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CARBON NANOTUBE BASED POLYVINYLALCOHOL-POLYVINYLPYROLIDONE NANOCOMPOSITE HYDROGELS FOR CONTROLLED DRUG DELIVERY APPLICATIONS

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ABSTRACT

Controlled drug release systems present a significant alternative to the conventional drug dosages providing drug release for prolonged time periods. Nanocomposite hydrogels offer an important potential for drug release with enhanced physicochemical properties. In this study, the preparation of carbon nanotube (CNT)-based Polyvinylalcohol-Polyvinylpyrolidone (PVA/PVP) nanocomposite hydrogels namely, CNT-25, CNT-50 and CNT-100 were succeedded via the freeze/thawing method with the addition of different amounts of CNT. The nanocomposite hydrogels were characterized by swelling tests, SEM, FTIR, DSC and BET measurements. It was determined that CNT-50 was the most suitable hydrogel for drug release studies having better morphological properties with homogenous distribution of CNT throughout the polymeric nanocomposite matrix. The release of 5-fluororacil (5-FU) as a model drug was investigated in-vitro. The release of 5-FU from CNT-based PVA/PVP nanocomposite hydrogels was exhibited controlled release for one week at pH 7.4. The amount of released 5-FU was effectively increased with the addition of CNT into the hydrogel matrix. Korsmeyer-Peppas model was well fitted for determining the release mechanism of 5-FU from CNT-based PVA/PVP nanocomposite hydrogels corresponding the combination of diffusion of the drug and the dissolution of polymer chains.

Keywords: Drug release systems, Nanocomposite hydrogels, Carbon nanotube, PVA/PVP hydrogels

1. INTRODUCTION

Controlled drug release systems have received much attention enabling the sustained release of the drugs at determined rates for required time periods [1-3]. These release systems offer good alternatives with high efficiency providing the reduced toxicity and increased patient compliance to avoid the disadvantages of the conventional dosage forms [4]. Hydrogels have been utilized in many biomedical applications including drug release with their high biocompatibility, significant swelling characteristics and 3-D macroporous network structure [5-7]. Poly(vinylalcohol) (PVA) hydrogels can be prepared via physical cross-linking with freeze-thawing process resulting a flexible, macroporous, stable and strong gel matrix [8, 9]. In this method, there is no need to use any toxic chemicals such as cross-linkers and initiators. Thus physically-crosslinked PVA hydrogels present an excellent potential for the biomedical applications having high cytocompatibility [10]. Poly(vinylpyrolidone) (PVP) is another biomaterial that is widely used in biomedical applications due to its high biocompatibility and hydrophilic character [11]. The preparation of PVA/PVP hydrogels via freeze/thawing method and their various applications were reported elsewhere [12-16]. Recently, it has reached a tremendous importance in the development of novel systems with improved drug release profile and thus, hydrogel nanocomposites, which means the incorporation of the nanosized particles into the hydrogel matrix, have gained much interest since they enhance mechanical, physicochemical and drug release properties [17, 18]. Carbon nanotubes (CNT) are the most important components that are used in the composition of the hydrogel nanocomposites due to their remarkable mechanical, electrical and thermal properties and large surface area [19-21]. Also there have been many reports about the utilization of CNT as drug carriers indicating their potential for drug release systems with good biocompatibility [22-24]. Therefore the incorporation of CNT into the hydrogel structure has presented an attractive approach to develop CNT-based hydrogels as innovative drug delivery instruments [25].

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In this study, we report the preparation of CNT-based poly(vinylalcohol)/poly(vinylpyrolidone) (PVA/PVP) nanocomposite hydrogels for drug release applications. Firstly, these hydrogels were prepared via freeze/thawing method with different CNT compositions. In order to investigate the drug release profile of the hydrogels, 5-fluorouracil (FU) was selected as a model drug and was loaded into the nanocomposite hydrogel matrix. The nanocomposite hydrogels were characterized using swelling tests, SEM measurements, FTIR, DSC and BET analysis. The drug release mechanism was evaluated by fitting the experimental data to zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic model equations.

2. MATERIALS AND METHODS

2.1. Materials

Polyvinylalcohol (PVA) (Mw: 145000) was purchased from Merck. Polyvinylpyrrolidone (PVP) (Mw: 40000), multiwalled carbon nanotubes (10 nm x 4.5 nm x 4 μm) (CNT) and dimethyl-sulfoxide (DMSO) were obtained from Sigma. Potassium chloride, sodium hydroxide, hydrochloric acid, potassium dihydrogen phosphate and sodium chloride were utilized for adjusting the phosphate buffer solutions to pH 7.4 and all were obtained from Merck. The water used in the experiments was ultra-purified using Direct Q-3 purification system from Milipore (Molsheim France).

2.2. Synthesis of CNT-Based PVA/PVP Hydrogels

The CNT-based PVA/PVP hydrogels were synthesized using the same method described in our earlier publication for the preparation of PVA/PEG hydrogels via freeze/thawing [26]. Briefly, PVA was dissolved in distilled water to prepare 5 % aqueous solution by using a magnetic stirrer for 2 h at 90 ºC and then the solution was slowly cooled to room temperature. 5 % solution of PVP was prepared at room temperature. Then, CNT was stirred in the solution of H_2O/DMSO (3:1, v/v) for 4 h [27]. The polymer solutions were mixed under magnetic stirring at room temperature for 2 h. The mixture was placed on the 24-well plate. The blend solution was directly kept frozen at -16 ºC for 16 hours. Afterwards, the frozen hydrogels were thawed at room temperature for 8 hours. This process of freeze/thawing was repeated for 5 times. Table 1 shows the feed composition for preparation of the hydrogels. To remove unreacted polymers, water changed with fresh water periodically for four days.

Table 1. The feed composition for preparation of the hydrogels

Code	PVA, %	PVP, %	CNT, mg
PVA/PVP	5	5	-
CNT-25	5	5	25
CNT-50	5	5	50
CNT-100	5	5	100

2.3. Characterization of CNT-based PVA/PVP hydrogels

The swelling behavior of the dried samples were observed in pH 7.4 buffer solution at 37 °C. A known disc samples were put into shaker water bath fixed at 50 rpm. The samples were taken out from the buffer solution, swollen hydrogels were filtered and weighed. The water content of the hydrogels were determined according to the following eqution:

$$\text{Swelling \%} = \frac{\text{Ws-Wd}}{W_d} \text{x} 100 \quad (1)$$

where W_s and W_d represent the weighs of swollen and dried state samples respectively.

Synthezised hydrogels were also characterized using scanning electron microscopy (SEM) measurements with Quanta Feg 650 scanning electron microscope. The chemical structure was determined by Fourier transform infrared spectroscopy (FTIR) (FTIR 8000 Series, Shimadzu, Japan). The glass transition temperatures (T_g) of the samples were identified using Differential Scanning Calorimetry (DSC) analysis. The experiments were performed using Shimadzu DSC-60H. The samples were heated at 10 °C/min between 25 °C and 160°C in nitrogen atmosphere. The specific surface area measurements were carried out by Brunauer–Emmitt–Teller (BET) method (Quaniochome, Autosorb IQ).

2.4. Drug Loading and Release Behaviour

To investigate the drug release behavior of the hydrogels, 5-FU was chosen and used as a model drug. The experiments of 5-FU loading onto the nanocomposite hydrogels were carried out in distilled water using 500 mg/L of 5-FU aqueous solution for 2 days. Amount of drug loading was determined spectrophotometrically at 266 nm using Shimadzu UV-1800.

For release experiments, dried hydrogel discs containing 5-FU were placed in shaker water bath 20 mL buffer solutions pH 7.4 at 37 °C and 50 rpm. At determined time, 0.5 mL of buffer solution was taken from the release medium, and 0.5 mL of buffer solution was put into the drug release medium.

$$\text{Cumulative release (\%)} = \frac{C_n V + \sum_{i=1}^{i=n-1} C_i V_i}{m} x100 \quad (2)$$

where V is the drug solution volume (mL), V_i is the sample volume (mL), m is the hydrogel weight (mg), C_n and C_i are the initial drug concentration and concentrations in the drug releasing medium at determined time interval respectively. All the data were repeated in triplicate.

3. RESULTS AND DISCUSSION

3.1. Characterization

To determine the effect of the amount of CNT on the swelling behavior of the hydrogels, the swelling characteristics of the nanocomposite hydrogels were investigated and listed in Table 2. The results demonstrate that the addition of CNT into the PVA/PVP hydrogels increased the swelling percentage with increasing the amount of CNT. The reason for this was caused by the incorporation of CNT into the polymeric matrix leading higher surface area. However, the water uptake of CNT-100 was lower than that of CNT-50 hydrogels since the distribution of CNT was heterogeneously distributed throughout the hydrogel matrix. These results are confirmed with the results reported elsewhere [21].

Table 2. The swelling percentages of PVA/PVP and CNT based hydrogels

Polymer	% Swelling
PVA/PVP	237.2 ± 14.2
CNT-25	241.9 ± 15.5
CNT-50	357.2 ± 9.9
CNT-100	272.6 ± 12.6

The SEM images of PVA/PVP and CNT-based PVA/PVP hydrogels were demonstrated at Figure 1. It was seen that PVA/PVP hydrogels showed porous structure indicating the gelation via the freeze/thawing procedure. Figure 1.B showed the incorporation of CNT into the PVA/PVP hydrogels. CNT-25 hydrogels showed homogenously distributed and porous structure presenting a good alternative for the drug release carrier systems. CNT-50 hydrogels demonstrated homogenously distributed and porous morphological properties but a more smooth structure than CNT-25 hydrogels. However it was observed that in the CNT-100 hydrogels matrix structure non-homogenous accumulation resulting a

non-uniform distribution of carbon nanotubes through the hydrogel matrix. Therefore CNT-50 hydrogels were selected to use for the further studies due to the proper morphological structure.

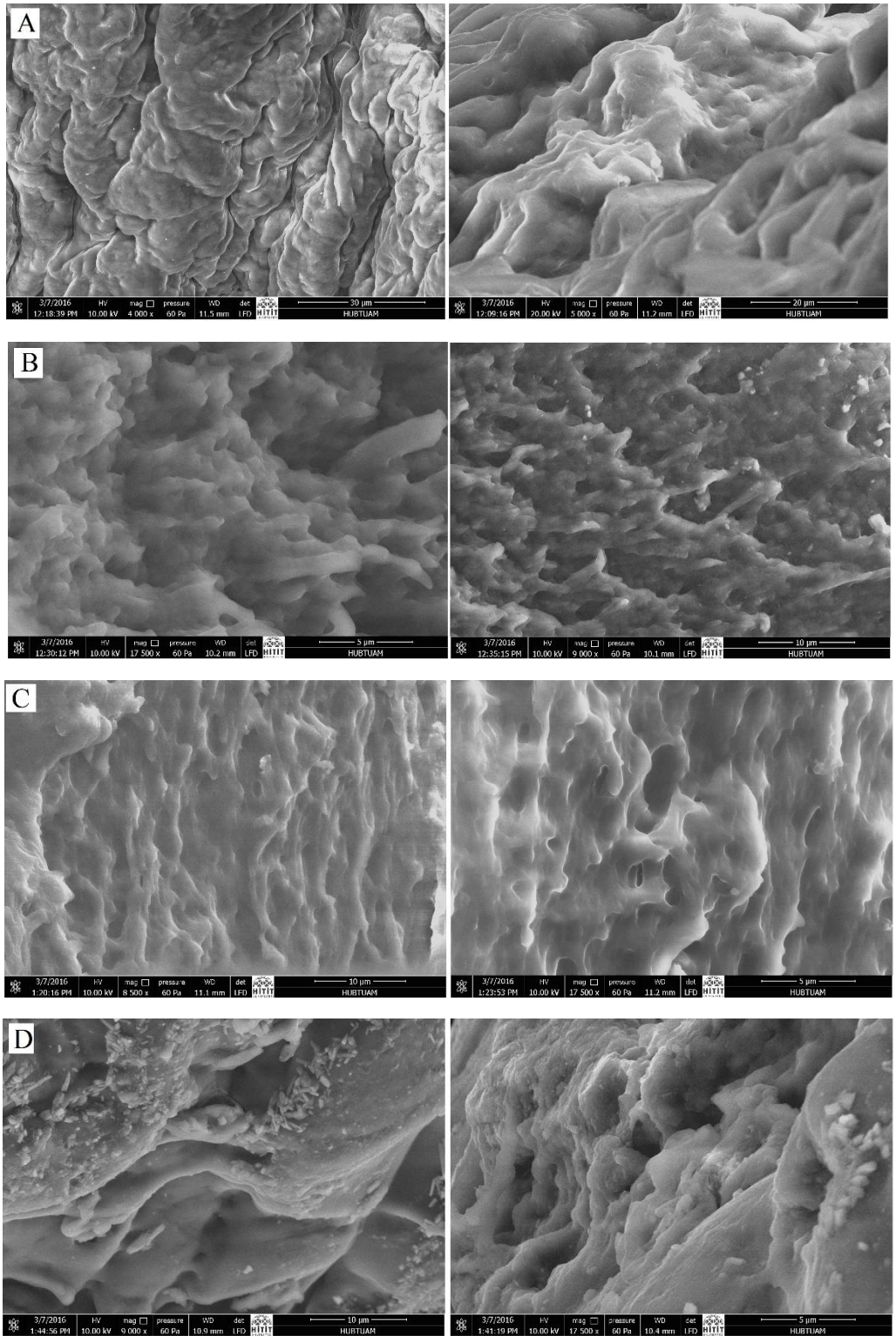

Figure 1. SEM images of PVA/PVP hydrogels. A.) PVA/PVP, B.) CNT-25 hydrogel, C.) CNT-50 hydrogel, D.) CNT-100 hydrogel.

The FTIR spectrum of PVA/PVP and CNT-50 hydrogels were demonstrated in Figure 2. The intensity of the bands at around 3300 cm^{-1} and 2915 cm^{-1} was decreased with the addition of CNT to the polymeric structure. The intensity of the band at 1650 cm^{-1} was increased with the incorporation of CNT through the hydrogel matrix attributed to the formation of C - C band between CNT and polymer chains. The new bands at 2941 cm^{-1}, 1420 cm^{-1} and 1138 cm^{-1} were appeared and the broad band at 1083 cm^{-1} was disappeared. All these changes in the spectrum was due to the presence of the CNT in the polymeric hydrogel structure [28].

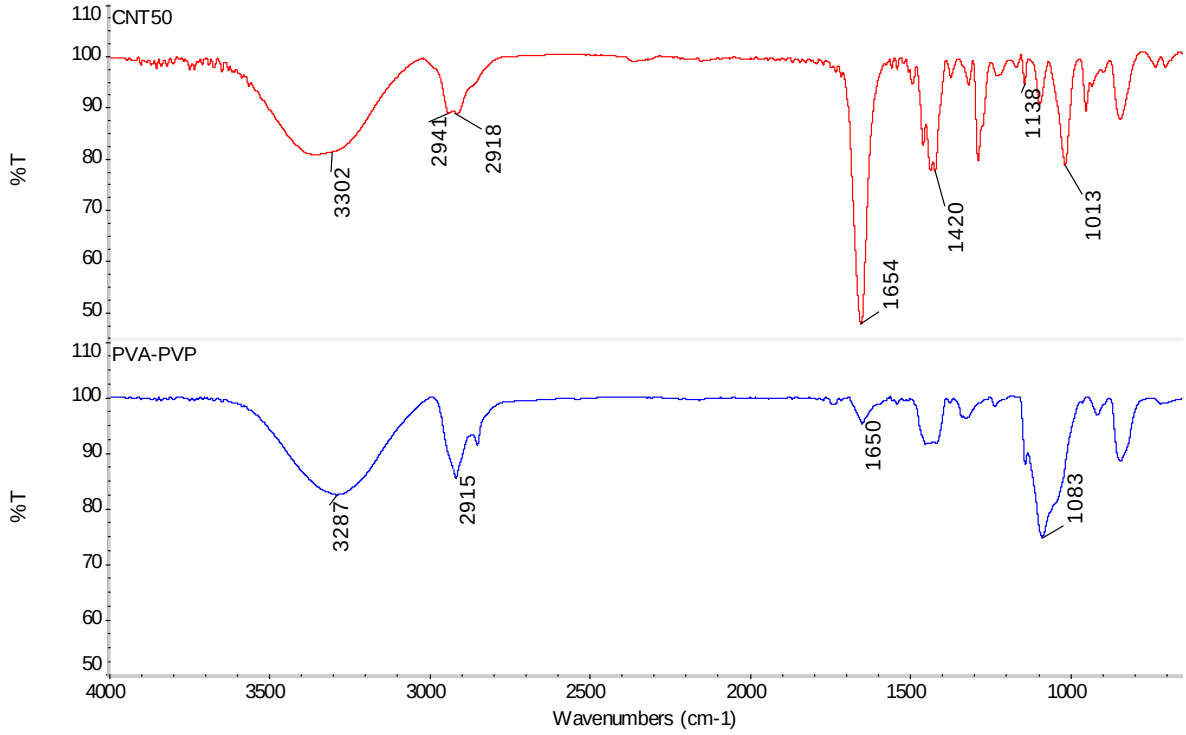

Figure 2. FTIR spectrum of PVA/PVP and CNT-50 hydrogels

DSC analysis is one of the most common methods for the determination of chemical structures of polymeric materials. Figure 3 shows the profiles of DSC curves of PVA/PVP hydrogel and CNT-50 hydrogel. It was observed a large melt peak at around 230 °C for PVA/PVP hydrogels and at around 225 °C for CNT-50 hydrogels indicating the significant influence of CNTs for the crystallization of polymers. The reason for this is the increase in the crystallinity of the nanocomposite hydrogels where CNT acts as nucleation sites for the polymer-carbon nanotube interactions. The values of T_g of PVA/PVP and CNT-50 hydrogels were calculated as 126.426 ˚C and 144.115 ˚C respectively. The results show that the incorporation of CNT was successfully achieved.

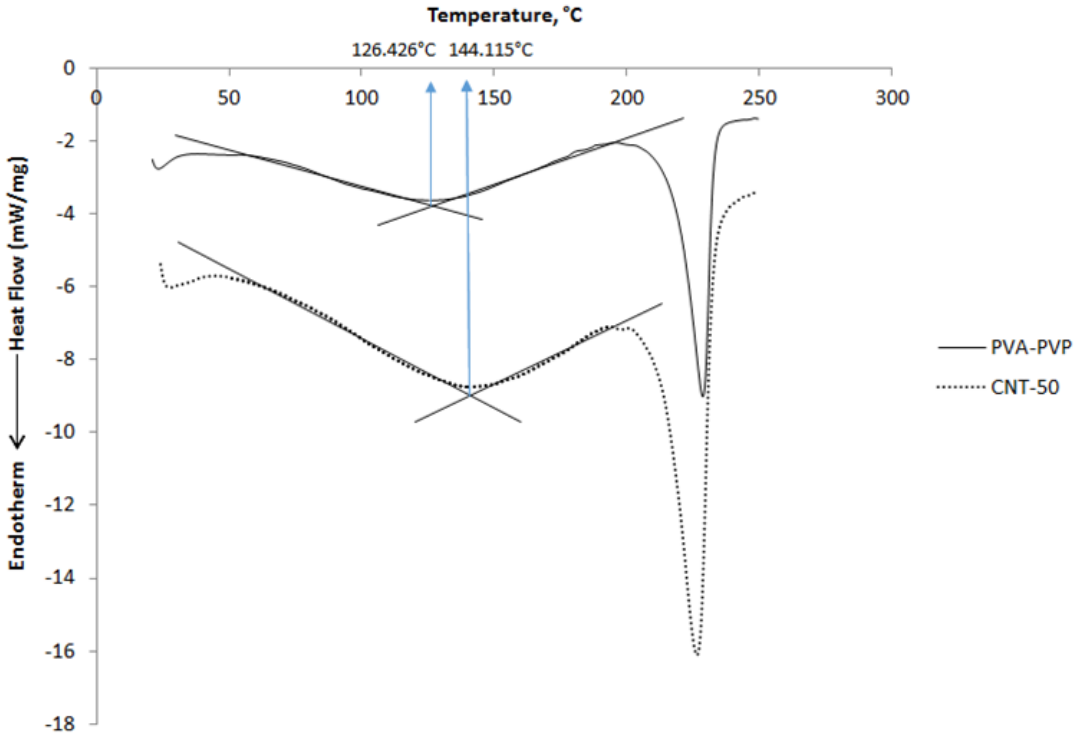

Figure 3. DSC curves of PVA/PVP and CNT-50 hydrogels

The large surface area is one of the important parameters for drug delivery applications. The incorporation of the nanomaterial is a general approach to enhance the surface area of the hydrogels. There have been many reports about the nanocomposite hydrogels with improved surface area [29, 30]. In this study, it was determined due to the results of BET analysis that the surface area of CNT-50 hydrogel was increased by 42 % with respect to PVA/PVP hydrogel with the incorporation of CNT to the hydrogel structure.

3.2. Drug Loading and Release Tests

The loading experiments of 5-FU as the model drug were performed ex-situ using the drug solution of 500 ppm at room temperature. It was found that the loading efficiency of the 5-FU onto CNT-50 hydrogel was higher than that of PVA/PVP hydrogels. It was obtained that the presence of CNT increased 5-FU loading capacity via π-π interactions. These results are in parallel with the results obtained from surface area measurements.

The in-vitro 5-FU release tests were performed at 37 °C at pH 7.4. The in-vitro release profiles were determined by plotting the cumulative release of the drug with respect to loaded amount of the drug. As shown in Figure 4, it was found that the cumulative released amount of 5-FU from the CNT-50 hydrogel (93 %) was higher than that of PVA/PVP hydrogel (43 %) after 144 h. The release of 5-FU from the CNT based hydrogels could be fitted to 3 regions. In the first region that is between 1 and 6 h, second region from 6 h to 72 h and the last region between 72 h and 144 h. In the first region, initial burst release was observed with 38 % of the drug was released from PVA/PVP hydrogels indicating the weak performance of this material for drug release applications. The cumulative release of 5-FU from CNT-50 hydrogels was only 25 % in this time period indicating the prevention of burst release of 5-FU by introducing of CNT into the hydrogel structure. In the second region, the prolonged and slow release of the drug from CNT-50 hydrogels was determined which attributes to the presence of CNT. In the last region, the cumulative release of 5-FU from both hydrogels remains constant.

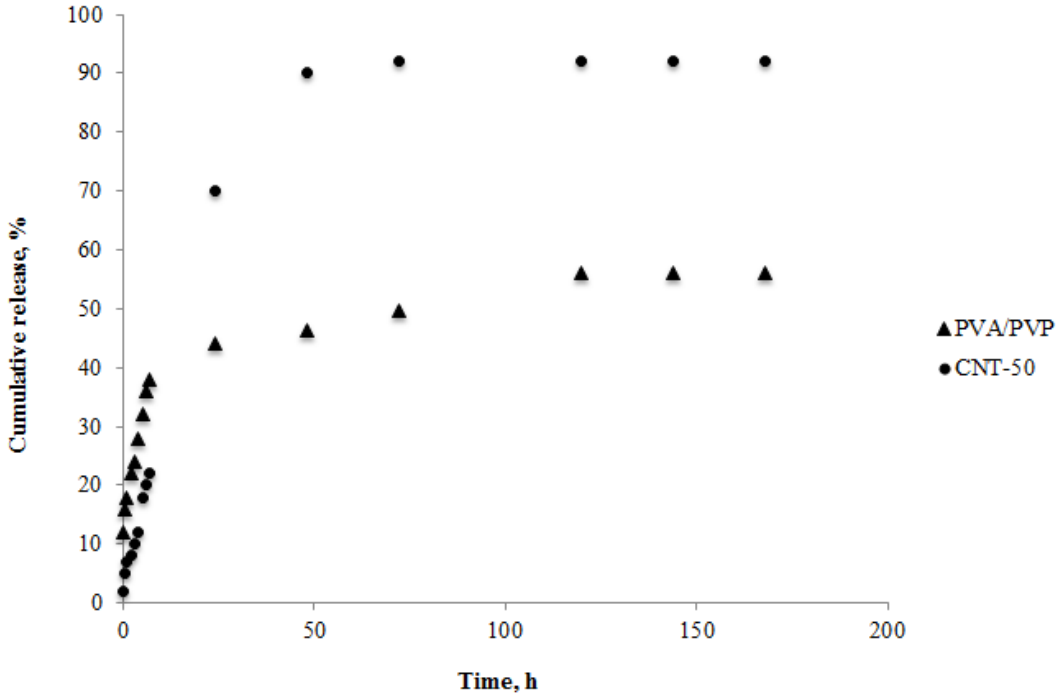

Figure 4. The release profiles of 5-FU of CNT-50 and PVA/PVP nanocomposite hydrogels

The comparison of percentage of cumulative release and release time of the drug delivery polymeric systems including CNT reported in the literature and listed in Table 3. The cumulative release percent of multi-walled CNT/PVA composites after 12 h was reported as 30 %. The composites were prepared via aqueous mixing and they wee used for the release of diltiazem for patch therapy [30]. PVA/PAA/multi-walled CNT nanofibers were prepared via electrospinning and utilized for the electro-responsive transdermal ketoprofen release. It was determined that the cumulative release percent was found as 90 % after 10 h [31]. The pH-responsive and electro-responsive microcapsules were developed with multi-walled CNT and PVA. After the composite microcapsules were modified using oxyfluorination, the fabrication of composite microcapsules was increased due to the hydrophilic functional groups. The cumulative drug release was defined as 80 % after 30 h period [32]. It was reported that the cumulative release was achieved as 85 % after 10 h with polyethylene oxide/pentaerythritol triacrylate/multi-walled CNT electrospun nanofibers [33]. It was seen that the percentage of cumulative release and release time obtained in this study are comparably higher than that of the results reported in the literature. Also it was determined that the controlled drug release of 5-FU was achieved with CNT-50 hydrogels indicating the strong interactions between drug molecules and composite hydrogels.

Table 3. The drug delivery polymeric systems including CNT reported in the literature

Polymer content	Cumulative release percent, %	Release time, h	Reference number
PVA	30	12	[31]
PVA and PAA	90	10	[32]
PVA and PAA	80	30	[33]
PEO	85	10	[34]
PVA and PVP	93	144	This study

PAA: polyacrylic acid, PEO: polyethylene oxide

3.3. Mathematical Modeling

The 5-FU release mechanism from PVA/PVP and CNT-50 hydrogels was determined with 4 different release kinetic models, which are zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic models [35, 36]. The zero-order kinetic model describes the systems, which are not related to the drug concentration while the first-order kinetic model defines the systems, which depend on drug concentration. Higuchi model proposes the correlation of drug release to square root of time and related with Fickian diffusion. Korsmeyer-Peppas kinetic model describes the drug release from swelling-controlled systems. In this model, n indicates the information about release mechanism of the drug, which the drug release kinetics model fits to Fickian/diffusion model when n approximates to 0.5, non-Fickian model when n is between 0.5 and 0.85 and case II transport model when n is 1 respectively [37]. The release parameters of these kinetic models were listed in Table 4. It was seen obviously that Korsmeyer-Peppas model fitted the most to the both PVA/PVP and CNT-50 hydrogel systems due to the correlation coefficients of the applied kinetic models. It was observed that the 5-FU release from PVA/PVP hydrogels fitted to Fickian release behavior indicating that the dominant factor for drug release was swelling of the polymeric hydrogels. The release mechanism of 5-FU from CNT-50 hydrogels followed the non-Fickian release model indicating the 5-FU release was governed by the combination of diffusion of the drug and the dissolution of polymer chains.

The drug release profiles of PVA/PVP and CNT-50 hydrogels were evaluated using different mathematical drug release models, which are explained in detail below:

The zero order model is presented as:

$$q_t = q_0 + k_0 t \tag{3}$$

where q_t is the amount of drug released in time t, q_o is the initial amount of drug in the solution (usually $q_o = 0$), k_o is the release rate constant of zero order kinetic model, and t is the drug release time.

The first order model is expressed as:

$$\mathrm{In}(q_t) = \mathrm{In}(q_0) - k_1 t \tag{4}$$

where q_t is the amount of drug dissolved in time t, q_o is the initial amount of drug in the solution, and k_1 is the first order release rate constant.

The Higuchi model is formulated as:

$$q_t = k_H \sqrt{t} \tag{5}$$

where q_t is the amount of drug released in time t, and k_H is the release rate constant of Higuchi kinetic model.

Korsmeyer-Peppas model is presented as:

$$q_t / q_\infty = k_k t^n \tag{6}$$

Table 4. The release parameters of CNT-50 and PVA/PVP nanocomposite hydrogels

Polymer Code	Zero order equation		First order equation		Higuchi equation		Korsmeyer-Peppas equation		
	k_0	R^2	k_1	R^2	k_H	R^2	n	$1.11k_k$	R^2
PVA/PVP	0.0150	0.472	0.0092	0.496	0.472	0.978	0.223	1.11	0.952
CNT-50	0.0438	0.732	0.0257	0.575	0.687	0.805	0.624	12.7	0.974

4. CONCLUSION

The nanocomposite hydrogels have been gaining more attention with enhanced physicochemical characteristics for drug release systems. In this study, CNT-based PVA/PVP nanocomposite hydrogels were prepared via freeze/thawing method and their performances for drug release were also evaluated using 5-FU as a model drug. As regards to drug release behavior, CNT-based PVA/PVP nanocomposite hydrogels and PVA/PVP nanocomposite hydrogels were compared and the contribution of CNT to enhance the effect of controlled release of hydrogels was determined. It was found that Korsmeyer-Peppas release kinetic model was fitted well to of CNT-based PVA/PVP nanocomposite hydrogels. The release mechanism of CNT-based PVA/PVP nanocomposite hydrogels was determined as non-fickian diffusion. It was concluded that the nanocomposite hydrogels prepared in this work offer great potential for drug release applications.

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