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Original Research

Promising psyllium-based composite containing TiO_2 nanoparticles as aspirin-carrier matrix

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Abstract

Composite nanomaterials represent a new trend in the biomedical field. Coupling inorganic/organic constituents with non-toxicity/biocompatibility properties leads to develop the new systems having special characteristics that can be used in various bio-applications. This paper describes the preparation and characterization of psyllium-based composites containing TiO_2 nanoparticles in order to develop new therapeutic strategies for aspirin drug delivery. The structural characteristics of obtained materials were investigated by FTIR spectroscopy. The UV–vis spectrophotometric analysis was performed to evaluate the aspirin release behavior under different pH conditions at 37 °C. Combining psyllium (as an excellent source of fiber) with TiO_2 inorganic unit (as vehicle of aspirin) it was found that polymeric-TiO_2 networks have promising potential for controlled aspirin release as therapeutic agent.

Keywords: Psyllium; Titanium dioxide; Aspirin; *In vitro* release

1. Introduction

The class of organic/inorganic nanocomposites has already gained an important place in materials chemistry areas with various applications as optoelectronic devices, catalysts, sensors or biomaterials [1,2]. As organic part of composite nanomaterials various natural polymers are generally used that can act as binders, matrix, stabilizers, emulsifiers, gelling agents, *etc.* due to their non-toxicity, biocompatibility and also, by availability and economical reasons [3,4]. They can be classified depending on their source (algal, plant, microbial or animal origin), charge (non-ionic, anionic polymers), shape (linear or branched) or monomeric units (homo- or hetero-) [5]. As inorganic part of composite nanomaterials due to their non-toxicity/biocompatibility properties, the nanoparticles of metal (gold, silver, copper) [6] or metal oxides such as TiO_2 [7] and ZnO [8] are widely used. With particle size reduction (less than 100 nm), the physical, chemical and biological properties can be designed for optimal size/surface characteristics [9] to drug delivery, biodetection of pathogens or biological molecules (proteins), tissue engineering, tumor killing and other biomedical applications [10,11].

The embedding of nanoparticles into a polymeric matrix leads to obtain the composite materials with multiple unique characteristics that are derived by combining properties of constituents into a single material. The functionalities of components can induce physical or chemical interactions between organic molecules and surface nanoparticles that lead to develop more effective systems for specific applications [1,2]. For all these aspects, the nanocomposites can provide the opportunities to create more effective drug-delivery platforms with high functionality, biocompatibility and minimizing potential adverse health risks [1,2].

The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) (aspirin, ibuprofen, ketoprofen, diclofenac, aceclofenac *etc.*)

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in treatment of pain and inflammation is well known. However, gastrointestinal, cardiovascular or renovascular adverse events could appear during prescribing these medications [12]. In order to obtain the benefit of NSAIDs as anti-inflammatory and analgesic drugs and also, to reduce or remove the mentioned effects, new strategy for drug formulations was evaluated [12,13]. In this experimental research the applicative potential of titanium dioxide nanoparticles associated with psyllium-based matrix for aspirin embedding to drug delivery is investigated.

2. Experimental details

Psyllium husk was procured from local natural products market. Polyvinyl alcohol (Serva, Germany), Tween 80 (Merck, Germany), titanium dioxide (Degussa AG, Germany), aspirin (Sinteza Oradea, Romania) and ethanol (Riedel-de Haen, Germany) were used in order to obtain the proposed materials.

The psyllium-based matrix was prepared by mixing the natural polymer with twice distilled water in order to obtain a 2% homogenous gel material; thus an appropriate amount of polyvinyl alcohol relating to psyllium content (1:5 mass ratio) was added. And then, 100 mg/ml polymer of aspirin mixed with ethanol:Tween 80 (10:1 volume ratio) was embedded in 10 ml polymer composite matrix and stirred till uniformity. Another sample was prepared under the same condition and then 4 mg of TiO_2/1 ml polymer composite was added and homogeneously mixed. Samples containing 1 ml of each of the two obtained pastes were frozen and then were lyophilized under low temperature and high vacuum in order to completely dry the samples. Finally, two porous materials were prepared and the samples were noted MA (free TiO_2) and MAT (containing TiO_2).

The characterization of prepared materials was performed with FTIR spectrometer terms (JASCO FT/IR-6100) using a KBr pellet technique and *in vitro* drug release behavior employing a UV–vis spectrophotometer (JASCO V-550).

The aspirin release studies were conducted using the dissolution media that simulate gastric and intestinal fluids. Based on instructions for simulated body fluids described by Marques et al. [14] the simulated gastric medium (SGF) was prepared using a solution 34 mM of NaCl and an appropriate volume of HCl to obtain a solution of pH = 1.2. The composition of intestinal fluid (SIF) at pH = 6.5 included NaCl:NaOH:NaH_2PO_4 in water in mass ratio of 15:1:10. If necessary, the pH of biological fluids was adjusted with 1 M NaOH and HCl. All experiments were performed in a shaking water bath at 37 ± 0.2 °C.

3. Results and discussion

3.1. FTIR characterizations of composite nanomaterials

The FTIR spectra of samples are presented in Fig. 1. The prepared composites do not show significant modifications in the recorded spectra, except changes of absorption intensity of

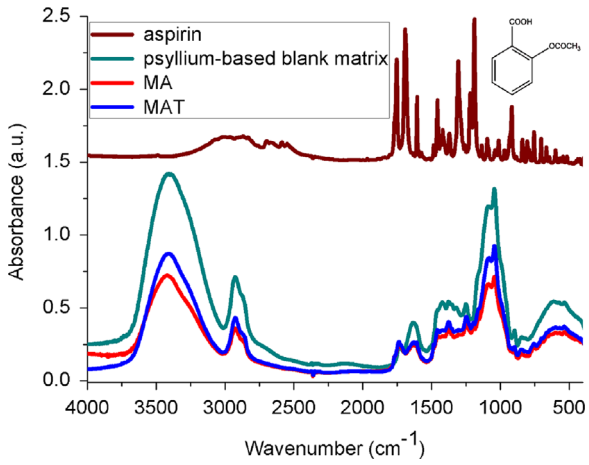

Fig. 1. FTIR spectrum of aspirin and polymeric composite materials.

Table 1
Main IR absorption bands assignments of each components of matrix.

Sample	Frequencies (cm^{-1})	Bond vibration
Psyllium	3441	–OH stretching of the hydroxyl groups in carbohydrates (arabinose, xylose and traces of other sugars) [16,18]
	2923	asymmetric –CH and $–CH_2$ stretching [15,18]
	1377	–CH, $–CH_2$ and –OH in-plane bending in carbohydrates [15,18]
	1037	C–O stretching region due to C–O and C–O–C stretching characteristic of the natural polysaccharides [15,16,18]
	893, 553	pyranose rings [15,18]
PVA	3380	O–H stretching vibration of hydroxyl groups [17]
	1734	C = O stretching of the acetate group [17]
	2940	backbone aliphatic $–CH_2$ symmetric stretching [17]
	2853	C–H stretching [17]
	1094	C–O stretching [17]
Tween 80	3420	O–H stretching [19]
	1734	C = O stretching [19]
	1642	C = C stretching [19]
	1351	$–CH_3$ symmetrical [19]
	1107	C–O stretching [19]

the peaks, probably due to incorporation of used constituents in the complex structure of the psyllium. The functional groups present in the constituents are similar, so the absorption bands of the obtained composites overlap those of the starting materials, especially predominant component (psyllium).

The appearance of absorption bands in the presented spectra can be correlated with the characteristic vibrational frequencies of functional groups from each component and they are shown in Table 1, in agreement with the literature [15–19].

In case of aspirin, the peak about 3000 cm^{-1} is assigned to O–H stretching vibration of carboxylic groups [20]. The characteristic peaks of the aspirin FTIR spectrum at 1757 cm^{-1}, 1692 cm^{-1} and 1601 cm^{-1} are attributed to O–CO– stretching frequency, –COO vibration and respectively, to skeletal in-plane vibration of aromatic ring [20–22]. Also, the peaks at 1304 cm^{-1}

and 1191 cm^{-1} are assigned to C–O stretching vibration of ester/carboxylic group [20]. The FTIR spectrum of TiO_2 shows a broad band at about 3400 cm^{-1} due to O–H stretching vibration due to adsorbed H_2O molecules on the titanium dioxide nanoparticles surface [23]. This band is overlapped with broad band of hydroxyl frequencies of organic compounds. In the IR-spectral regions of 653–550 cm^{-1} (Ti–O stretching) and 495–436 cm^{-1} (Ti–O–Ti stretching) [24], the vibrations are also covered by pyranose rings vibration [18,21]. The intensity and shape changes of band observed in 1800–1500 cm^{-1} suggest the hydrogen bonds formation (physical intermolecular interactions) –OH… O═C, between –OH groups of psyllium and O═C from carboxyl group of aspirin. These results indicate that TiO_2 nanoparticles and also, aspirin molecules have been successfully incorporated into psyllium-based matrix.

3.2. *In vitro* drug release studies

The prepared lyophilized materials samples were immersed in the simulated biological fluids (SGF and SIF) and were kept in a shaking water bath at 37 ± 0.2 °C during the drug release experiments. At predetermined time intervals, defined volume of dissolution media was extracted for UV–vis analysis and replaced with the same volume of fresh fluids to maintain a constant volume.

The first step of aspirin release from psyllium-based composite materials was studied in SGF at pH=1.2 (50 ml) for 2 h. Then, the samples were placed in SIF at pH=6.5 (50 ml) up to 4 h for a total period of 6 h. The content of aspirin released was measured recording the UV–vis absorbance of the solution at wavelength 280 nm at 10, 30, 60 and 120 min for SGF immersion and then at 1 h up to 6 h for SIF placement. The *in vitro* release profile of the aspirin from the polymer composite matrix in different dissolution media was followed over a period of approximately 6 h and is presented in Fig. 2. Data presented in the drug release figure have lower standard deviation (SD) that shows the release drug regularity nearly at constant level of the drug.

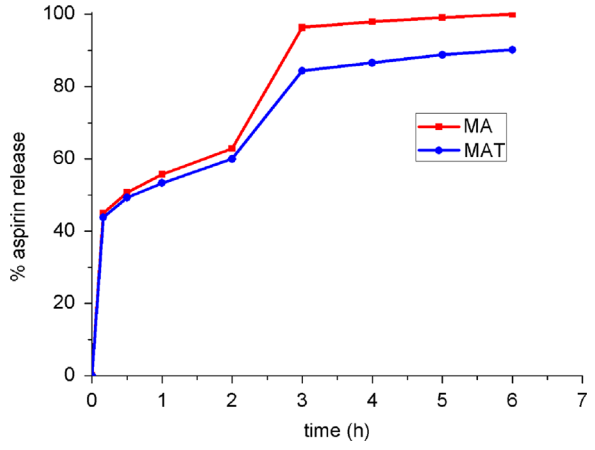

Fig. 2. Aspirin dissolution at pH 1.2 and 6.5 from polymer composite without TiO_2 content (MA sample: SD ± 0.32) and from polymer composite with TiO_2 nanoparticles (MAT sample: SD ± 0.41).

It can be observed that a drug release of about 45% occurred at pH=1.2. The release profile of aspirin shows two almost linear regions. The first of these regions took place in the first 30 min that translated by a fast dissolution of aspirin from the polymer composite matrix followed by a slower release rate that continued for approximately 2 h. As a result of replacement of composite materials in intestinal media, the aspirin release profile presents a similar trend to that mentioned above. At pH 6.5, aspirin release was faster, roughly linear and was reached ~100%. A small difference between two release drug profiles is observed in acidic media. In the first case (MA sample), the slight increase of drug release rate occurs due to higher solubility of aspirin in this solution. In the second case (MAT material), the aspirin release delay can be explained by physical adsorption of aspirin molecules onto the TiO_2 nanoparticles. A visible lower aspirin release from MAT composites is observed in the SIF media, the highest percentage reaching about 90%. Thus, the total release of drug was highly sensitive to the contribution of titanium dioxide nanoparticles and TiO_2 amount added to the composite system may influence the release behavior of aspirin.

3.3. Drug release kinetics

In vitro release studies were performed in triplicate and the data were fitted into different kinetic models, such as: zero-order, first-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas. The highest value of regression coefficient (R^2) indicates a good correlation and a better linearity; the kinetic model leads the mechanism of drug release (Table 2).

The ideal kinetic models for drug release were estimated using the following graphical plots: cumulative amount of drug released *vs.* time (zero-order model), log cumulative percentage of drug remaining *vs.* time (first-order model), cumulative percentage drug release *vs.* square root of time (Higuchi model), cube root of drug percentage remaining in matrix *vs.* time (Hixson–Crowell model) and log cumulative percentage drug release *vs.* log time (Korsmeyer–Peppas model) [25].

Table 2
Kinetic models for aspirin release from psyllium-based matrices expressed by the values of regression coefficient (R^2).

pH	Sample	Zero-order	First-order	Higuchi	Hixson–Crowell	Korsmeyer–Peppas
1.2	**MA**	0.946	0.974	0.998	0.966	0.979
	MAT	0.946	0.971	0.996	0.964	0.977
6.5	**MA**	0.974	0.929	0.991	0.990	0.990
	MAT	0.984	0.985	0.994	0.993	0.990

Regression analysis after plotting the cumulative percentage drug release *vs.* square root of time shows a linear relationship that describes a Higuchi model (Fig. 3).

This relationship describes the aspirin dissolution from psyllium-based matrix in both simulated gastric fluid and also, in simulated intestinal medium. The drug release mechanism is dictated by the penetration of fluid into matrix that dissolves the drug and then this one diffuses into the exterior medium [25].

Mechanism of drug release from a polymeric system was described by plotting an exponential equation (Korsmeyer–Peppas): $M_t/M_\infty = kt^n$, where M_t/M_∞ corresponds to fraction of drug released at time t, k is the diffusion rate constant and n is the release exponent that indicates the mechanism of drug release. Fig. 4 shows the mechanism of drug release data fitted with the Korsmeyern–Peppas model. The analysis of drug release mechanism was performed related to different values of n (Table 3) [26–28].

The n values for the Korsmeyer Peppas model were 0.133 for aspirin release from polymeric matrix in SGF, 0.052 for the same sample in SIF, both n values being smaller than 0.5. These results indicate that the releases are in agreement with a quasi-fickian diffusion mechanism. Thus, aspirin diffuses partially through a swollen matrix as a result of structural rearrangements in the polymer support. The active principles partially diffuse from matrix; the process is still in evolution. The drug release can take place during a longer time period.

4. Conclusions

The psyllium-based composites containing titanium dioxide nanoparticles as nanomaterial matrix for aspirin drug release were prepared. The influence of TiO_2 addition as carriers in

Table 3
Interpretation of diffusion release mechanisms (26–28).

Release exponent (n)	Drug transport mechanism	Description of the drug release kinetics
$n < 0.5$	quasi-fickian diffusion	partial diffusion
$n = 0.5$	fickian diffusion	molecular diffusion of the drug due to a chemical potential gradient
$0.5 < n > 1$	non-fickian (anomalous) diffusion	both diffusion and relaxation (erosion) release
$n = 1$	Case 2 transport	relaxation release polymeric matrix
$n > 1$	Super Case 2 transport	erosion of polymeric chain

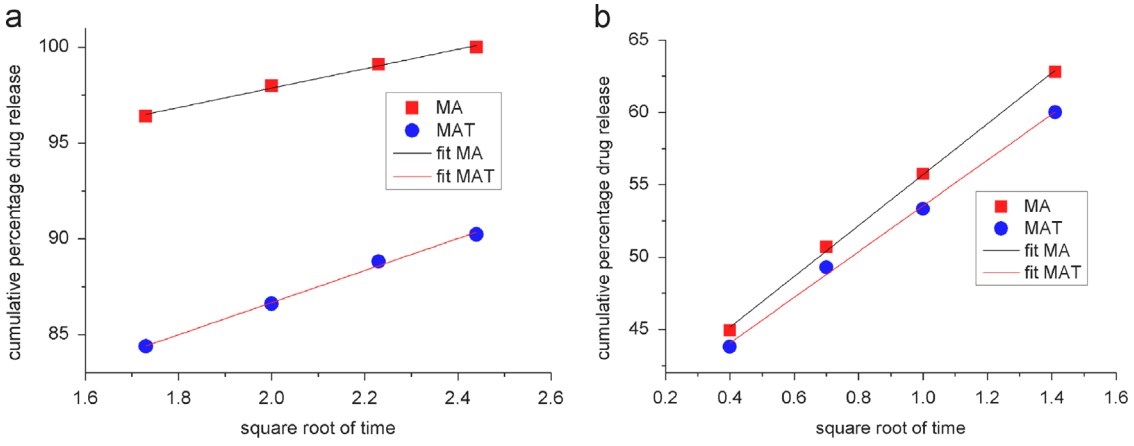

Fig. 3. Higuchi model for mechanism of aspirin release: (a) in SGF (pH=1.2) and (b) in SIF (pH=6.5).

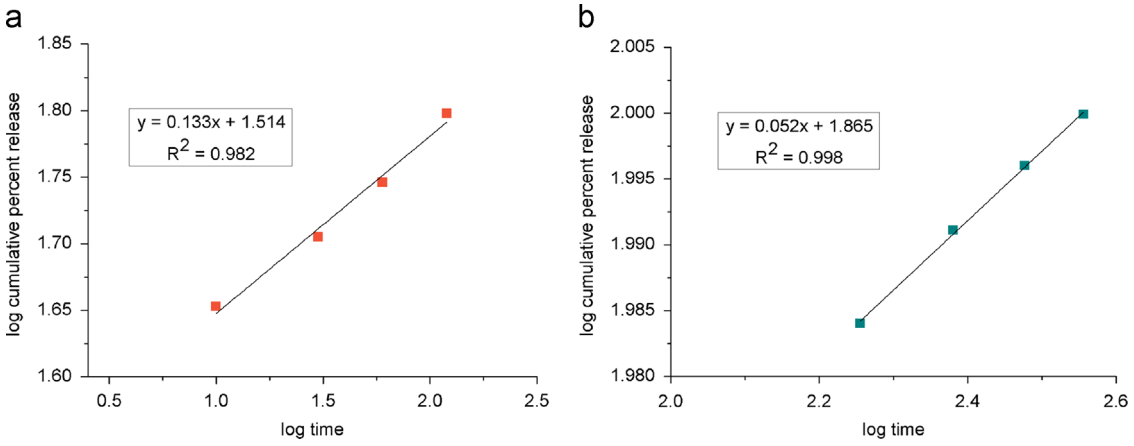

Fig. 4. Korsmeyer Peppas model release kinetics of aspirin: (a) in SGF (pH=1.2) and (b) in SIF (pH=6.5).

order to provide drug protection in simulated fluids was evaluated. A slowest delay in the release profile of aspirin from the obtained composites is observed. The results indicate that oxide is susceptible to protect the drug, as possible efficient transporter of it. The kinetics of aspirin release was best expressed by the Higuchi model according to drug dissolution from polymeric matrix. The values of diffusion parameters show a drug release mechanism controlled by a quasi-fickian diffusion type, suggesting the controlled release of aspirin. The obtained results lead to promote psyllium-based nanocomposite materials for biomedical applications with further more intense investigations of the diffusion mechanism through systems with complex interfaces.

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