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Sol-Gel preparation and In vitro kinetic Release Study of Albendazole-Immobilized MWCNTs

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This study aims at preparation and characterization of novel drug delivery system based on functionalized multi-walled carbon nanotubes (MWCNTs) with tetraethyl orthosilicate (TEOS) using sol-gel technique, in presence of albendazole (ABZ) which used as a drug model. The prepared materials were characterized using Fourier transform infrared spectroscopy (FTIR), transmission electron microscope (TEM), particle size distribution analysis using DLS technique and thermogravimetric analysis (TGA). *In vitro* kinetic release study of the immobilized ABZ was carried out using enzyme-free simulated gastric fluid (SGF) at pH 2.5 and 37^{0}C as well as by using the different mathematical models (zero order, first order and higuchi). Moreover, *in vitro* cytotoxic effect on the human normal fibroblast cell line (BHK-21) using SRB assay was also investigated. The results indicated that FTIR, TGA and particle size analysis of the prepared materials illustrating the successful immobilization of ABZ onto the functionalized MWCNTs. Besides, TEM images showed that the immobilized ABZ onto oxidized MWCNTs had agglomerated fibers without damage. Moreover, i*n vitro* cytotoxic study revealed that the immobilized ABZ had low toxic effect on BHK-21 cell line in comparison with the free drug. The cumulative ABZ released resulted in a biphasic release behavior with rapid initial burst phase.

Keywords: Albendazole; MWCNTs; sol-gel technique; in vitro kinetics release; cytotoxicity.

Introduction

Benzimidazoles are the largest chemical class of the modern anthelmintic family which used in the domestic animals. Albendazole (ABZ, Fig1) is one of this family (heterocyclic aromatic organic compound) which was considered as abroad spectrum anthelmintic according to its chemical structure and mode of action [1]. It has the ability to infect the cycloskeleton through interaction with b-tubulin that leads to the impaired uptake of glucose [2, 3]. *In vitro* studies showed that albendazole is an active agent against helminths, some protozoa and intestinal parasites [4]. Also, it is a white crystalline powder which is insoluble or slightly soluble in water. However, it is soluble at low acidic pH values [5]. The dose of albendazole depends on the target parasite and it can be administered through different ways such as orally (tablets) or as suspension [6]. Sol-gel method has a numerous advantages and used in many different fields [7]. It is conducted by two mechanisms (hydrolysis and condensations) resulting in highly porous, permitting the entrapment and controlled release compounds [8-11]. The most widely used silicate precursor is tetraethyl orthosilicate (TEOS) using water and ethanol solvents mixture [12-14]. Various drug delivery and drug targeting systems are currently applied or under development using nanoparticles for the control release. Furthermore, nanocarriers are ideal entities as drug carriers that deliver

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poorly water soluble agents at the desired site [15]. Carbon nanotubes (CNTs) have unique properties to be promising candidates as drug delivery systems with high pharmacological profiles [16-18]. They are consisted of rolled graphene sheets in a cylinder shape that are microns to millimeters in length and divided to single-walled (SWCNTs) and Multi-walled (MWCNTs) [19-26]. Functionalization of CNTs is the best method to improve their properties by adding hydrophilic groups to be more dispersibility and solubility in the aqueous media [27-32]. In this paper, we report the preparation, characterization of functionalized MWCNTs with TEOS and loading with ABZ using sol-gel technique. Moreover, FTIR, TEM, TGA and particle size distribution analysis were carried out. Besides, *in vitro* kinetics ABZ release using SGF at pH 2.5 and 37^{0}C and *in vitro* cytotoxic effect against BHK-21 cell line were investigated.

Material and Methods

Materials

Multi-walled carbon nanotubes (MWCNTs), carbon content 95%, diameters 6–9 nm× 5 µm, and tetra ethyl orthosilicate (TEOS) were obtained by Aldrich. All other chemicals and reagents were used as received.

Oxidation and purification of MWCNTs [33]

Pristine MWCNTs was functionalized by treating them with olive oil. 10g of MWCNTs were dispersed in mixed 30% nitric acid and olive oil with ratio (3:2 v/v) in a flask of 500 mL. The flask was then refluxed at 110^{0}C for 2 hrs with continuous stirring to produce oxidized MWCNTs. The resulting material was collected via filtration under vacuum and then washed thoroughly using 500 mL of chloroform to remove the remaining oil. The obtained material was washed with ultra-pure water till neutralize the filtrate (pH 7.0). The collected solid was dried under vacuum at 70^{0}C for 12 hr and kept for further modification and analysis.

Functionalization of MWCNTs using sol-gel technique

The sol-gel method was used in the preparation of the nanomaterials through hydrolysis and polycondensation of tetraethyl orthosilicate as source of SiO_2 containing HCL as catalyst [34, 35] in the presence of ox-MWCNTs and drug model ABZ. The silicate solutions with the molar ratio TEOS:C_2H_5OH:H_2O:HCl 1:6:8:0.6 were stirred for 1 hr. After reflux for 2 hr, 100 mg of Ox-MWCNTs and 2 mg of ABZ were added and sonicated followed by addition of benzoin methyl ether (2.0 mmol). First, ox-MWCNTs and drug moieties were crosslinked by means of the sol-gel process, followed by UV photoinitiated radical reaction of the carboxylic groups. The sol was cast and gelled into plastic molds and kept at room temperature for 3 days. The prepared materials were kept for further investigation.

In vitro cytotoxicity evaluation using SRB assay

Potential cytotoxicity of the prepared nanomaterials was tested using the method of Sehkan et al. [36] as follows: Normal fibroblast (BHK-21) cell line was plated separately in 96-multiwell plate (10 cells/well) for 24 hr before treatment with the prepared materials to allow attachment of the cells to the wall of the plate. Different concentrations of the obtained materials under investigation (0, 10, 25, 50 and 100) µg/mL were prepared for each individual dose. Monolayer cells were incubated with the prepared materials for 48 hr in 5% carbon dioxide atmosphere at 37°C. After 48 hr cells were fixed, washed and stained with sulpho-rhodamine-B stain (SRB). Excess stain washed with acetic acid and recovered with Tris-EDTA buffer. Colour intensity was measured in an ELISA reader. The relation between surviving fraction and the prepared formulation concentrations was plotted to get the survival curves of the used cell line.

Drug loading using sol gel technique

Different concentrations of ABZ were loaded onto functionalized MWCNTs using sol gel technique. The first step was taken place by adding constant ratio of Et-OH: H_2O: TEOS (1:1:2) then adding 1 drop of 0.1 N HCL (35%) to increase the hydrolysis rate at pH 2.5 with continuous stirring for 4 hr. During the second step, different concentrations of ABZ were added (50, 100, 150, 200, 250 and 300 mg), followed by a small amount of diethyl amine (about 2 mL), then left for solidification. The solidified samples were grinded and kept for further analysis.

In vitro kinetic released of the immobilized ABZ

30 mg of the prepared formulation was incubated in 30 mL of SGF at 37^{o}C. The study was carried out in Julabo shaking water bath incubator with reciprocating motion (100 rpm). At periodic intervals (0.03, 0.16, 0.25, 0.5, 1, 1.5, 2, 3, 4 and 24 hr), samples of the release medium were taken out

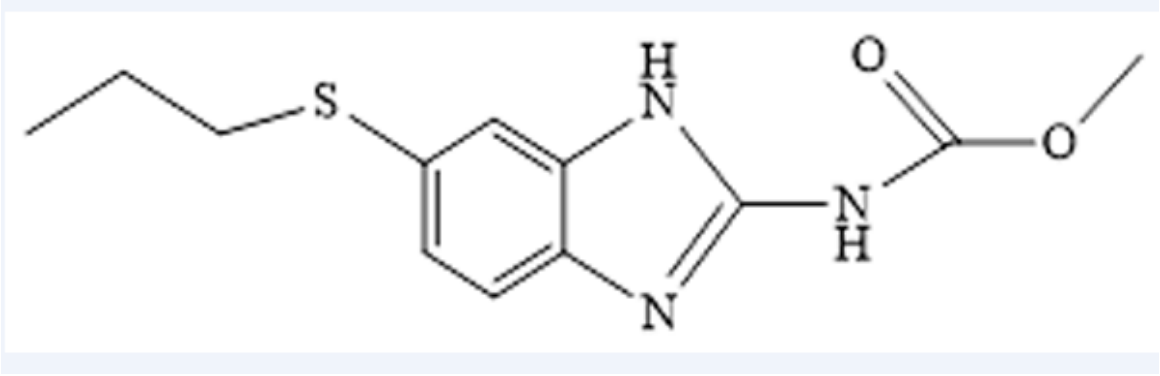

Fig. 1. The chemical structure of albendazole.

for determination of the amount of ABZ released and the volume was replaced with fresh after each estimation using UV spectroscopy at wave length 314 nm. These studies were carried out in triplicate. The data represent the average from three independent experiments. The ABZ release profiles were obtained through plotting the cumulative percent of the total ABZ released from each preparation. To examine the drug release kinetics, the release data were fitted to models representing zero order, first order and Higuchi's square root of time. The correlation coefficient (R^2) values were calculated to determine the best fitting model [37].

Characterization

FTIR spectra were recorded using a jasco-400 Model FTIR spectrophotometer. The UV- spectra were taken using double beam Agilent model. The morphologies were carried out with a JEOL transmission electron microscope JEM-1230. The Particle size distribution analysis were recorded with a Malvern Zetasizer 3000 HAS. Thermal analysis was carried out using Shimadzu DTG-60 at a heating from 30 to 1000ºC.

Results and Discussion

Characterization of the prepared materials

As reported in the literature, the oxidation of CNTs was usually done in a mixture of sulfuric and nitric acids that introduced carboxyl and other polar groups to the tips and the side walls of the CNTs as well as negative zeta potential in the aqueous media. On the other hand, the oxidation of CNTs using olive oil exhibited excellent stability in the aqueous media even after several months [38].

Figure 2 shows FT-IR spectrum of the immobilized ABZ onto MWCNTs (b) in comparison with the spectra of the free ABZ (a) and TEOS (c). In case of the immobilized ABZ onto MWCNTs spectrum, the broad band that appeared with high intensity at 3423 cm^{-1} corresponds to the stretching vibration of -OH (str) groups indicating the esterification of the carboxyl groups by TEOS. Besides, the characteristic peaks at 3178-3025, 1606, 1404, 1080, 111 and 790 cm^{-1} were assigned to alkyl chains of ABZ (CH_3 and CH_2) and C-H (str, aromatic), C=O (str), C-O (str), Si-O-Si, C-O-C, and Si-C [39], respectively. These peaks were shifted with changes in their intensities. This may be due to the presence of ABZ during sol-gel process which led to Si-O-Si interactions enhancement. It can be concluded that the presence of ABZ, which acts as catalyst during sol-gel process, accelerated the reaction in the presence of oxidized MWCNTs.

Figure 3 shows TEM images which indicated that there are no MWCNTs structural damaged occurred. It is probably due to the mild condition of olive oil as compared to the used mixture of the concentrated acids which caused severe structural damage to the nanotubes structure through tubes scission. On the other hand, the loaded sample revealed exhibited tubular shape with an increasing in the diameters.

Figure 4 and Table 1 show the particle size distribution analysis of the prepared materials by correlation with intensity using DLS technique. The particle size of the immobilized ABZ was about 241 nm relative to that in the case of oxidized MWCNTs and the free ABZ (about 495 and 293 nm, respectively). This may be due to the covalent attachment of ABZ with the oxidized MWCNTs and TEOS.

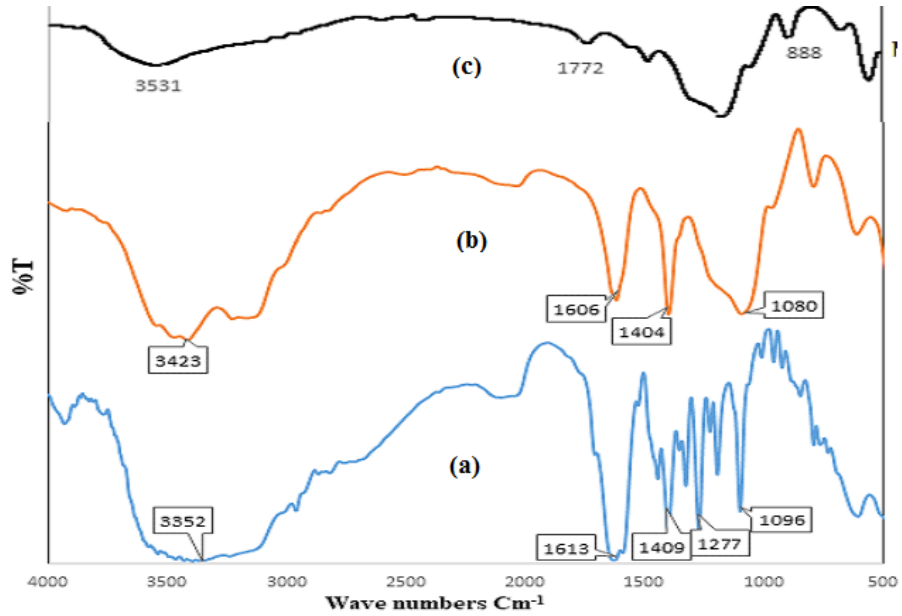

Fig. 2. FTIR spectra of (a) ABZ, (b) immobilized ABZ, and (c) TEOS.

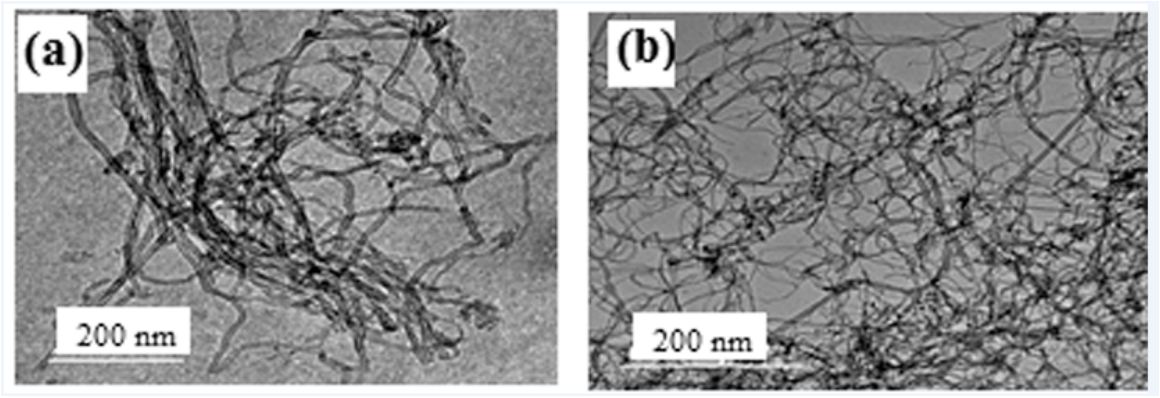

Fig. 3. TEM images of (a) immobilized ABZ and (b) oxidized onto MWCNTs.

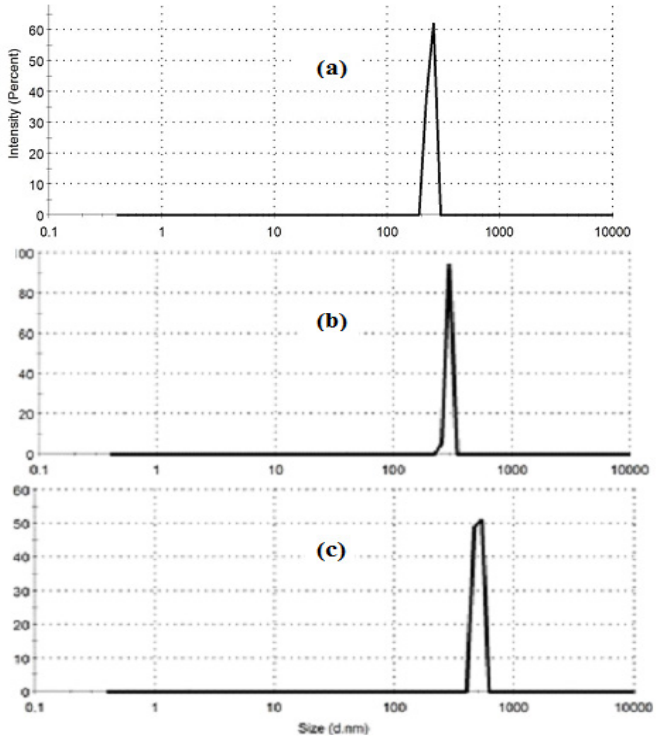

Fig. 4.The particle size distribution analysis of (a) immobilized ABZ in comparison with (b) free ABZ and (c) oxidized MWCNTs using DLS technique.

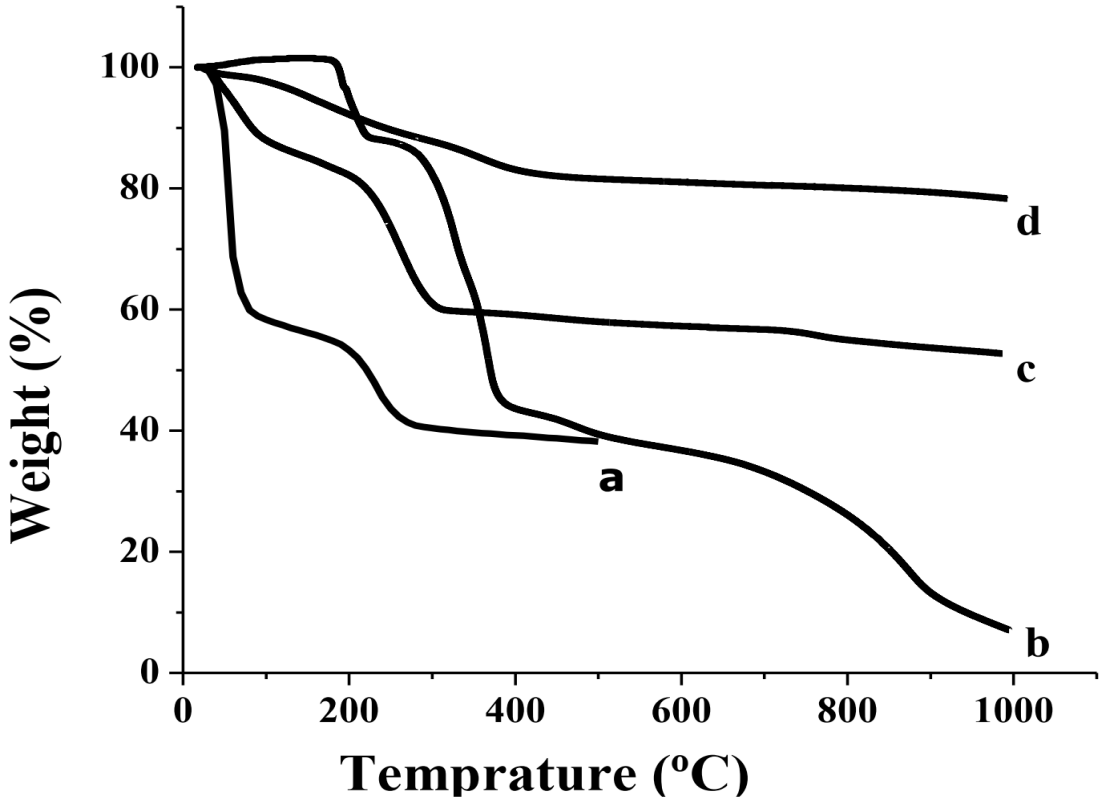

Fig. 5. TGA diagrams of (a) free ABZ, (b) immobilized ABZ, (c) oxidized MWCNTs and (d) TEOS.

TABLE 1. The particle size distribution analysis of the prepared materials using DLS technique.

Sample	Particle size (nm)
Ox-MWCNTs	241±30.49
ABZ	293 ±32.39
Immobilized ABZ	495±63.07

TABLE 2. TGA data of the prepared materials at temperature range 30-1000°C.

Temp. ^{0}C / Sample code	Weight loss % at different temperature			
	Room temp-147	147-345	345-455	> 455
TEOS	40.55	21.24	---------	----------
ABZ	-------	14.32	43.73	36.23
OX-MWCNTs	12.02	----------	----------	9.627
Immobilized ABZ	12.59	27.54	7.03	----------

Figure 5 and Table 2 show TGA diagrams and weight loss (%) data at temperature range 30-1000 ºC of the immobilized ABZ in comparison with the oxidized MWCNTs, TEOS and the free ABZ. It can be observed that Ox-MWCNTs exhibited high thermal stability (weight loss about 9.6% at > 455ºC), while, after ABZ immobilization, it had two decomposition steps. The first starts at 147-345ºC and the second one at 345-455ºC with weight loss about 27.5 and 7.0%, respectively. This may be due to the presence of ABZ molecules. Besides, these data confirmed that the successful ABZ immobilization onto oxidized MWCNTs using sol-gel technique was taken place *via* covalent bonds.

It can be concluded that immobilization of ABZ onto functionalized MWCNTs using sol-gel was taken place *via* covalent rather than adsorption technique.

In vitro kinetic released of the immobilized ABZ

The cumulative release profile of ABZ from the ABZ immobilized MWCNTs with different concentrations (50, 100, 150, 200, 250 and 300 mg/mL) is represented in Fig 6. It is noticeable that a biphasic release behavior with rapid initial burst phase. Besides, about > 50% of the drug was released from the formulation in the first 200 min followed by a slower and sustained release for the duration of the study. Such a release profile was previously reported for soyasapogenol B adsorbed onto MWCNTs functionalized with the modified montmorillonite [40]. Mathematical process of ABZ from the prepared formulations obeyed Higuchi release kinetics that had the highest correlation coefficient R (0.7346) compared to the other calculated mathematical models (Table 3).

In vitro cytotoxic study of the immobilized ABZ

The normal fibroblast cells were selected in order to investigate the potential safety of the formulation on the healthy cells. However, further studies may be required to examine the mode of action of each formulation.

Table 4 shows *in vitro* cytotoxic examination of the immobilized ABZ against BHK-21 normal cell line using SRB assay relative to the free drug. It was observed that the immobilized ABZ had low cytotoxicity (about 4.4 %) against BHK-21 cell line at concentration up to 100 µg/mL in comparison with that in the case of the free drug (77.8 %). These data proved that the oxidized MWCNTs did not increase the toxicity of the free ABZ drug. In other words, the cytotoxicity of ABZ could be retarded after immobilization onto MWCNTs.

TABLE 3. In vitro Kinetic released parameters of the immobilized ABZ using different mathematical models.

Sample	Q_{24h} mean± SE (%)	R^2 (mean ±SE)				
		Zero order	1st order	Higuchi	Kors-Peppas	Hixson
Immobilized ABZ	66.95±1.44	0.3201.5±	0.3591.7±	0.7341.5±	0.7191.2±	0.5271.6±

$Q_{24h:}$ percent of ABZ released after 24 h and R^2: Correlation coefficient.

TABLE 4. In vitro cytotoxic examination of the immobilized ABZ against BHK cell line using SRB assay relative to the free drug.

Conc. µg/ml / Sample code	% Dead cell			
	12.5	25	50	100
ABZ	21.1	63	76.3	77.8
Immobilized ABZ	1.5	2.9	3.7	4.4

Figure Captions

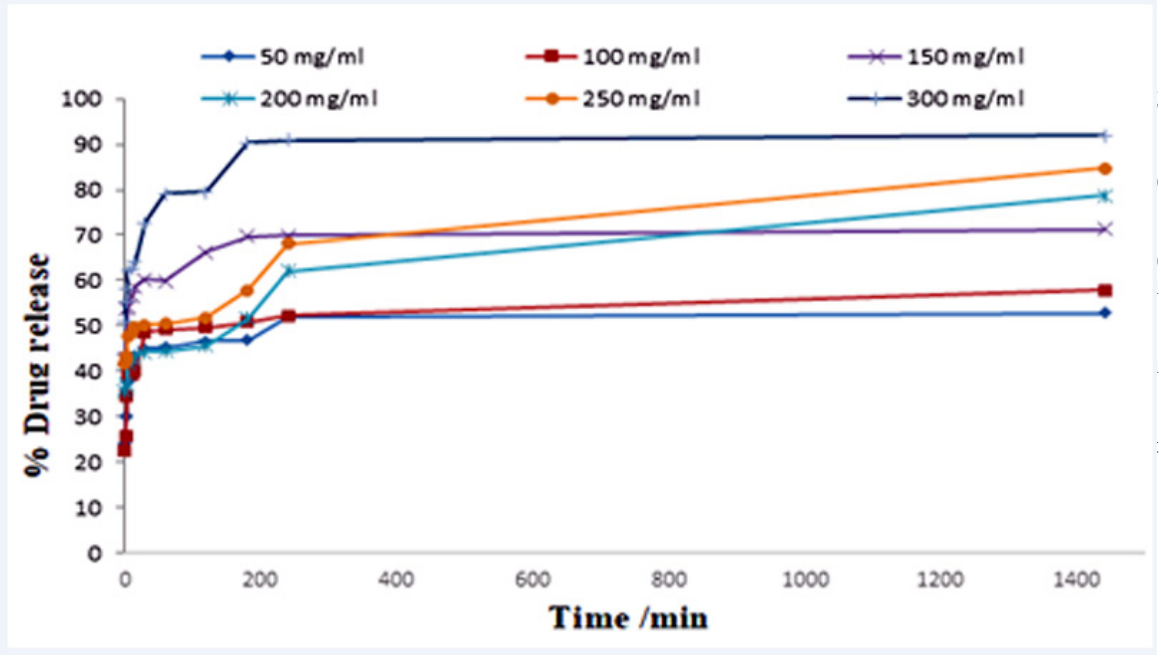

Fig. 6. In vitro ABZ released profiles at different concentrations in SGF at pH 2.5.

Conclusion

ABZ could be successful immobilized onto oxidized MWCNTs using sol-gel technique. Besides, FTIR, TGA, TEM and particle size analysis proved that ABZ was attached with the side chains of the oxidized MWCNTs via covalent rather than adsorption binding. The presence of the oxidized MWCNTs decreased the cytotoxicity of the immobilized ABZ against BHK-21 cell line. Moreover, the cumulative ABZ released profile exhibited a burst release behavior up to 50 % after 30 min at concentration about 300 mg/mL The oxidized MWCNTs can acts as a promising carrier for antihelmences drugs with low toxicity against normal cells. It is recommend to make further investigation in the future about several formulations of the different drugs using oxidized MWCNTs.

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تحضير بطريقة السائل الجيلاتيني ودراسة ديناميكية الإفراز في المختبر لألبيندازول محمل علي انابيب الكربون نانومتريه متعددة الجدران

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يهدف البحث إلي تحضير وتوصيف نظام جديد لتحميل الدواء مبني علي انابيب الكربون النانومتريه متعددة الجدران الوظيفيه بإستخدام البيندازول كنموذج للدواء بطريقة السائل الجيلاتيني. تم توصيف المواد المحضره بإستخدام مختلف اجهزة التحاليل مثل: الأشعه تحت الحمراء، الميكروسكوب الإلكتروني النافذ، التحليل الحراري الوزني وتحليل توزيع احجام الجزيئات بطريقة الضوء الديناميكي المشتت.

تم دراسة ديناميكية إفراز البيندازول المحمل في السائل المحاكي للمعده عند درجة أس هيدروجيني ٢,٥ ودرجة حراره ٣٧ درجه مئويه بإستخدام نماذج حسابيه متعدده. كذلك تم إختبار السميه الحيويه للدواء المحمل بالمقارنه بالدواء الحر بإستخدام نوع من الخلايا الفيبروبلاست الطبيعيه.

اثبتت نتائج الاشعه تحت الحمراء والثبات الحراري بالإضافه إلي حجم الجزيئات إمكانية تحميل دواء البيندازول علي انابيب الكربون النانومتريه متعددة الجدران بطريقه مبسطه. تم التقليل من تأثير إستخدام الاحماض المركزه في عملية الاكسده للأنابيب الكربون النانومتريه متعددة الجدران عن طريق إستخدام زيت الزيتون بدلا من حمض الكبريتيك المركز وإثبات ذلك بصور الميكروسكوب الإلكتروني النافذ. بالإضافه إلي تقليل السميه الحيويه للدواء المستخدم بعد التحميل بالمقارنه بالدواء الحر حتي تركيز ١٠٠ ميكروجرام لكل مللي.

أثبتت دراسة ديناميكيه الإفراز للدواء المحمل مع مرور الزمن سرعة الإفراز حوالي اكثر من ٥٠٪ خلال اول ٢٠٠ دقيقه ثم الإفراز البطيء ليوم كامل عند تركيز ٣٠٠ ملليجرام لكل مللي. ديناميكية الإفراز تتبع نموذج هيجوشي والتي تؤكد علي إتحاد جزء من الدواء المحمل علي جدران انابيب الكربون النامتريه متعددة الجدران.

الحصول علي تلك النتائج تشجع علي الإستمرار في إستخدام انابيب الكربون النامتريه متعددة الجدران الوظيفيه كأنظمة تحميل واعده في المستقبل للتقليل من الاثار الجانبيه وفتح افاق جديده لنماذج مختلفه من الدواء .