, MCM-41, PEG/NaY and nanocomposite shows in Figureure 4a-d. There is a considerable change between two samples. From the micrographs, it was found that the NaY and MCM-41 were dispersed in the polymer network. Several areas show fine network structure .It means that NaY and MCM-41 have good collaborate with PEG and improves the network of it which may be favorable for drug adsorption (Yi et al., 2008).

Swelling behavior

As it was mentioned before, the sample is synthesized by changing one monomer composition when the others are constant in each step. This changing in one monomer composition leads to developing optimized composition of synthesized gel. Thus, optimized gel has a higher swelling rate in swelling experiments.

The maximum amount of swelling rate is 10min for PEG/NaY and 30 min for PEG/MCM-41(Figure5a, b). For the higher time, the swelling rate decreases. The swelling ratio of composite with hydrogel depends on the hydrophilicity of polymer chain and porous material and structure of hydrogel network (Li et al., 2008)

4. Drug release by PEG/Porous materials

Release Profiles

The release of the ibuprofen from PEG/NaY and PEG/MCM-41 were studied at different pH levels and the time periods so as to simulate gastrointestinal fluids (Figure 6a-c). As mentioned earlier ibuprofen has low solubility in acidic pH and we see in the IBP-only dissolution profile that with increasing the pH of the medium, the solubility of

the drug has been increased. However the profile shows an increase of release percent with increasing the time (up to 150 min) at any pH level. We can see nearly the same profile like as IBP-only profile with except to release percent and we have the best percent for drug release at pH=6.8. The orders of release all pH were as follows :PEG/NaY> PEG/MCM-41> NaY> MCM-41. Also, Figures7a-b shows the effect of temperature on the release of ibuprofen for PEG/NaY and PEG/MCM-41 in pH 6.8 that with increasing temperature the release of drug decreased. It has been widely demonstrated that the release of drug from PEG/porous material depends on the strength and nature of the drug and composite chemical bonds [Figure.8]. This can be explained by ability of porous material in ion-exchange interaction. It seems, NaY zeolite with Na_{56} (Al_{56} Si_{136} O_{384}) formula and by almost spherical cages (12A° of diameter) tetrahedral interconnected through smaller windows (7.4A° of diameter) defined by 12 oxygen rings is a good adsorbent for ibuprofen related to MCM-41.But, we have interaction between $Si\text{-}O^-$ in calcinated MCM-41 and ibuprofen. Also, literature review show that the drug release from NaY with Si/Al up to 60 is faster related to MCM-41(Horcajada, 2006). The adsorption concentration of ibuprofen increased with added PEG.PEG is a hydrophilic nonionic polymer that can be interacts from hydroxyl group with surface of porous material and ibuprofen by hydrogen bonding. Different factor such as stability of composite and strength of bond between of drug and composite can affect on the rate of release. The hydrophilic groups such as hydroxyl on the PEG and porous material hydrolyzed on the buffer solutions and it seems the rate of hydrolyzed rather than for PEG related to hydroxyl group on the porous material (Babazadeh et al., 2006; Zendehdel et al., 2011).

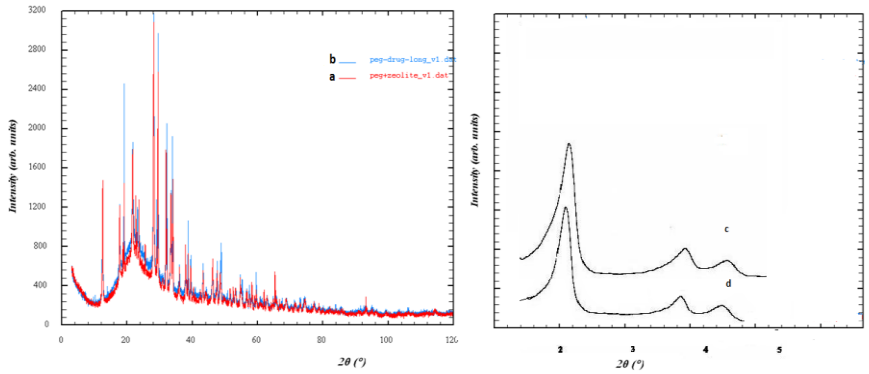
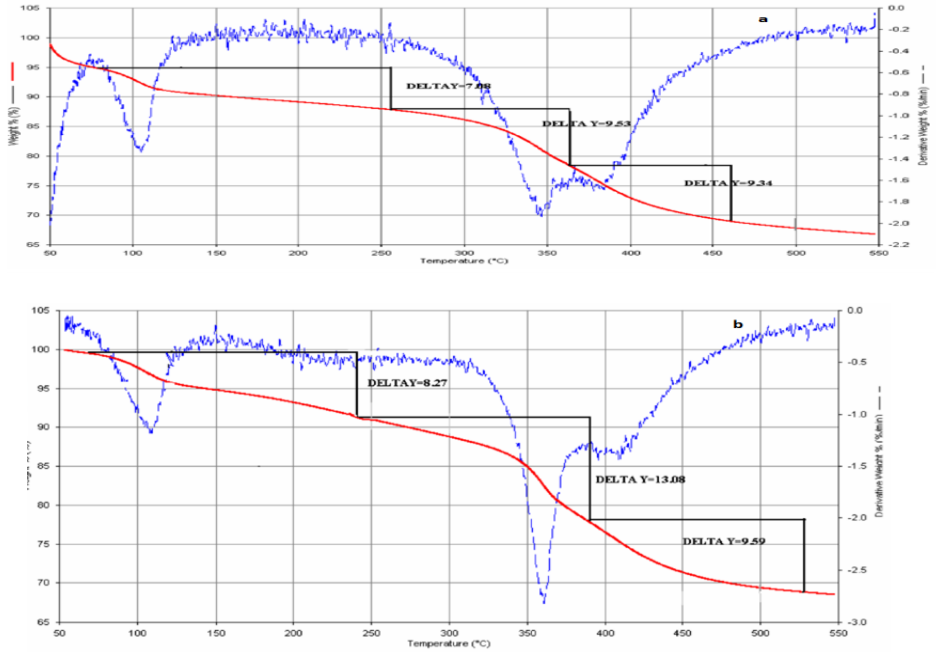


Figure1.XRD pattern for PEG/NaY before (a) after (b) drug loading, PEG/MCM-41 before (c) after (d) drug loading



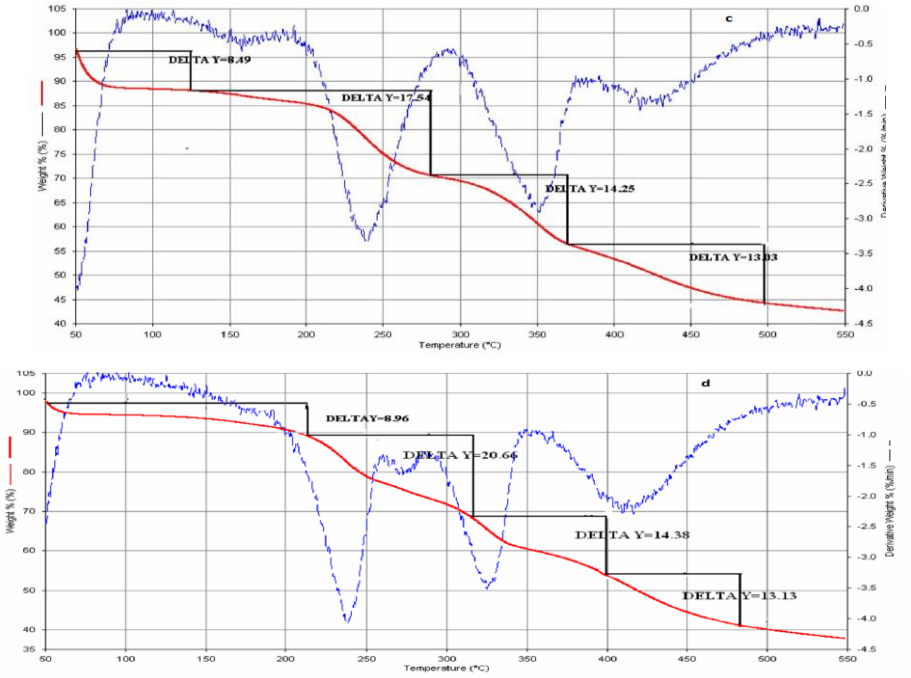
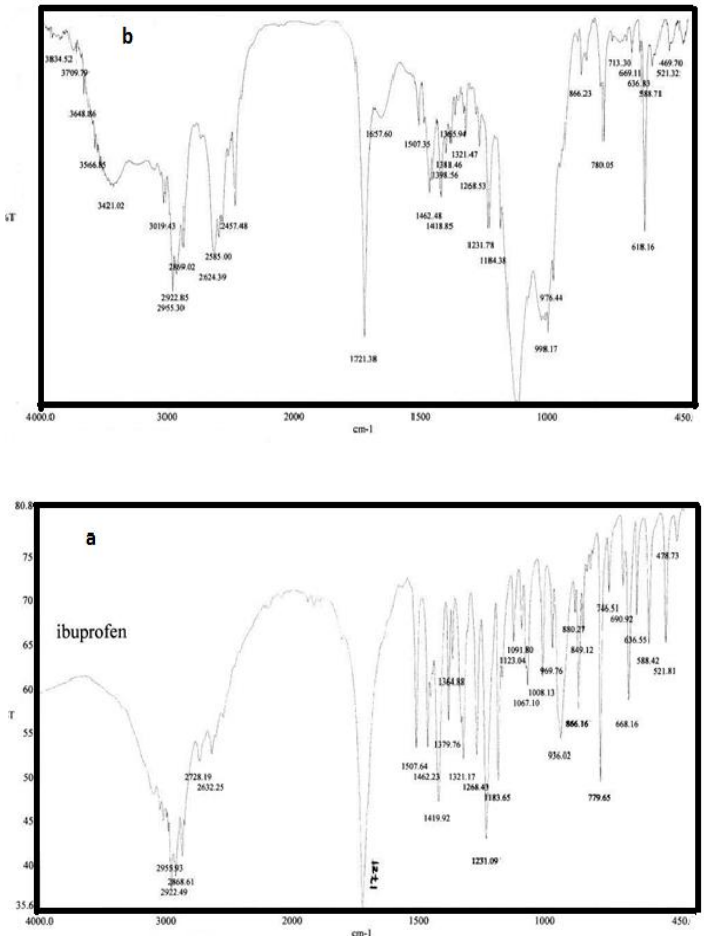


Figure 2.TGA/DTA for PEG/ NaY before (a) after (b) and, PEG/MCM-41 before (c) after (d) drug loading



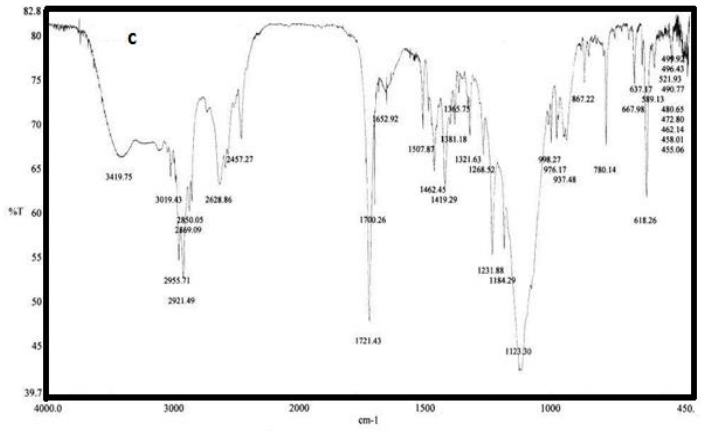


Figure 3.FT-IR for ibuprofen (a) PEG/NaY (b) PEG/MCM-41 (c) after drug loading

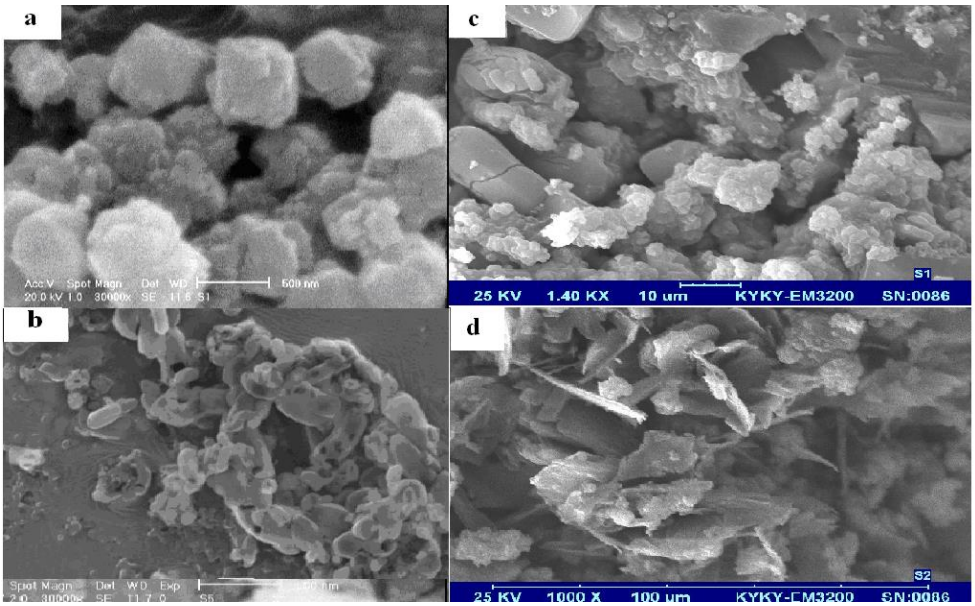
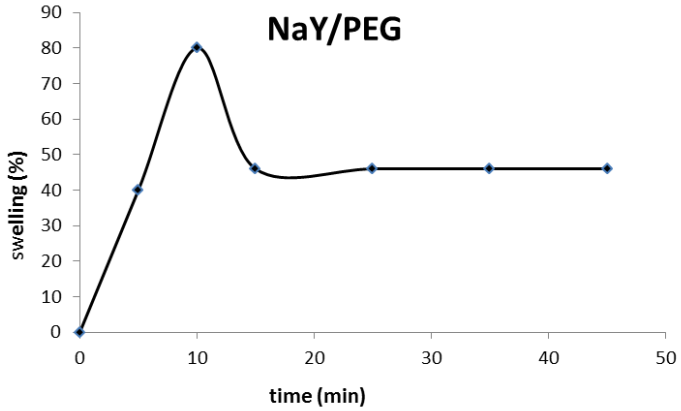


Figure 4.SEM for NaY (a) MCM-41(b) PEG/NaY(c), PEG/MCM-41 (d)



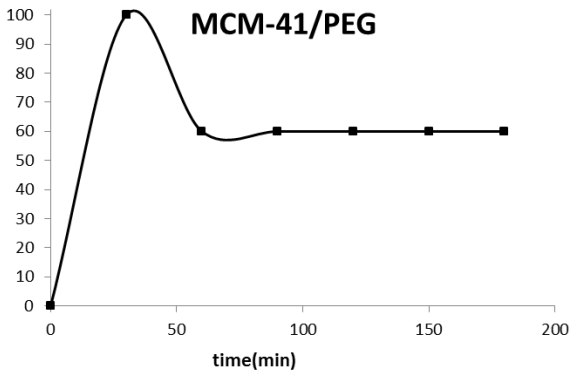


Figure 5. swelling behavior for PEG/NaY, PEG/MCM-41

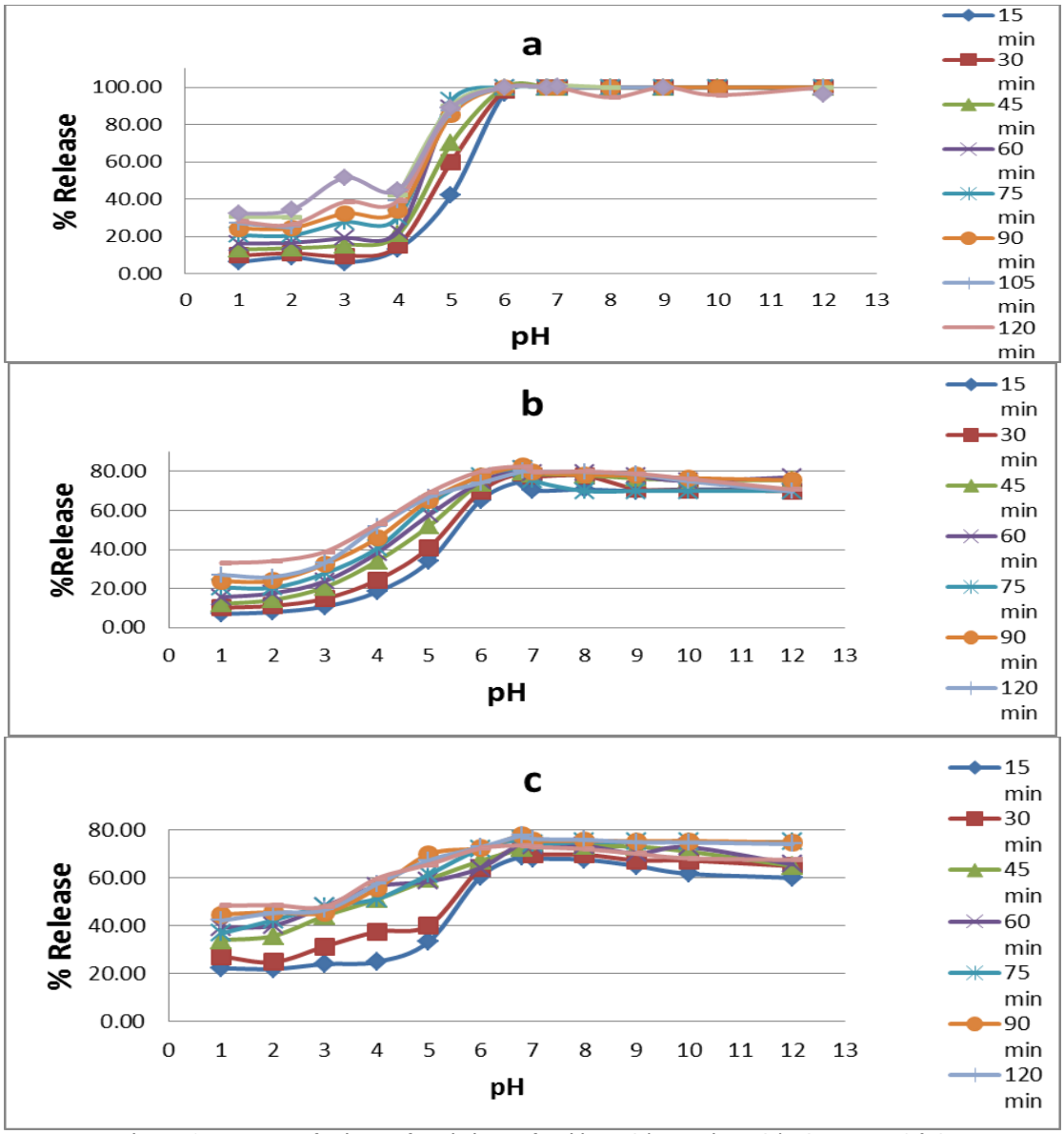


Figure 6. Percent of release for a) Ibuprofen b) PEG/NaY c) PEG/MCM-41 at 37 C

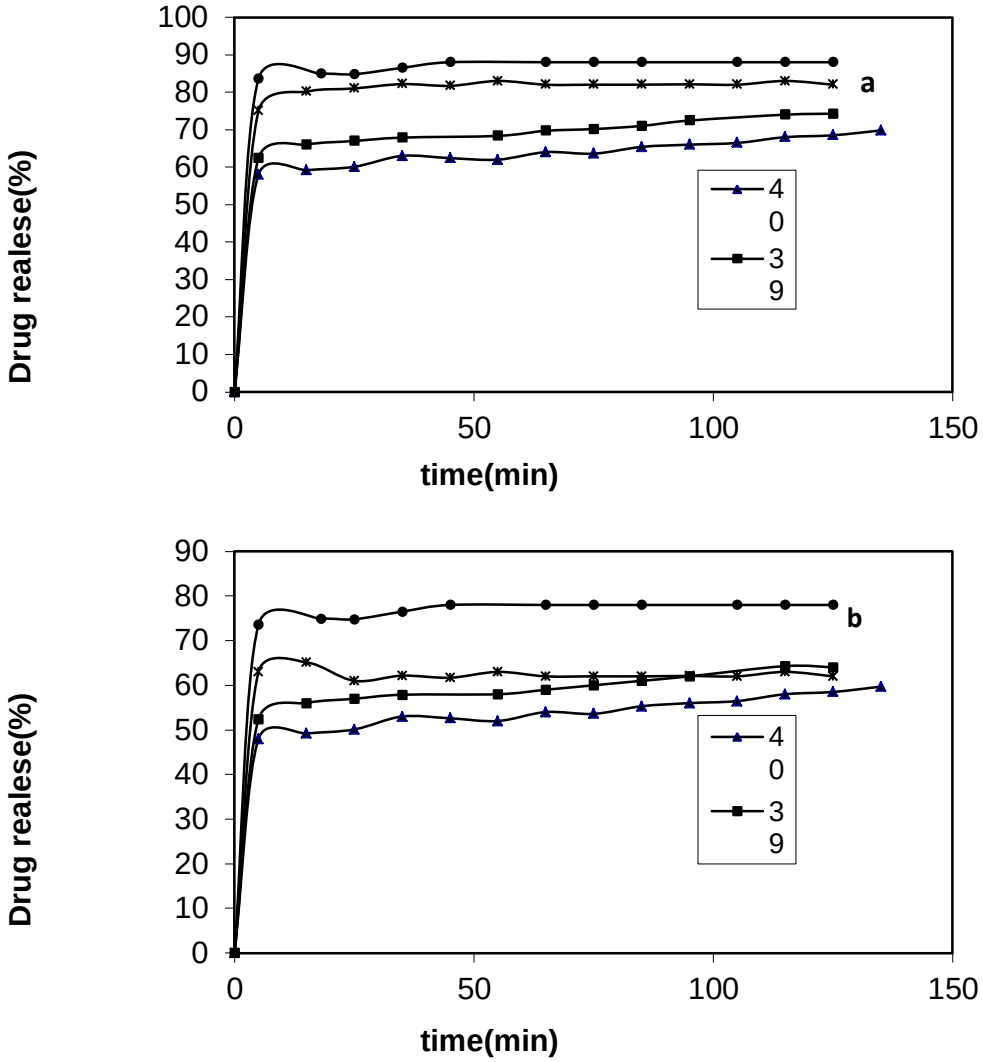


Figure 7.The effect of temperature for a) PEG/NaY b) PEG/MCM-41 at pH=6.8

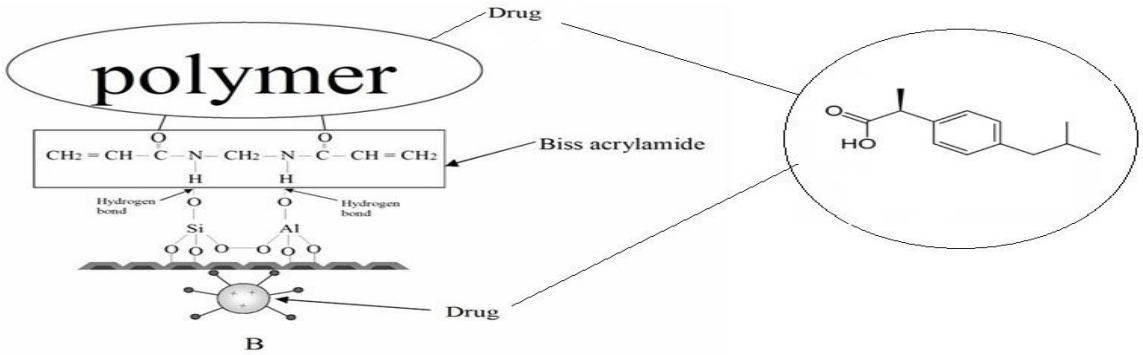


Figure 8. Schematic representation of formation hydrogen bond interaction and ion exchange between drug and the polymer network and the surface of zeolite, MCM-41

CONCLUSION

In this work poly ethylene glycol (PEG)/NaY zeolite and PEG/MCM-41 nanocomposites synthesize and characterized by using FT-IR spectroscopy, XRD, TGA and SEM that result show good interaction between PEG and porous material.In the second step ibprofen loaded onto these nanocomposites .The release of iboprofen studied in different pH controlled time and temperature by using HPLC. Result show that these nanocomposite have further release related to NaY , MCM-41 and the orders of release in all pH were PEG/NaY> PEG/MCM-41> NaY> MCM-41and the best pH is 6.8.It seems this behaviour of drug release for these nanocomposite is probably due hydrogen bonding interaction between drug and the hydroxyl group on the composite framework.

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