

Evaluation of synthetic zeolites as oral delivery vehicle for anti-inflammatory drugs

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ABSTRACT

Objective(s): In this research, zeolite X and zeolite Y were used as vehicle to prepare intestine targeted oral delivery systems of indomethacin and ibuprofen.

Materials and Methods: A soaking procedure was implemented to encapsulate indomethacin or ibuprofen within synthetic zeolites. Gravimetric methods and IR spectra of prepared formulations were used to assess drug loading efficiencies into zeolite structures. Scanning Electron Microscopy (SEM) was also utilized to determine morphologies changes in synthetic zeolites after drug loading. At the next stage, dissolution studies were used to predict the *in vivo* performance of prepared formulations at HCl 0.1 N and PBS pH 6.5 as simulated gastric fluid (SGF) and simulated intestine fluid (SIF), respectively.

Results: Drug loadings of prepared formulations was determined between 24-26 % w/w. Dissolution tests at SGF were shown that zeolites could retain acidic model drugs in their porous structures and can be able to limit their release into the stomach. On the other hand, all prepared formulations completely released model drugs during 3 hr in simulated intestine fluid.

Conclusion: Obtained results indicated zeolites could potentially be able to release indomethacin and ibuprofen in a sustained and controlled manner and reduced adverse effects commonly accompanying oral administrations of NSAIDs.

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Introduction

Microporous materials, which have unique pore size, higher surface area and pore volume, have been widely employed as vehicles for controlled drug delivery.

Drug delivery systems, such as porous silica materials, have exhibited good properties for application as drug delivery carriers and a great deal of research has been conducted to explore its potential.

Faujasite is a mineral group in the zeolite family of silicate minerals. Zeolites are crystalline, micro porous, hydrated aluminosilicates that compose of extending three dimensional structure of $[\text{SiO}_4]_4$ and $[\text{AlO}_4]_5$ tetrahedra bonded to each other by the sharing of oxygen atoms (1). Generally, their structure can be considered as inorganic polymer built from tetrahedral TO_4 units, where T is Si^{4+} or Al^{3+} ion and each O atom is shared between two T atoms (2). The faujasite framework consists of

sodalite cages which are connected through hexagonal prisms (Figure 1). The pores are arranged perpendicular to each other. The pore, which is formed by a 12-membered ring, has a relatively large diameter of 7.4 Å. The inner cavity has a diameter of 12 Å and is surrounded by 10 sodalite cages. Depending on the silica-to-alumina ratio of their framework, synthetic faujasite zeolites are divided into X and Y zeolites. In X zeolites ratio is between 2 and 3, while in Y zeolites it is 3 or higher. The negative charges of the framework are balanced by the positive charges of cations (Na^+ , Ca^{+2} , Mg^{2+}) in non-framework positions.

Nowadays, commercial synthetic zeolites are used more frequently than natural zeolites due to the purity of crystalline products and the identical particle sizes (3).

The main advantages of synthetic zeolites in comparison to natural ones are that they can be

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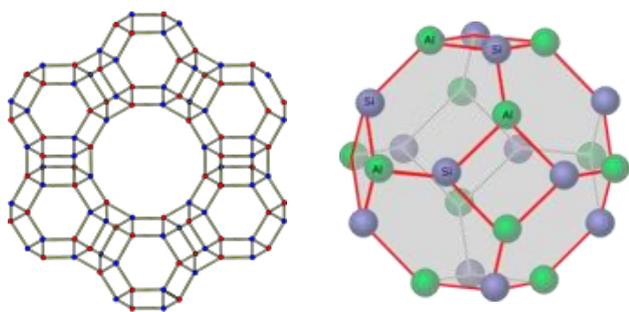


Figure 1. Crystal structure (a) and individual cage of zeolite

engineered with extensive variety of chemical properties, much more thermal stability and various pore sizes (4).

Because of the specified pore structure and pore geometry, zeolites can be implemented for size selective separation of molecules in chromatographic procedures (5-7).

Existence of aluminum in zeolite structures enhances the defects in these materials and as a result, zeolites can be active catalysts for specific chemical reactions, such as hydrogenation (8).

Moreover, zeolites could play an important role in regulation of the immune system as they act as nonspecific immune-modulator, same as super-antigens, so they could be used as antibacterial agents or in the adjuvant treatment of cancer (9, 10).

Zeolites use as a carrier for small drug molecules because of their biocompatibility, low toxicity and small pore size that could be matched to the size of drug molecules perfectly (11-13).

Due to unique characteristics of porous carriers, they have been applied in development of novel drug delivery systems such as floating drug delivery system, sustained drug delivery system and encapsulation of drugs with low aqueous solubility (14-16). Zeolites have enormous amounts of pores that provide the entrapment of drugs. These properties allow them to encapsulate drugs with high efficiency and release them in a sustained and controllable manner (17, 18).

There are numerous researches in order to explore biomedical applications of zeolites including imaging (19-23), wound treatment (24) and drug delivery (25-28).

One of the outstanding pharmacological applications of zeolites and mesoporous silicates is the entrapment of ions such as Cu^{2+} , Zn^{2+} , Na^+ , K^+ along with drug molecules within their pores to obtain a sustained release delivery system (29). In this regard, zeolite-based formulation of zinc and erythromycin has been used in the treatment of acne (30).

Furthermore, mechanical activated zeolite Y-magnetite nanocomposites have been successfully loaded with doxorubicin for preparation of a sustained release system (31).

Zeolite Y is also used to produce controllable release dosage of anthelmintics drugs (32) and sustained release capsules of ibuprofen (33).

A CuX zeolite based formulation of cyclophosphamide has been developed for cancer chemotherapy (34) and as a result it was proved that zeolites could improve the essential biological and mechanical characteristics of drug delivery systems.

In the wake of this burgeoning research, the aim of current study was to verify the possibility of exploiting synthetic zeolites as delivery systems for targeted release in the intestine. Zeolite X and zeolite Y were considered for the encapsulation of ibuprofen or indomethacin because of their pore structure. The choice of ibuprofen or indomethacin as a model drug, in this study, was explained by their short half-life, low water solubility and bioavailability, and their adverse effects which cause damage to stomach (35, 36).

Therefore, ibuprofen or indomethacin was first encapsulated into zeolite X or Y, by a soaking procedure, and then its release was assessed at different pH conditions mimicking intestine fluids or gastric juice.

Materials and Methods

Materials

Zeolite X and Y were supplied by SPAG, Iran. Ibuprofen and indomethacin was purchased from Merck, Germany. All chemicals and solvents were obtained from commercially available suppliers (Merck, Germany) and used without further purification.

Drug loading

Ibuprofen or indomethacin loading into the zeolites X and Y was achieved as follows: 20 g of zeolite X or Y were soaked, for two days, at room temperature, under continuous stirring, in a solution of 8 g of ibuprofen or indomethacin in methanol (300 ml). Finally, the solvent was removed by filtration using 0.22 μm polyester filter paper, and the samples were dried by rotatory evaporation under vacuum, at 30°C.

The loading of drugs into the zeolites X or Y was determined by thermogravimetry analysis (TGA).

TGA was performed using a TGA instrument (Mettler, Switzerland) at a heating rate of 10 C/min under a nitrogen purge of 40 ml/min, from 30 to 600°C.

Characterization

FTIR: Chemical analysis of zeolite samples were obtained with FTIR. About 10 mg of samples and 100 mg of KBr were used to prepare a KBr plate. The mixture of KBr and samples were grinded 3-5 min. The die was putted together with the powder into the Qwik Handi-Press and the powder was pressed for 2 min to form a pellet. The sandwiched plates were placed in the spectrometer Perkin-Elmer Model 1000 to record IR spectra.

SEM: Scanning Electron Microscopy images (LEO1450VP, England) were used to take images of zeolite samples. The powder of zeolite samples were mounted on an aluminium base with adhesive carbon tape and coated with 2-5 nm gold under vacuum for 5 min to prevent charging and distortion prior to SEM-picture taking.

XRD: XRD patterns of the samples were determined using a Phillips analytical x-ray B.V. (USA), consisting of a PW3710 diffractometer and an X-ray tube (30 mA and 40 kV) with a copper anode. The experiment was performed at a scanning rate of 0.033 degrees per second at an angle of 2θ and a range of 5–35 degrees. Nitrogen adsorption: Surface area (BET) was measured using N₂ adsorption with Quantachrome Autosorb 1-MP. As-received zeolite samples were outgassed at 300°C prior to sorption measurements. Instead, after the encapsulation of drugs, samples were evacuated at 50°C before adsorption measurements, because melting point of the drugs, indomethacin and ibuprofen, were 75.89 and 158°C respectively.

Dissolution studies

A flow through cell dissolution apparatus with six cells dissolution tester equipment (Pharma test, Germany) was used in all experiments.

During the test, the 900 ml of dissolution mediums were stirred using USP apparatus I, at 100 rpm and were warmed up to 37°C.

The dissolution mediums were 0.1N HCl solution, pH 1.2 (simulated gastric juice) and phosphate buffer 0.2 M, pH 6.8 (simulated intestine fluid).

For each interval, samples (n=3) were collected from the vessels by a peristaltic pump (Alitea, Sweden) at the following times: 15, 30, 45 and 60 min. The concentration of each sample was determined using multi-cell transport spectrophotometer (Shimadzu, Japan) at 221 nm for ibuprofen and 319 nm for indomethacin.

Simple model independent approach that uses a difference factor (f_1) and a similarity factor (f_2) was used to compare dissolution profiles (37). The difference factor (f_1) calculates the percent of the difference between the two curves at each time point and is a measure of the relative error between the two curves by following equation 1:

$$f_1 = \frac{\sum_{t=1}^n |R_t - T_t|}{\sum R_t} \times 100 \quad (1)$$

Table 1. Drug loading contents and specific surface area in zeolite X and Zeolite Y

Samples	Drug loading (% TGA)	Specific surface area (S_{BET} , m ² /g)
Zeolite Y		713.33
Ibuprofen +zeolite Y	26.32	450.90
Indomethacin +zeolite Y	25.75	622.2
Zeolite 13X		452.21
Ibuprofen +zeolite 13X	25.28	420.21
Indomethacin +zeolite 13X	24.54	388.70

Where n is the number of time points, R_t is the dissolution value of the reference formulation at time t and T_t is the dissolution value of the test formulation at time t. The similarity factor (f_2) is a measurement of the similarity in the percent (%) dissolution between the curves (equation 2):

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

For curves to be considered similar, f_1 values should be close to 0 and f_2 values should be close to 100. Usually, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100), which means an average difference of no more than 10% at the sample time points, confirms similarity of the two curves and consequently of the performance of the test and reference products.

Results

Characterization

FTIR: Demonstration of ibuprofen or indomethacin loading was indicated by FTIR experiments. Adsorption bands in the range of 3750–3000 cm⁻¹ are due to the stretching vibrational frequency of the silanol groups. Some characteristic adsorption peaks such as carbonyl peak of ibuprofen or indomethacin, indicated by arrows in Figure 3 and 4 were observed both in ibuprofen or indomethacin zeolite samples, verifying that the model drugs were successfully encapsulated into the zeolites.

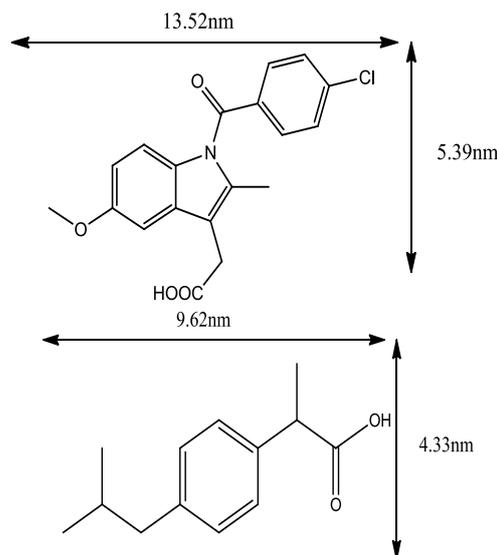


Figure 2. indomethacin (left) and ibuprofen (right) molecules

SEM: Figure 5 represent the scanning electron micrograph for indomethacin loaded zeolite X.

Samples prepared from zeolite X formulations containing indomethacin were nearly spherical. However, the control samples prepared from zeolites X were polygonal.

The spherical shapes of drug loaded zeolites demonstrated successful encapsulation of model drug into pores and surface of microporous zeolite particles.

XRD: The representative powder X-ray diffraction (pXRD) patterns of zeolite X and Y before and after drug (indomethacin and ibuprofen) loading are shown in Figures 6 and 7. Characteristic pXRD peaks corresponding to zeolite X and Y were observed. The pXRD patterns after drug loading were similar to the parent zeolite powder X-ray diffraction patterns indicating that the zeolite X and Y framework structure did not change. However, there was an overall reduction in intensity of the peaks after loading indicating a slight decrease in the crystallinity after drug adsorption.

Loading of drug

The actual loading of ibuprofen or indomethacin into the zeolites X or Y was determined by thermogravimetry analysis (TGA). As shown in Table 1, the loading fractions in all cases were estimated from the ratio of the weight loss between 250 and 600°C to the total initial weight. The weight loss due to drug uptake was 25.28% and 24.54% for zeolite 13x+ibuprofen and zeolite 13x+indomethacin and 25.75% and 26.32% for zeolite Y+indomethacin and zeolite Y+ibuprofen, respectively. TGA thermo grams zeolite 13x+ibuprofen, zeolite 13x+indomethacin, zeolite Y+indomethacin and zeolite Y+ibuprofen have been shown in Figures 6 and 7.

Nitrogen adsorption: A decrease in the surface areas after drug loading in zeolite samples was observed, confirming that the drug was loaded in the pores of the zeolites (Table 1).

Drug delivery profiles

The dissolution profiles of the formulations in simulated gastric juice and simulated intestine fluid are shown in Figure 9 and 10, respectively. Figure 9 shows the time dependent release rates of zeolites formulations of ibuprofen or indomethacin in comparison with the free drug in simulated gastric juice at pH 1.2.

As shown in Figure 10 after 180 min, when the pH value was 6.8, zeolites X and Y were almost deprived of ibuprofen or indomethacin.

Discussion

Ibuprofen and indomethacin are used as analgesic and anti-inflammatory; their molecular size are about $10 \times 4.5 \text{ \AA}$ and $13.5 \times 5.5 \text{ \AA}$, respectively (Figure 2). Due to their size, they can be best model for studying drug adsorption into pores of microporous zeolites with

pore diameters of less than 2 nm (20 Å) (see Figure 1). Reduction in the surface areas after drug loading confirmed this theory. There was not found any significant difference between drug loadings (24-26%). This may be due to similarity between structures of drugs and also zeolites x and y. During 60 min at pH 1.2, very small quantity of drugs (ibuprofen-zeolite X=1.77%, ibuprofen-zeolite Y= 2.41%; indomethacin-zeolite X= 2.27%, indomethacin zeolite Y= 3.29%) was released.

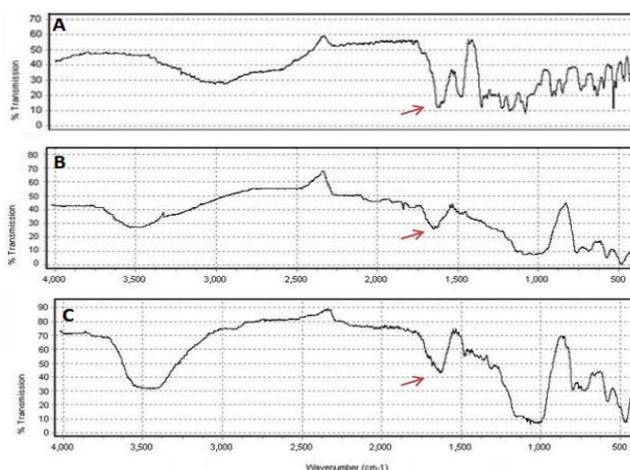


Figure 3. IR spectra of (A) Indomethacin, (B) Indomethacin+zeolite X, (C) Indomethacin+zeolite Y

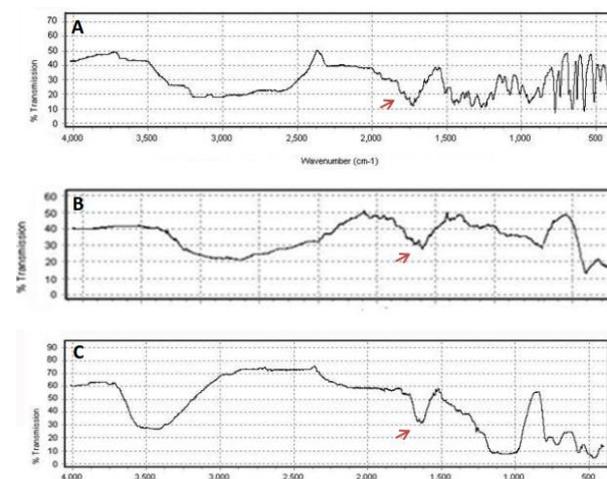


Figure 4. IR spectra of (A) Ibuprofen, (B) Ibuprofen +zeolite X, (C) ibuprofen +zeolite Y

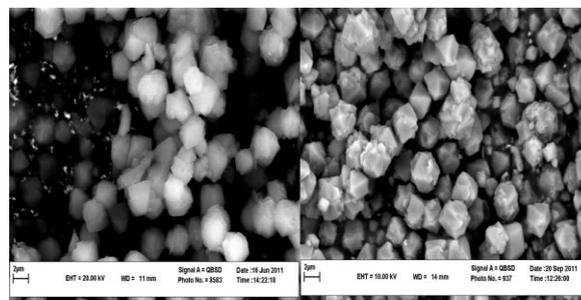


Figure 5. SEM images of Zeolite X (The right); Indomethacin loaded zeolite X; (The left)

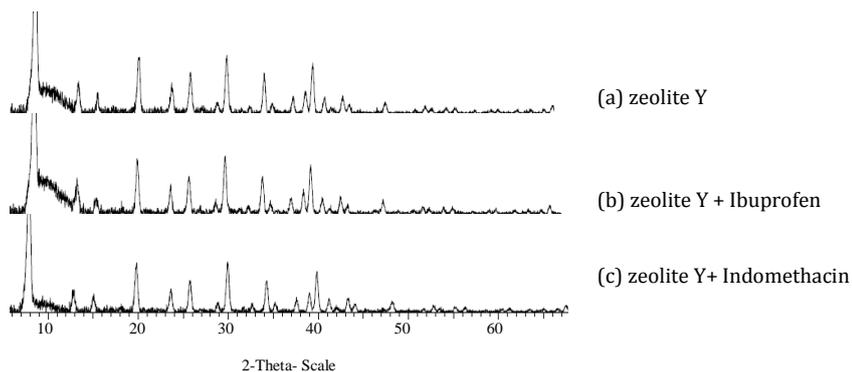


Figure 6. XRD patterns of zeolite with drugs

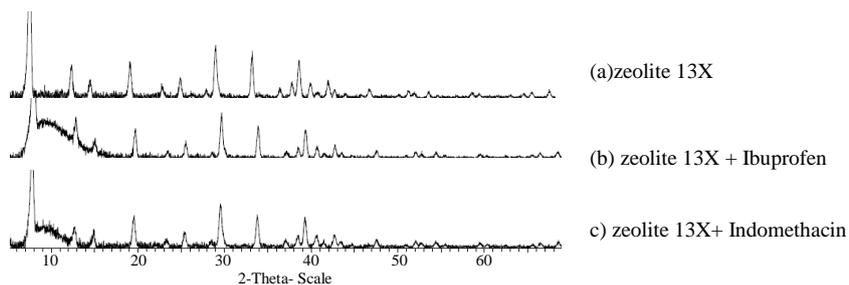
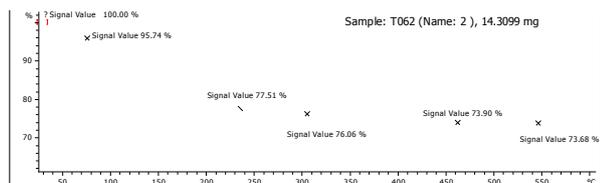
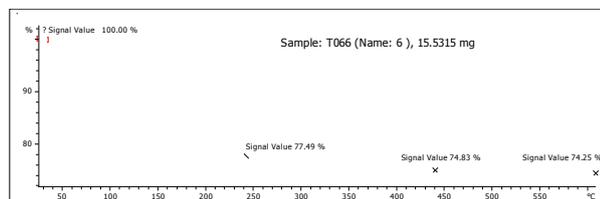


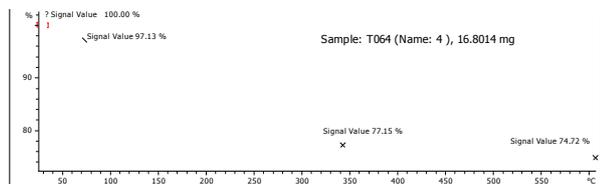
Figure 7. XRD patterns of zeolite 13X with drugs



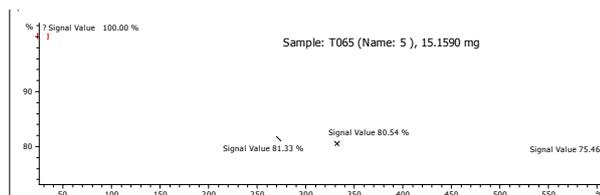
(a) zeolite Y + Ibuprofen



(b) zeolite Y + Indomethacin



(c) zeolite 13x + Ibuprofen



(d) zeolite 13x + Indomethacin

Figure 8. TGA thermograms for different zeolite drug combinations

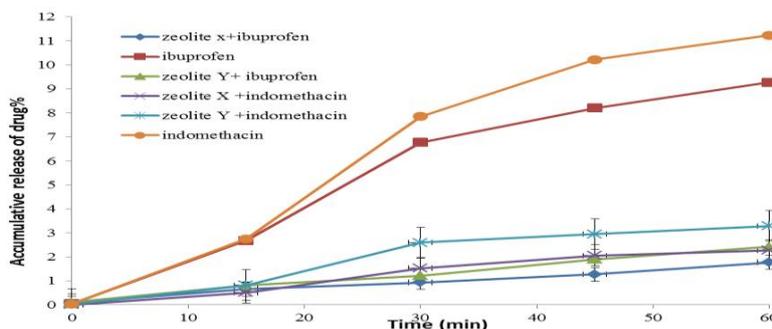


Figure 9. Drug release profiles of prepared formulations in simulated gastric juice

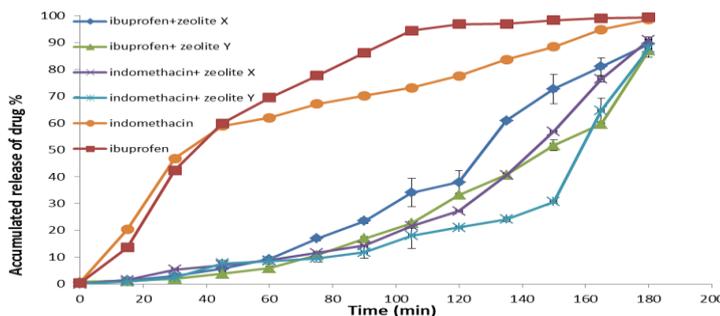


Figure 10. Drug release profiles of prepared formulations in simulated intestine fluid

An explanation for this phenomenon could be that the formation of neutral charge at active sites of zeolites under acidic condition, promoted better entrapments of drugs in zeolites active sites.

At pH 6.8 (simulated intestine fluid), both model drugs have negative charge and are most in an ionic form with high solubility which cause dissociate from the active sites of zeolites as a result of an electrostatic repulsion and solubility enhancement of drugs in ionic form. Since, pKa of indomethacin is more acidic, it is probable that ionic form of ibuprofen in the intestine should be more than indomethacin, therefore ibuprofen exhibited higher dissolution rate from matrixes at pH 6.8 (simulated intestine fluid). This feature demonstrates that the grade of dissociation of drug is determinant for the interaction with zeolite.

The f_1 and f_2 factors calculated from release profiles at pH 1.2 and pH 6.8 for all prepared formulations (Table 2 and 3) indicated that all formulations containing model drugs, exhibited significant differences from control samples (drugs without zeolites).

Conclusion

Synthetic zeolites were studied to verify their ability to encapsulate and release anti-inflammatory drugs

Table 2. Difference factor (f_1) of dissolution profiles of matrices in simulated gastric juice (n=3)

Matrices	f_1
Ibuprofen+zeolite X versus control	82.84
Ibuprofen+zeolite Y versus control	76.58
Indomethacin+zeolite X versus control	80.18
Indomethacin+zeolite Y versus control	69.90

Table 3. Difference factor (f_1) of dissolution profiles of matrices in simulated intestine fluid (n=3)

Matrices	f_1
Ibuprofen+zeolite X versus control	53.37
Ibuprofen+zeolite Y versus control	64.18
Indomethacin+zeolite X versus control	57
Indomethacin+zeolite Y versus control	65.89

such as ibuprofen and indomethacin. Obtained results demonstrated that zeolite X and Y exceptionally potential to produce capable oral drug delivery systems for ibuprofen and indomethacin. In current research a simple soaking procedure was able to entrap 24-26% of model drugs in zeolite X and Y.

Drug loading was indeed confirmed by IR spectra. We found that less than 10% of the drug was released at the gastric level, a result that clearly indicates the effectiveness of this system in reducing the adverse effects commonly accompanying oral administrations of NSAIDs.

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