Regular Article

PHYSICAL CHEMISTRY RESEARCH
Published by the
Iranian Chemical Society
www.physchemres.org
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Phys. Chem. Res., Vol. 9, No. 1, 57-68, March 2021
DOI: 10.22036/pcr.2020.232018.1775

Grafting Drugs to Functionalized Single-wall Carbon Nanotubes as a Potential Method for Drug Delivery

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(Received 19 May 2020, Accepted 29 October 2020)

The mesalazine and fluvoxamine drugs were grafted to single-walled carbon nanotubes (SWCNTs) aiming at precise drug delivery. First, carboxylic groups in SWCNT were converted to corresponding acyl chlorides. Next, in order to form the amide bonds, acyl chloride-SWCNTs were mixed with chemotherapeutic agents having NH_2 and NH functional groups. Then, the covalently grafted drugs to SWCNT were characterized by UV-Vis, IR spectroscopy, and transmission electron microscopy methods. Finally, the prepared organic compounds were used for releasing drugs at pH: 1.3, which is corresponding to clinical aspects of the human body, and were examined for the potential of drug delivery in patients. Accordingly, the in-vitro kinetic as well as the mechanism of the released drugs were investigated.

Keywords: Single wall carbon nanotube, Kinetic, Drug release, SWCNT-drug grafting

INTRODUCTION

In recent decades the National Institute of Health has reported the application of nanotechnology for the control of biological systems, diagnosis and treatment conventionally referred to as “nanomedicine” [1,2]. Single wall carbon nanotubes (a single rolled layer of graphene making a single-walled carbon nanotube with a diameter between 0.4 and 2 nm) were first introduced in 1993 by Sumio Iijima [3-5]. The main advantages of these materials are as follows: high resilience, high current carrying capacity, high thermal conductivity, strong covalent bonding, high tensile strength, solution-based chemical transformations, and solubility in organic solvents [6,7]. Carbon nanotubes (CNTs) have various properties enabling them to support drugs. Functionalized CNTs can cross cell membranes [8-11]. Accordingly, they are used for carrying particularly high-interest drug delivery strategies. To deliver drugs to the cell, first, the drug must attach to a carrier through covalent or non-covalent bonding interactions. Inorganic nanoparticles (NPs) contain toxic heavy metals, but CNTs are relatively nontoxic since their structures are made purely of carbon atoms [12]. They supply a completely separate environment for the drug while preserving it from damage and reaction with healthy cells also permitting the drug to circulate in the blood for a lengthy period until it reaches and is delivered to the target site with negligible side-effects [13]. CNTs have been used for a variety of biological molecules which include proteins, enzymes, nucleic acids drugs, and RNA since they are dissolved in water and can penetrate through cells by themselves (without apparent cytotoxicity) [14-16]. Hence, CNT-based drug delivery is a promising alternative for the treatment of different diseases such as infections, metabolic diseases, and autoimmune diseases, also for usage in gene therapy [12]. Some of the general side effects of drugs are lack of selectivity, poor pharmacokinetics, damage to healthy tissues, and low solubility. For overcoming these problems, CNTs have been used as nanocarriers for drug delivery [17]. Accordingly, for conjugating the drugs to nanocarriers, two methods of covalent and noncovalent bonding are used [18,19]. The physical incorporation or encapsulation of drug molecules into carrier systems involves electrostatic ionic interactions, hydrophobic

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interactions and physical entrapping of drugs in the carrier matrix [20]. Although the physical encapsulation of drugs is a popular technique, certain disadvantages are associated with it. For hydrophobic drugs encapsulation in the core of micelles, dose dumping may occur if micelles undergo hemodilution below the critical micelle concentration. Moreover, challenges have been encountered in entrapping hydrophilic drugs in carrier systems using physical encapsulation [21]. These challenges have resulted in physical encapsulation with low loading efficiencies. Due to this, drug delivery scientists are resorting to covalently linking drugs to nano-drug delivery systems as an alternative method to physical encapsulation [19].

The medicinal standpoint of the present research is covalent grafting of mesalazine and fluvoxamine drugs to SWCNTs that can be considered as a new method for potential drug delivery. These drugs are used as an anti-inflammatory and to treat social anxiety disorder, respectively. The used drugs were linked up with SWCNTs via amino groups, present in drug structure, and formation of amide bonds between them. The products were characterized in different ways. Then, hydrolysis reactions were carried out in a buffer solution (pH 1.3) at 37 °C, relevant to the human gastric simulated conditions. Drug release kinetics and release mechanisms were afforded by obtaining experimental data at different time intervals.

EXPERIMENTAL

Materials

The pure SWCNTs without functional groups were purchased from Petrol Co. (Tehran, Iran). $SOCl_2$, HCl, H_2SO_4, HNO_3, H_2O_2 (30 wt%, aq), deionized water, and NaH (60%) were purchased from Merck and used without further purification. Dimethylformamide (DMF) was dried over $MgSO_4$ for 72 h and then distilled once. Tetrahydrofuran (THF) was refluxed on Na/benzophenone for 8 h and distilled twice before use. Buffer solution (pH = 1.3) was prepared by the addition of an aqueous solution of KCl (25 ml, 0.2 M) to HCl (33.6 ml, 0.2 M) in a volumetric flask. The cellophane membrane dialysis bag was purchased from Polymer Co., Iran. Drugs, such as mesalazine and fluvoxamine were received from Alborz-Daro antibiotic manufacturer, Iran.

Instruments

Infra-red spectra were taken by a PERKIN ELMER spectrophotometer using KBr pellet. All the UV-Vis spectrophotometric data were recorded using a Shimadzu UV-265 spectrophotometer. Transmission electron microscopy (TEM) images were prepared by Tecnai 20 instrument.

Functionalization of SWCNTs

To introduce carboxylic acid groups on the SWCNT surface, 0.1 g of full-length SWCNT was added to a 110 ml mixture of concentrated H_2SO_4 and HNO_3 acids (v/v 3:1). The mixture was to reflux at temperature 70 °C for 30 h. After cooling to the room temperature, the SWCNT–acid product was diluted in a minimum amount of deionized water (250 ml). The diluted nanotube-the acid mixture was then filtered off with a 0.45 µm polytetrafluoroethylene filter (PTFE-Millipore) to leave an SWCNT filter cake (oxidized nanotubes), it was then washed with water to reach a pH about 5. After this pH adjustment, the product was washed with ethanol and added into a solution of H_2O_2 (30 wt%, aq) and H_2SO_4 (12 M) with a ratio of 4:1. To produce a large number of open caps carboxylation, the mixture was refluxed for 2 h at 70 °C to crack the SWCNTs into shorter lengths. For removing the metal catalyst (accompanied with full-length SWCNT) from the suspension, HCl was added and then sonicated. The product was put in a vacuum desiccator at 180 °C for removing the water.

In the second step, for the generation of acyl chloride functional groups, 0.1 g of the produced SWCNTs was added to a mixture of 20 ml $SOCl_2$ and 1 ml DMF, then it was heated to 65 °C. After 24 h a solid precipitate was formed and filtrated. For removing the excess of $SOCl_2$, it was washed with pure THF. The compound was put in a vacuum desiccator and dried at room temperature for 5 min. For grafting, the weight ratio of the drug to SWCNT was 15:1 (used drugs contain NH, NH_2 in their structure). Each used drug was mixed with NaH (60%) and 1 ml DMF and it was stirred for 1 h. The product of acyl chloride SWCNT was added to the above mixture and maintained at 120 °C for 5 days. The obtained solid was filtered and washed with deionized water three times [18]. Finally, after stirring, a black solid was formed which was completely soluble in

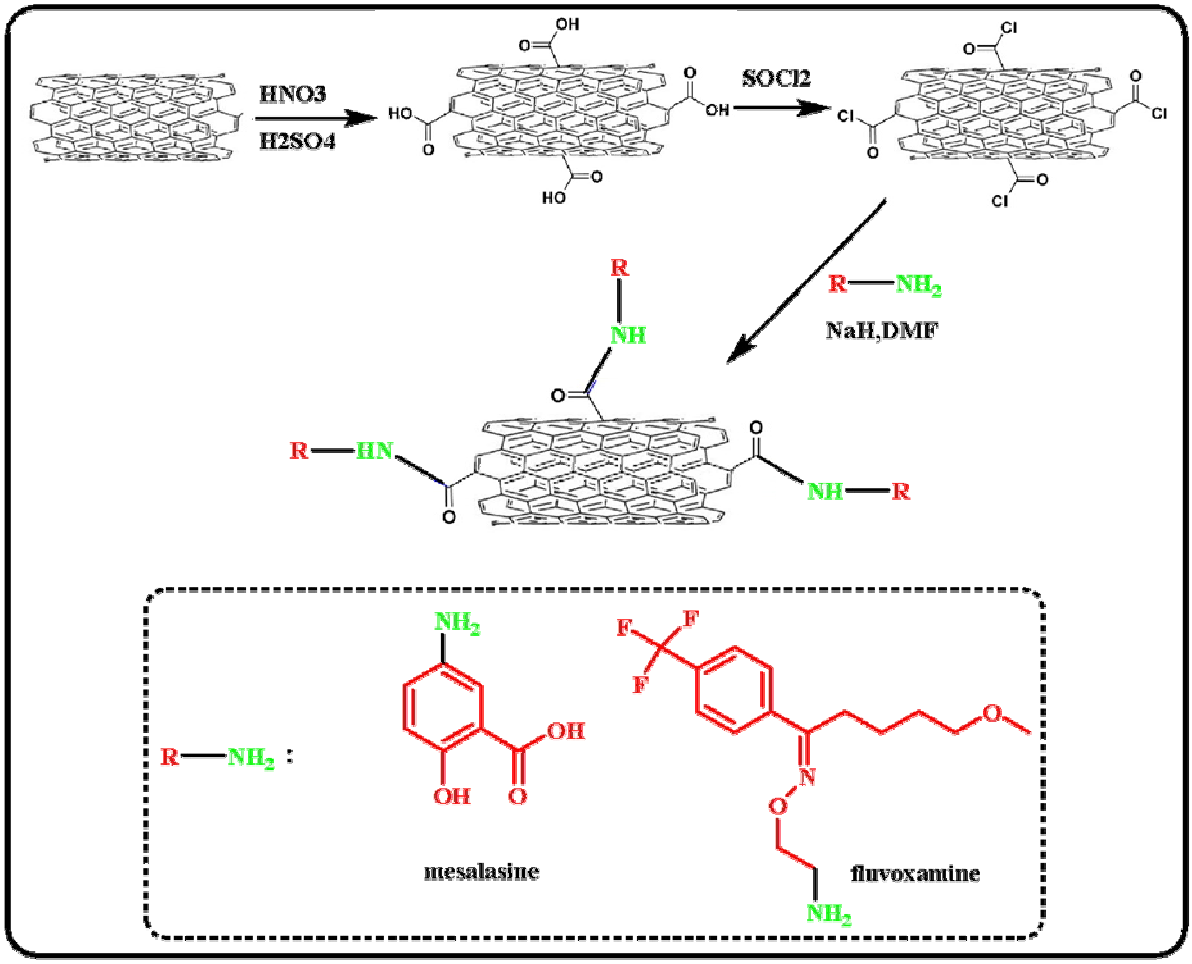

Fig. 1. Covalent grafting of various drugs to SWCNT.

DMSO and DMF and less soluble in water and CH_3CN; however, it was not soluble in dichloromethane, diethyl ether, chloroform, hexane, and acetone. Figure 1 shows the reaction of SWCNT with drugs.

RESULTS AND DISCUSSION

Characterization of the Products

The functional groups of drugs grafted to SWCNT were characterized by IR, UV-Vis (UV-Vis) spectroscopy, and size and topology of products were also followed by transmission electron microscopy (TEM).

First of all, a mixture of H_2SO_4 and HNO_3 was added to SWCNT followed by HCl. The IR spectrum of this compound is shown in Fig. 2. The carboxylic group of 1,741 cm (IR spectrum A, Fig. 2). IR spectra of the pure mesalazine and fluvoxamine drugs are also shown in Fig. 2 (B, D). IR spectra of C and E show the grafted SWCNT-mesalazine and fluvoxamine, respectively (Fig. 2). As shown in Fig. 2, when drugs are attached to SWCNT the amide bonds appear in a range of 1642 cm^{-1}. The main bands appearing in the IR spectra of the grafted drug to SWCNT are summarized in Table 1.

The functional groups of drugs grafted to single-wall carbon nanotubes were characterized by IR, UV-Vis (UV-Vis) spectroscopy, and transmission electron microscopy (TEM). The UV-Vis absorption spectrum of mesalazine and fluvoxamine (Fig. 3) displays a loss of features compared

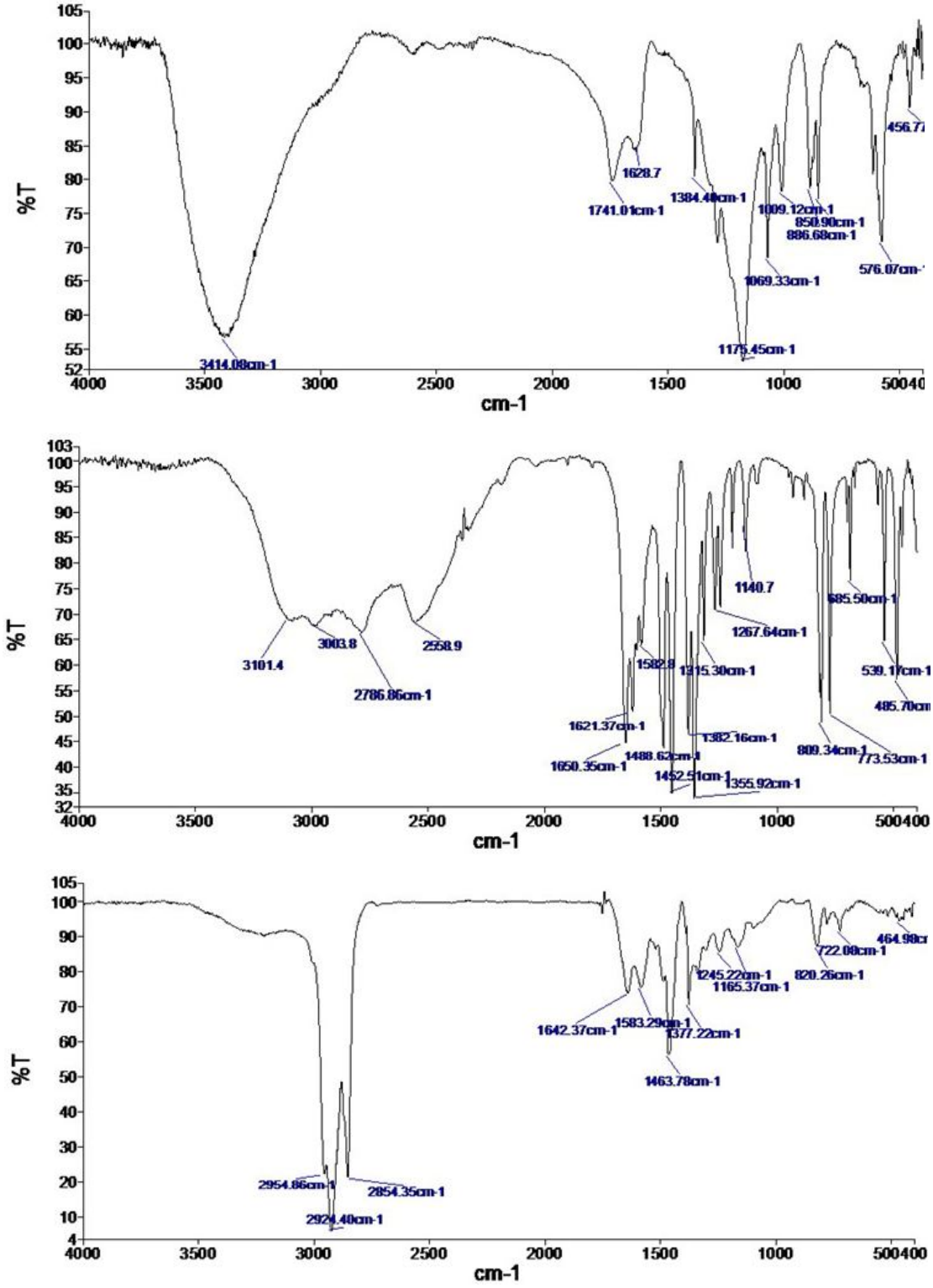

Fig. 2. Infrared spectra of SWCNT-COOH (a), pure mesalazine (b), grafted SWCNT-mesalazine (c), pure fluvoxamine (d), grafted SWCNT-fluvoxamine (e).

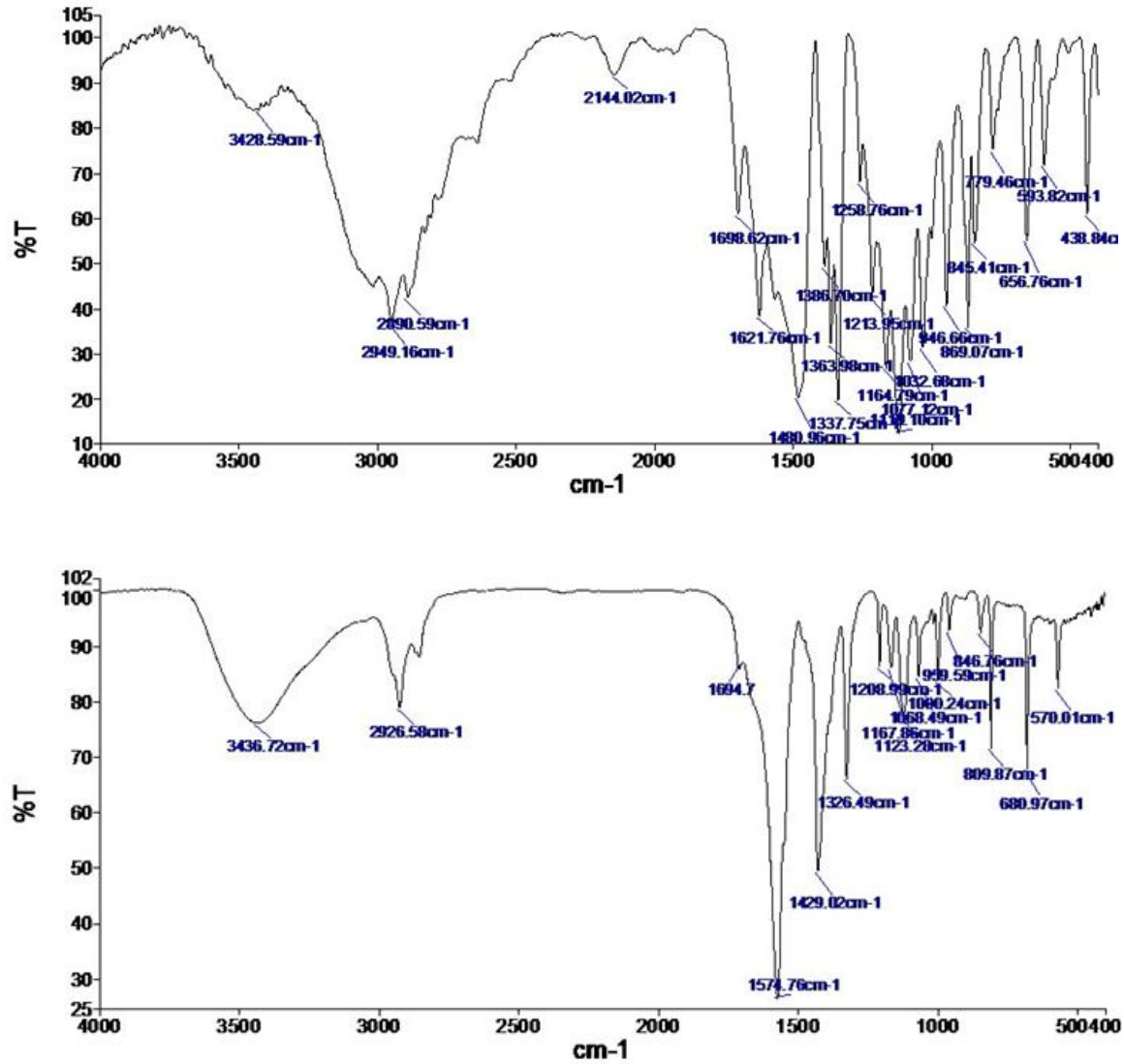

Fig. 2. Continued.

with that of SWCNT indicating a disruption in the electronic structure of nanotubes due to the adsorption of drugs on SWCNT. TEM studies have revealed the successful grafting of mesalazine and fluvoxamine to SWCNT (Fig. 4). In Fig. 4, the arrows indicate the grafted drugs to SWCNT [22].

In Vitro Release of Drugs from Grafted SWCNT-Drug Structures

Drugs used in this work were oral; so, the hydrolysis of drugs loaded on SWCNT was investigated under in vitro conditions. The media was simulated according to the gastric juice condition of the human body under acidic pH of 1.1-1.3 [22]. Breaking the amide bond in the acidic buffer (PBS: pH:1.3, at 37 °C) is a hydrolysis reaction [23]. Accordingly, the grafted drugs were released as the following procedure: SWCNT-mesalazine and SWCNT-fluvoxamine were separately added into cellophane membrane dialysis bags. Each dialysis bag was placed in a flask containing 50 ml of acidic buffer. After that, the

Table 1. IR Absorption Bands Obtained from the Acid-treated SWCNTs and Drugs Grafted to SWCNTs' Solid Samples

Compound	Region (cm^{-1})	Band assignments
SWCNTs-COOH	1741	Carboxylic acid C=O stretching
SWCNTs-COOH	3414	Carboxylic acid OH stretching
SWCNTs-mesalazine	1642	Amide C=O stretching vibration
SWCNTs-fluvoxamine	1694	Amide C=O stretching vibration
SWCNTs-mesalazine	1583	Amide NH bending vibration
SWCNTs-fluvoxamine	1574	Amide NH bending vibration

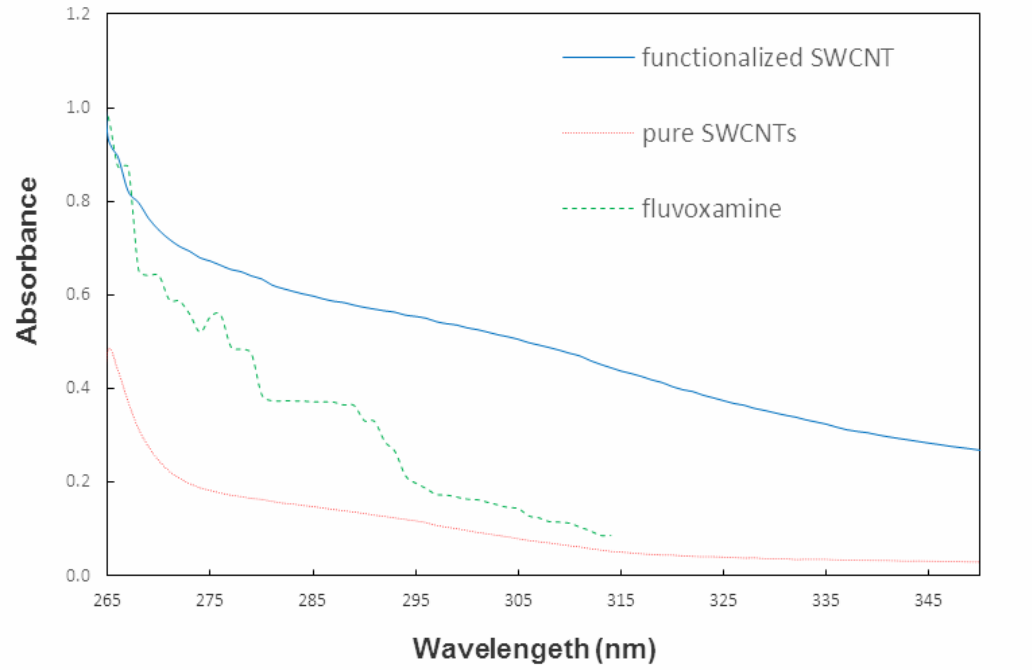

Fig. 3. The UV-Vis absorption spectra of fluvoxamine in dimethylformamide, pure SWCNTs, and functionalized SWCNT-fluvoxamine.

release of drugs from grafted SWCNT-drugs was identified by UV-Vis spectroscopy. The amounts of drug released were subsequently measured by the absorbance of the solution at the corresponding maximum wavelength of (λ_{max} = 232 nm for mesalazine and 252 nm for fluvoxamine under relevant pH). Samples were measured at different intervals, and the percentage of drug released was obtained from $(A/A_\infty) \times 100$, where, A and A_∞ are absorbances at any

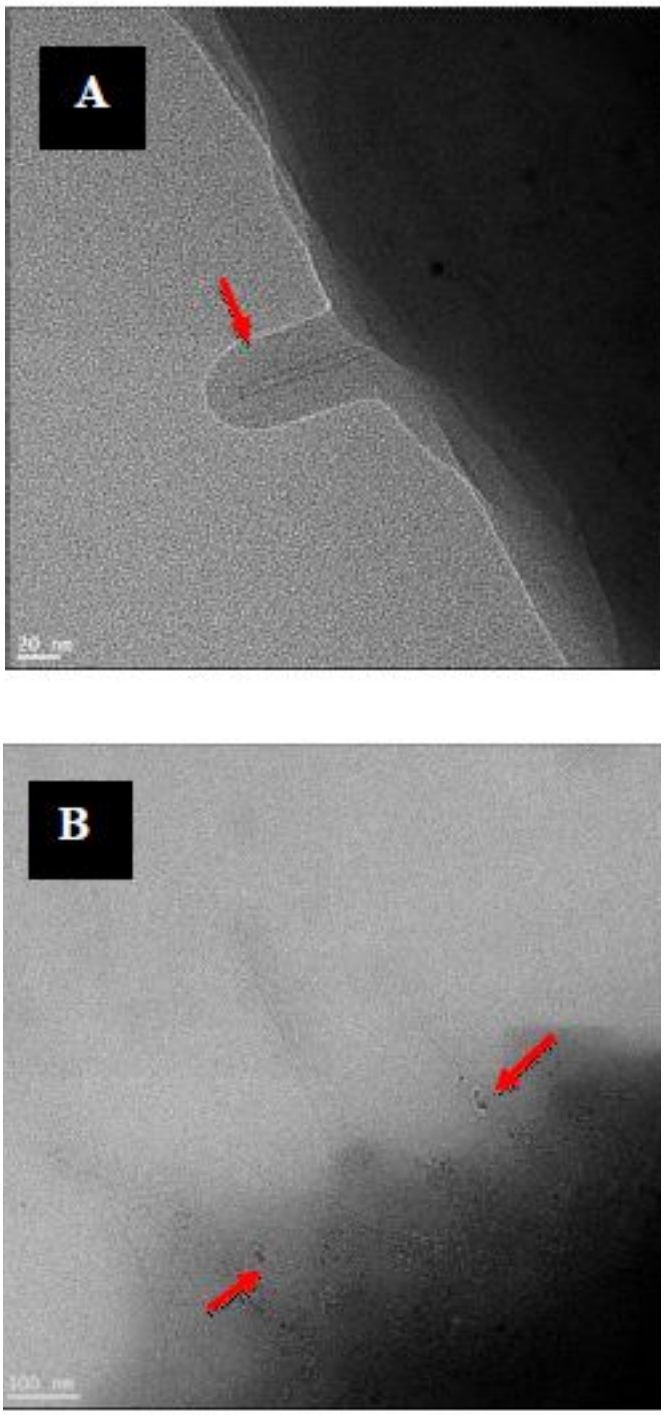

Fig. 4. Transmission electron microscopy images of grafted SWCNT-mesalazine (A), and grafted SWCNT-fluvoxamine (B). The arrows indicate the grafted drugs to SWCNT.

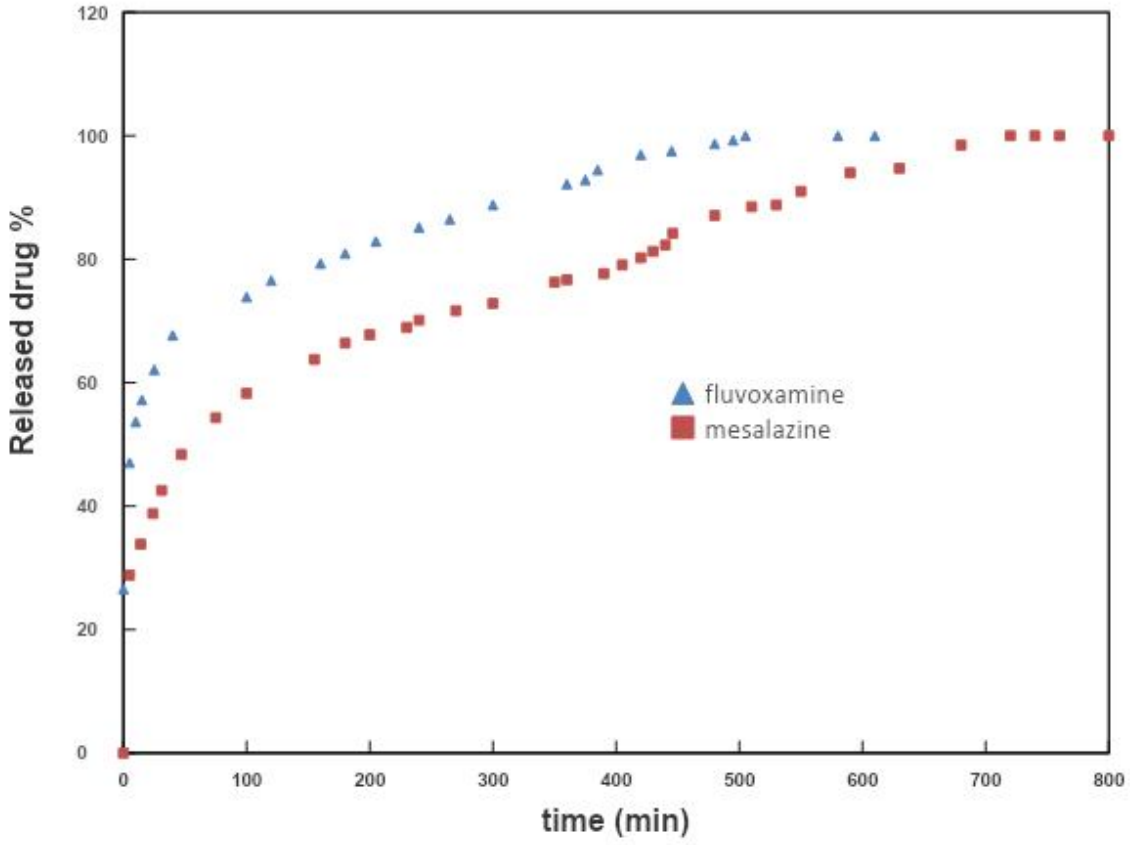

Fig. 5. Drug release *versus* time from the grafted-SWCNT system (pH = 1.3, T = 37 °C).

time (t) and infinite time (equilibrium condition). The cumulative release profiles and the releasing percentage of the drugs from SWCNT are presented in Fig. 5. It is obvious that the hydrolysis of drugs is completed gradually and is mostly controlled by the SWCNT media. The rate of drug release is rather fast during initial times (about 20 min of operations). For analyzing results, it was attempted to find the best proportion of the provided data with the well-known drug release kinetic models. Equation (1) is the first-order model that describes the systems in which the rate of the drug release is linearly proportional to the drug concentration on the matrix. Equation (2), introduced by Higuchi, [24] indicates the release of drugs from porous and insoluble matrices as a square root of time-dependent process based on Fickian diffusion [25-27]. Equation (3) provides a simple relationship describing drug release from a system. This equation has been derived from experiments by Korsmeyer *et al*. [28-30].

$$C_t = C_\infty (1 - e^{-kt}) \quad (1)$$

$$C_t = k_H \sqrt{t} \quad (2)$$

$$\frac{C_t}{C_\infty} = k_{KP} t^n \quad (3)$$

In these equations, C_t is the amount of drug released at time t, C_∞ is the maximum drug released, experimentally measured in long times (here more than 500 min), k is the first order drug release constant, k_H is the Higuchi rate constant, k_{KP} is the Korsmeyer-Peppas rate constant and n is the order of kinetic. To study the kinetics of drug release, data obtained from *in vitro* studies were plotted as $\ln[1-(C_t/C_\infty)]$ *vs*. time in the first-order model, as the

Table 2. Kinetic Parameters and Correlation Coefficient (r^2) for the Release of Drugs from Drug-loaded SWCNT

Model	Parameter	Mesalazine	Fluvoxamine
First-order	k (min^{-1})	0.0045	0.0085
	r^2	0.854	0.8219
Higuchi	k_H (ppm min$^{-1/2}$)	1.1314	2.0816
	r^2	0.7906	-0.353
Korsmeyer-Peppas	k_{KP} (min^{-n})	0.1320	0.3681
	n	0.249	0.156
	r^2	0.9879	0.9887

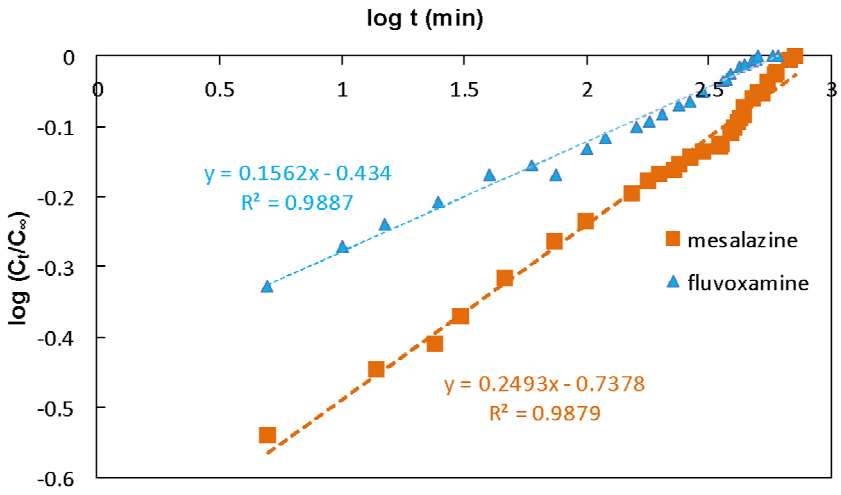

Fig. 6. Drug release kinetic plots by fitting data to the Korsmeyer-Peppas kinetic model.

amount of released drug *versus* square root of time in the Higuchi model and as log(C_t/C_∞) *vs*. log$t$ in Korsmeyer-Peppas model. The corresponding parameters were obtained from the slope and intercepts.

Table 2 shows the releasing kinetic parameters of the drug-loaded SWCNT, together with the coefficient of determination (r^2). The analysis of results reveals that the Korsmeyer-Peppas model reproduces the obtained data most accurately and the other models are not much relevant. Figure 6 illustrates the results according to the Korsmeyer-Peppas model.

Mechanism of Drug Release

For discussing the nature of the drug release mechanism, Korsmeyer *et al.* [28] reported a simple empirical model which described drug release from an SWCNT system. Some processes may be classified as either pure diffusion or purely erosion controlled; many others can only be

interpreted as being governed by both. The analysis of experimental data in the light of Eq. (3), as well as the interpretation of the corresponding release exponent values, leads to a better understanding of the balance between these mechanisms [31-33]. The equation can be written as:

$$\log\left(\frac{C_t}{C_\infty}\right) = \log k_{KP} + n \log t \quad (5)$$

where, C_t/C_∞ is the mass fraction of drug released at time t and n is a characteristic of the drug, here grafted to the SWCNT system. By determining the release exponent, it is possible to obtain information about the physical mechanism controlling the drug release from a particular device [34,35]. Based on the value of the exponent n, drug transport has been classified as given in table [35]. In this work, the exponent n is 0.249 and 0.156 (less than 0.45) under the conditions applied. Fickian diffusion is the dominant mechanism for drug release.

CONCLUSIONS

Briefly, SWCNTs were grafted covalently with mesalazine and fluvoxamine as follows: SWCNTs were oxidized with H_2SO_4 and HNO_3 and then the products reacted with $SOCl_2$. The drugs were attached to acyl chloride in SWCNTs, and eventually, amide bonds were formed. The covalent grafting of drugs increases the solubility of SWCNTs in both aqueous and organic solvents. In the second step, each drug was weighted and hydrolyzed in an acid buffer under simulated human gastric conditions. The absorbance of samples was measured by UV-Vis. Spectrophotometer and the drug-releasing from SWCNTs occurred slowly. So, this procedure was one of the useful methods for drug delivery. Further kinetic studies revealed that Korsmeyer-Peppas model precisely reproduces the experimental data and that Fickian diffusion is the dominant mechanism for the drug release under the conditions applied.

ACKNOWLEDGMENTS

The authors gratefully acknowledge partial support of this work by the Research Affairs Office of Bu-Ali Sina University (Grant number 32-1716 entitled development of chemical methods, reagents, and molecules), Center of Excellence in Development of Chemical Method (CEDCM), Hamadan, Iran.

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