Experimental investigation of thermal conductivity of medical nanofluids based on functionalised single-wall carbon nanotube and conjugated cisplatin

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Thermal engineering parameters such as thermal conductivity (TC) can play an important role in developing medical nanofluids with improved stability and better drug release. In this reported work, an engineering perspective is strategised for the development of medical nanofluids containing functionalised single-wall carbon nanotubes and conjugated cisplatin. These nanofluids were developed by two biocompatible phospholipids. For the first time, the change in TC values of this medical nanofluid was investigated. The change in the drug release was examined before and after dialysis with change in pH and temperature, *in vitro*. It was found that an increase in temperature leads to higher TC and a decrease in pH provides better thermophysical conditions for the drug release. These findings strongly suggest that TC could be an important parameter in the development of medical nanofluids for cancer treatment.

1. Introduction: Medical nanofluids are new types of nanosuspensions with significant improvements in some physical and chemical properties. They include carbon nanotube (CNT) suspensions that have been recently utilised by researchers. Because of some extraordinary intrinsic properties of CNTs, researchers have found many applications in medical and biological sciences, especially in biological imaging, detection and therapy [1–4].

There are some physical and chemical methodologies for the preparation of nanofluids, suggested and applied by researchers. The ultrasonic technique and ball milling process are the commonly utilised physical methods [5–8]. Alternatively, among the chemical methods, polymer wrapping and functionalisation techniques are commonly used by researchers, for instance, PEGylation of the CNT surface and film preparation [9–11]. These methods help us to have a counterbalance between electrostatic repulsions and Van der Waals attraction forces and also have a better dispersion of nanoparticles in base fluids [12, 13].

Covalent functionalisation of the CNT surface is considered as another chemical method. The most commonly used covalent functionalisation is through oxidative treatment which attaches oxidised functional groups to the CNT surface, such as carboxylic groups [14–16]. This increases the CNTs solubility, because of the generation of a more hydrophilic surface structure, which in turn reduces agglomeration of CNTs [17]. The carbon nanohorn as another type of carbon nanostructure is also utilised in medical sciences. Ajima *et al.* [18, 19] used the oxidised carbon nanohorn for better dispersion in solvent and entrapped the cisplatin (CP) drug using nanoprecipitation inside the carbon nanohorns.

This type of functionalised CNTs helps us to carry a wide range of drugs, RNA and DNA [20, 21]. The main advantage of this process is that we can increase the permeation and retention (EPR) effect of macromolecules in the tumour region because of the greater tendency of nanoparticles and macromolecular drugs to accumulate in tumour tissue compared with normal tissues [21].

It has been proven that CNT nanofluids take advantage of higher thermal conductivity (TC) over metal and metal oxide materials [22–25]. Initially, Choi *et al.* [22] measured the TC properties of CNT nanofluids by taking the effective TC of CNT dispersion in synthetic poly (α-olefin) oil, wherein they reported an increase of 160% in the TC value. This parameter can be used as an important factor to improve the thermal ability of medical nanofluids, especially in thermal ablation, when we decide to destroy tissue by the application of heat on tumour cells. The sensitivity of cancer tissues to induced heat is more than that of normal tissues [26].

Here, a new medical nanofluid has been developed, which can be used as a drug delivery system using oxidised SWCNTs (OX-SWCNTs) as a drug carrier and CP as an anticancer drug. The same formulation containing non-OX-SWCNTs was used as a control. Further, complexes were then covalently linked to CP molecules followed by dialysis to remove unlinked CP. Oxidised and non-oxidised supermolecular SWCNTs were characterised by different methods. Lastly, TC values and pH were used to determine the changes in the thermophysical properties of CP medical nanofluids and its drug release behaviour. These results can be applicable and effective in improving the performance of CP in cancer therapy.

2. Materials and methods

2.1. Materials: Purified SWCNTs of 100–1000 nm in length and 0.8–1.2 nm in diameter, prepared by a high-pressure CO conversion (Hipco) method, were purchased from the Nanointegris Company (USA). Two phospholipids have been used, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol) – 2000] (DSPE-PEG2000) and 1,2-dioctadecanoyl-sn-glycerol-3-phospho-1′-rac-glycerol (DSPG) were purchased from Avanti Polar Lipids Inc (Alabaster, AL, USA). The CP drug was obtained from the Tocris Company (USA). All other chemicals were purchased from Sigma-Aldrich without any further treatment.

2.2. Preparation of medical nanofluid:
First step: The surface of the nanotubes was first carboxylated by refluxing SWCNTs in a concentrated HNO_3–H_2SO_4 solution (3:1 v/v) at 70°C for 24 h. Then, several short-time bath sonications (Bandelin, Germany) were applied to disentangle the SWCNTs from each other. The suspension was centrifuged at 5000g with double-distilled water to naturalise the suspension and remove the impurities of the final product. Afterwards, the 0.45 μm pore-sized membrane filter was used to remove the aggregates. Finally, the solvent was filtered using a Whatman filter and then the SWCNTs were dried under vacuum at room temperature overnight. The OX-SWCNTs were stored at room temperature in a dry place for further use.

Second step: The π–π stacking and Van der Waals interactions of aromatic groups were utilised to increase the water solubility and better dispersion of the CNTs [9, 27, 28]. This process also leads to reducing the complex cytotoxicity. Furthermore, polymer wrapping will enable the formulation to delay their evacuation by the immune system, which is crucial for drug delivery of the anticancer drug [9].

Hence, the OX-SWCNTs were sonicated in an aqueous solution containing 1 mg OX-SWCNTs: 2.5 mg DSPG: 2.5 mg DSPE-PEG2000: 10 ml of water for 2 h (PL-OX-SWCNT). Similarly, non-oxidised polymer-wrapped SWCNTs were prepared (PL-SWCNT). The DSPG was used because of the effective negative charge of this phospholipid. CP molecules also have an electrostatic attraction with the DSPG. The suspensions were then centrifuged at 24 000*g* for 2 h, yielding well-suspended PL-SWCNTs and PL-OX-SWCNTs in the supernatant. Unbound phospholipids were removed by repeated filtration through 100 kDa Amicon centrifugal filters (Millipore, USA). Owing to the type of nanoplatform preparation and several purification techniques that we used before conjugation to CP, the weight concentration of SWCNTs was changed during this process. Therefore, it was not possible to control it carefully and this value was measured using a thermogravimetric analyser (Shimadzu Model TGA-50). Results show that the weight concentrations of the SWCNTs were about 0.034 and 0.032 mg/ml for the PL-SWCNT and PL-OX-SWCNT formulas, respectively.

Third step: Covalent linking of PL-SWCNTs and PL-OX-SWCNTs with CP. PL-SWCNTs and PL-OX-SWCNTs (0.5 ml) were sonicated in an ultrasonic bath for 15 min. Afterwards, 0.5 ml of CP solution with a concentration of 1 mg/ml was slowly added to the two mentioned constructs. These complexes were placed on a magnetic stirrer to react with each other at room temperature for about 24 h. The suspensions were then transferred into dialysis bags (MWCO: 4–6 kDa) and the end-sealed bags were submerged in 200 ml of phosphate buffer saline (PBS) (pH 7.4) and were stirred at 100 rpm and 37°C in the dark. At several intervals, the exchange medium was replaced with an equal volume of a fresh medium. The preparation process of the medical nanofluids is schematically shown in Fig. 1. Each step of production is shown in the Figure. Finally, TC measurement was used to determine the alteration of the TC values before and after dialysis. Henceforth, the PL-SWCNT and PL-OX-SWCNT loaded by CP are referred to as PL-SWCNT–CP and PL-OX-SWCNT–CP, respectively.

2.3. Instrumentation: Transmission electron microscopy (TEM) images were obtained using a LEO 912 AB electron microscope (Japan) operated at 120 kV. The Fourier transform infrared (FTIR) spectrum was recorded on a Nicolet FTIR-5DX spectrometer using KBr pellets. A thermogravimetric analyser (Shimadzu Model TGA-50) was used to measure the weight concentration of the CNTs. The UV–Vis spectrophotometry measurements were carried out in the range of 200–800 nm using a UV-1700 Pharmaspec (Shimadzu, Japan) system. The dynamic light scattering technique using a Malvern Zetasizer Nano ZS (Malvern, UK) was used to measure the particle size (nm) and zeta potential (mV). The zeta potential was evaluated by the loading of 20 µl of samples and 980 µl of MOPS buffer (10 mM) as diluent into a culvert [29].

TC measurement was done by a transient hot-wire instrument that was designed in another project. This method is known to be an accurate technique for measuring the TC of fluids. The details are elaborated elsewhere by Habibzadeh *et al.* [30].

3. Results and discussion

3.1. Characteristics of OX-SWCNT

3.1.1 Size: Fig. 2*a* shows the range of nanotube lengths (50–800 nm), which are covered with a high density of functional groups. The cutting sections are indicated by arrows. One advantage is

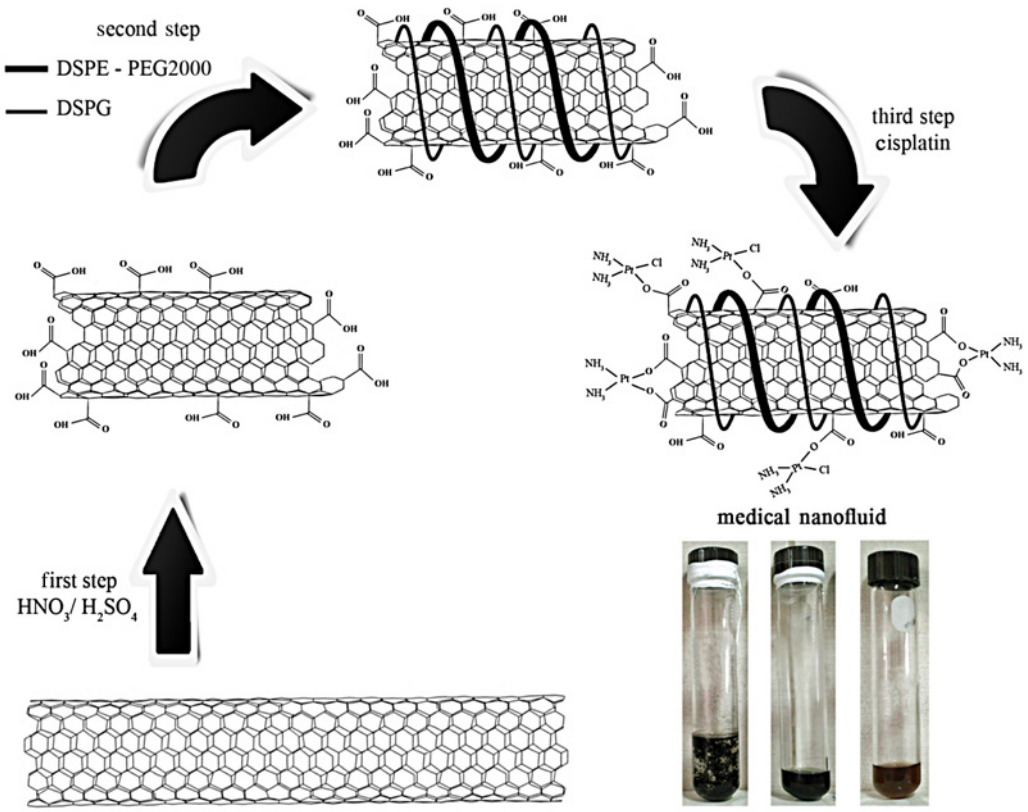

Figure 1 *Schematic preparation process of medical nanofluids*

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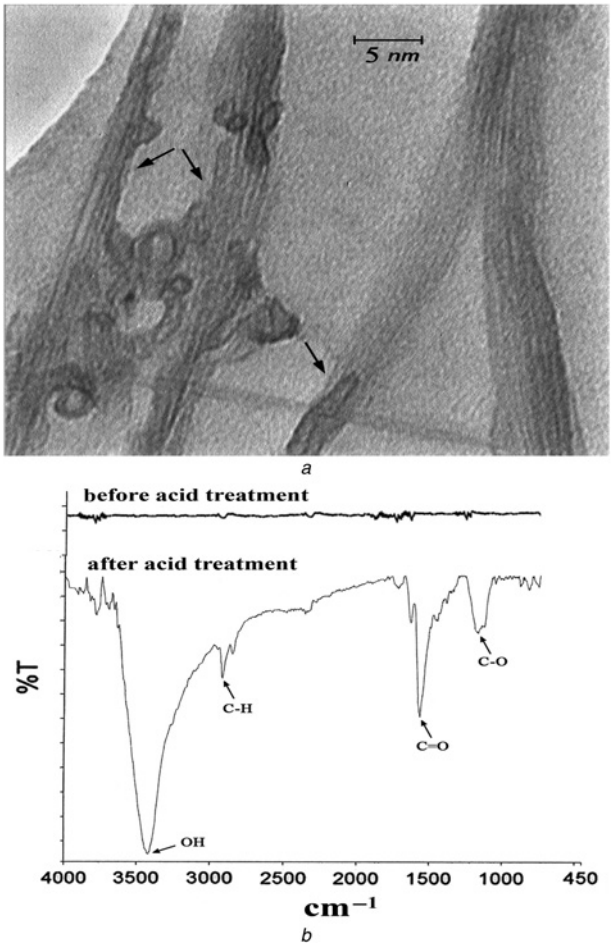

Figure 2 *TEM image of SWCNTs after acid treatment (Fig. 2a) cutting sections indicated by arrows); FTIR spectra of SWCNTs before and after acid treatment (Fig. 2b)*

that the presence of the functional groups possibly reduces Van der Waals interactions between SWCNTs, resulting in disentangling the nanotube bundles. Accordingly, a slight increase in the solubility of the aqueous tubes is achieved. In addition, polyethylene glycol is used as a hydrophilic polymer to enhance the water solubility of the CNTs.

3.1.2 FTIR spectroscopy: FTIR spectroscopy was used to evaluate the surface functional groups of CNTs after acid treatment. Fig. 2*b* displays the FTIR spectrum of the OX-SWCNTs. Because of carbonyl stretching of the carboxylic group, the treated OX-SWCNTs show the absorption band at 1590 cm^{-1}. The broad line at 3420 cm^{-1} and the line at 1170 cm^{-1} show the –OH stretching mode of the –COOH group and C–O bonds and the two clear peaks at 2878 and1180 cm^{-1} indicate the C–H and C–O stretching vibrations, respectively. Therefore, this spectrum shows that the chemical treatment process provided the suitable nanoplatform of oxidised SWCNTs for the attachment of the CP drug.

3.2. Medical nanofluid characteristics

3.2.1 UV–Vis: The presence of CP was checked in the final formulation by UV−Vis spectrometry. These results show CP loading before (B) and after (A) dialysis (Figs. 3*a* and *b*). The CP loading on SWCNTs was indicated by the absorption peak centred at 210 nm. This peak emerged from the PL-OX-SWCNT–CP spectra; however, it disappeared in the PL-SWCNT–CP ones after dialysis, indicating increased CP attachments to the PL-OX-SWCNTs rather than to PL-SWCNTs. It should be noted

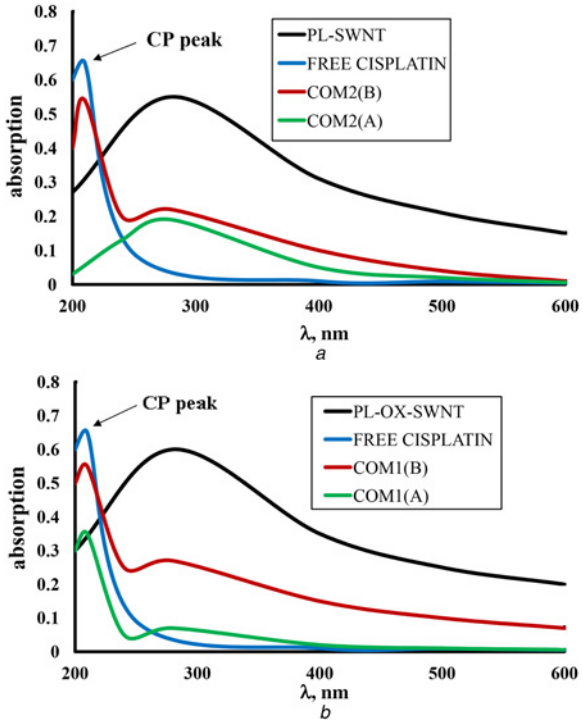

Figure 3 *UV–Vis spectra of PL-SWCNT (Fig. 3a) and PL-OX-SWCNT conjugated to CP before (B) and after (A) dialysis (Fig. 3b)*

that a low concentration of platinum for the PL-SWCNT–CP was detected in AAS experiments in the next step which was in contradiction with the UV results. The main reason for this phenomena is yet unclear, but it may be because of two reasons: (i) the different binding type of platinum in these two systems and (ii) the low accuracy of the UV test for this experiment. CP can join electrostatically to the negative charge of the DSPG phospholipid and also entrap inside the CNTs in these complexes. However, the main part of CP molecules will release after dialysis. Therefore, we can only be sure that the covalent bonding is the main reason for CP conjugation in the PL-OX-SWCNT complex.

3.2.2 Particle size and zeta potential: The particle size distribution at 25°C for the CNT medical nanofluids was measured for oxidised and non-OX-SWCNT complexes. It can be ascertained that the overall trend is the same for all the samples and there is no dramatic difference between them. A bimodal distribution was observed at all figures that present two populations of particle sizes (not shown). The small range (7–25 nm) is related to cross-sectional area that is not real and the large one (200–800 nm) is related to the longitudinal perspective of the complex. Adjacent endothelial cells of blood vessels in tumour tissues have gaps between 170 and 800 nm. These gaps allow the nanoparticle complex to extravasate into extravascular spaces using the EPR effect and accumulate in tumour tissues [31]. Effective wrapping of CNTs provides two advantages for targeting with EPR mechanism. Firstly, it leads to the increase in circulation half-life in the blood vessels. Secondly, it is not eliminated by the renal excretion system.

The zeta potential analysis was applied to study dispersion and CP linkage to the CNT platform. The negative charge of carboxylic groups on the surface of treated SWCNTs was measured after acid treatment (−43 mV). By shifting the pH to alkaline values, the zeta parameter decreased, because of the deprotonation of carboxylic groups. These values tended to −25.1 and −41 mV after wrapping of SWCNTs and OX-SWCNTs by DSPE-PEG2000 and DSPG phospholipids. The significant change was observed after the addition of CP to the reaction flask and the zeta potential tended

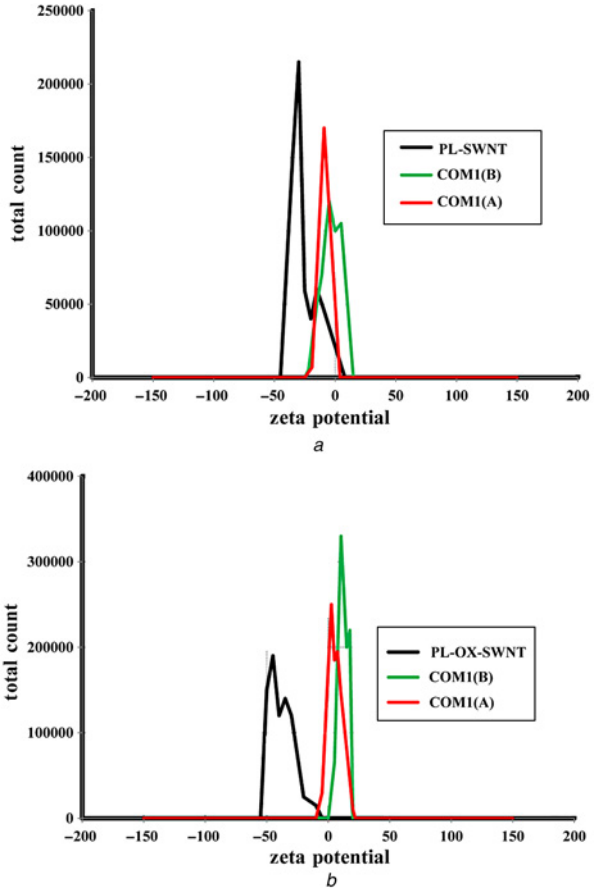

Figure 4 *Zeta potential of PL-SWCNT (Fig. 4a) and PL-OX-SWCNT (Fig. 4b) attached to CP before (B) and after (A) dialysis*

towards positive values. Figs. 4*a* and *b* show this change before and after dialysis. AAS is applied to analyse the CP concentration before and after dialysis. In a similar concentration of SWCNTs, the results of the data analysis showed that the amount of CP in PL-OX-SWCNT–CP is five times higher than the PL-SWCNT–CP complex. Changes in surface charge also demonstrated the same results.

3.3. TC of medical nanofluids

3.3.1 Effect of elapsed time: Fig. 5 represents a graph of the TC ratio (k_{mf}:k_{bf}) at room temperature with respect to time, where k_{mf} and k_{bf} values are the TC values of medical nanofluids and of DI

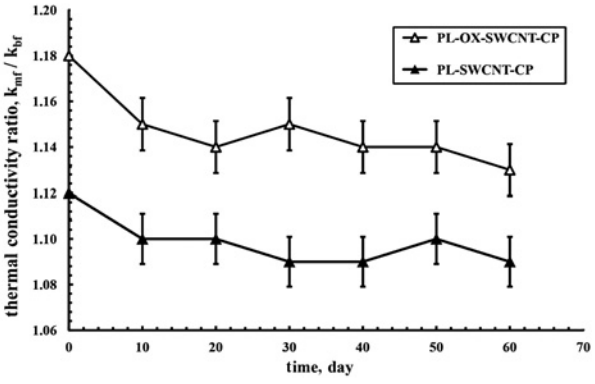

Figure 5 *Effect of elapsed time on TC values of medical nanofluids for PL-SWCNT (black up-pointing triangle) and PL-OX-SWCNT (delta) after dialysis*

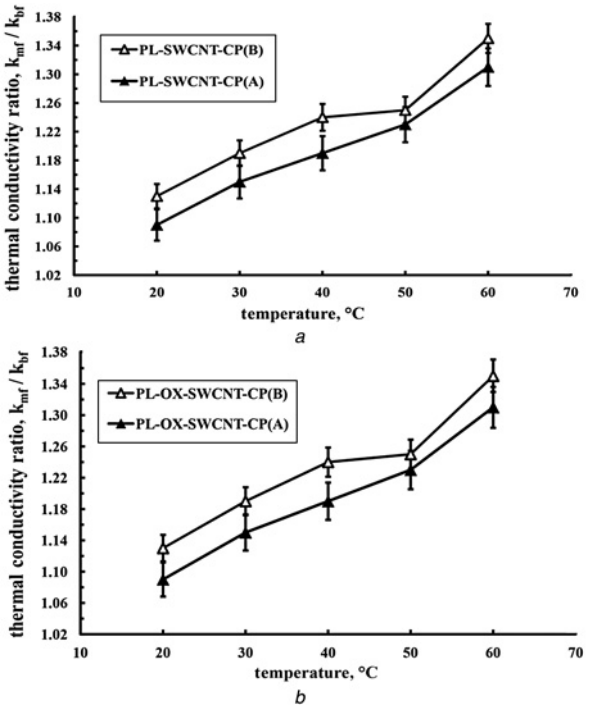

Figure 6 *Effect of temperature on TC values of medical nanofluids for PL-SWCNT–CP (Fig. 6a) and PL-OX-SWCNT–CP (Fig. 6b) before (B) and after (A) dialysis*

water, respectively. It is clear that the TC value of all medical nanofluids does not significantly change with time after preparation. However, there is an observable difference in the TC value of oxidised SWCNT in comparison with the non-OX-SWCNT. Another important observation was that the suspension was stable even after three months of nanofluid preparation, indicating no significant agglomeration in these nanofluids.

3.3.2 Effect of temperature: The rising trends of effective TC enhancements with respect to temperature for medical nanofluids are illustrated in Fig. 6. Enhancement of TC values in these nanofluids is mainly because of the micro- and nanoconvections induced by Brownian motions of dispersed nanoparticles. Elevated temperature increases the Brownian motions of nanoparticles and improves effective TC of nanofluids. Higher temperatures also result in lower average aggregate size, which is a vital parameter for effective TC enhancements. Smaller sizes of nanoparticles would lead to more effective convection because of particle motions. Temperature elevation also resulted in reduced viscosity of the nanofluid and change in the TC values of the solid particles' and base fluid densities. It is also clear that the TC values of the two formulas are considerably higher before dialysis because of the presence of CP. The CP molecules are metallic nanoparticles and have a positive effect on the TC enhancement of medical nanofluids.

3.4. Effect of temperature on drug release: After formula preparation, the target samples were dialysed in DI water and PBS buffer at pH = 7.4 (see Fig. 7). The PBS buffer and DI water were used as a dialysis environment to measure the CP concentration and the TC values of the medical nanofluid, respectively, the reason being that the PBS buffer simulates better biological medium and the DI water has a better result in TC measurement due to the absence of free ions.

The effect of temperature on drug release was investigated by analysing the output of CP from dialysis bags. The CP remaining

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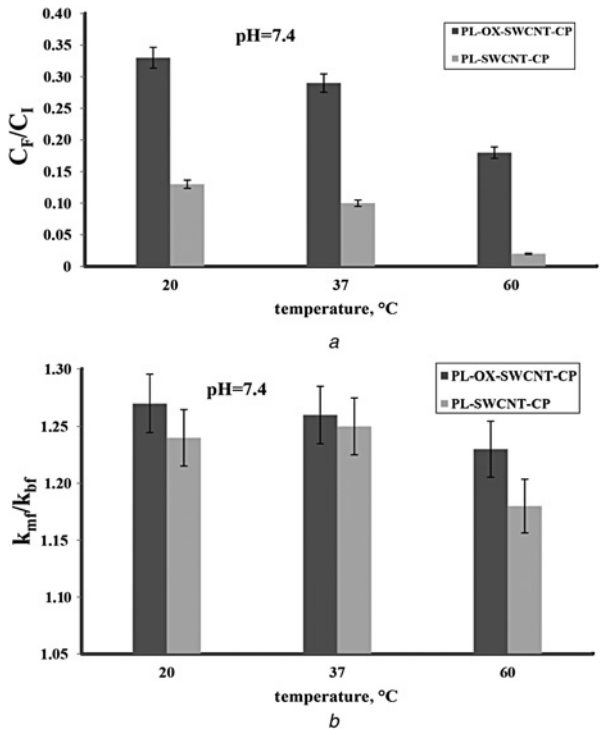

Figure 7 *Effect of temperature at pH = 7.4 on CP concentration (Fig. 7a) and TC value (Fig. 7b) of medical nanofluids for PL-SWCNT–CP and PL-OX-SWCNT–CP complexes after dialysis*

in the main formulation was calculated by the following equation

$$C_F = C_I - \sum (C_i)$$

where C_i is the CP concentration in DI water at each level of dialysis, C_F and C_I are the CP concentrations of the final and initial formulation, respectively. A heating magnetic stirrer (VELP Scientifica, Italy) was used to prepare a uniform medium with a specified temperature. All the experiments were performed in the dark because of the presence of CP.

The temperature was set at three constant points, 30, 37 and 60°C, see Figs. 8*a* and *b*. The results indicated that an increase in temperature resulted in reduced CP concentration and TC values of the target sample. Meanwhile, because of the increased concentration of CP in DI water and the PBS buffer, the concentration of CP and TC values of the dialysis medium was increased by raising the temperature.

Brownian motion and liquid layering were suggested as the potential mechanisms for TC enhancement, particularly with the presence of CP nanoparticles and SWCNTs, the situation is reinforced. In the target sample, the TC values of the medical nanofluid reduce slightly with increase in temperature. This is because of the separation of CP molecules which are electrostatically attached to the surface of the macromolecules with weak molecular binding. Meanwhile, the rise of the CP concentration and the TC values in the dialysis fluid is quite tangible. Another important point is that because of the weaker binding in the non-OX-SWCNTs, more drug release was observed. These values are, respectively, about 45 and 85 per cent for oxidised and non-OX-SWCNTs, which show more than 40 per cent of CP molecules attached weakly to the surface or entrapped inside the SWCNTs. On the other hand, the reduction of TC values in the oxidised and non-OX-SWCNTs is 5 and 3 per cent, which shows the greater impact of the SWCNTs as compared with the CP on the TC values of medical nanofluids.

3.5. Effect of pH on drug release: The effect of pH in CP concentration and TC values was investigated at two constant temperatures, 37 and 60°C. As in Section 3.4 above, DI water and the PBS buffer were used as the dialysis medium; HCL and NaOH were used to adjust the pH. The results of CP concentration and TC values are shown in Fig. 8. Here, the results clearly indicate that the acidic environment has a significant effect on the drug release of CP. This is an advantage

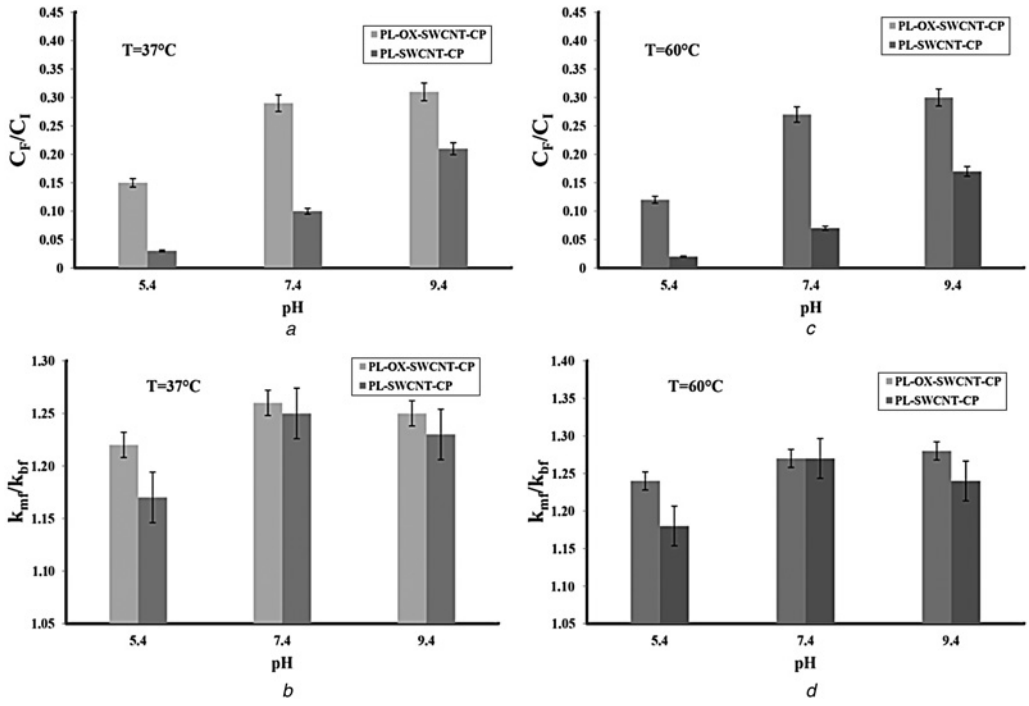

Figure 8 *Effect of pH at 37 and 60°C on CP concentration (Figs. 8a and c) and TC values (Figs. 8b and d) of medical nanofluids for PL-SWCNT–CP and PL-OX-SWCNT–CP complexes after dialysis*

for its use in therapeutics as the tumour tissues have an acidic pH. This finding also proved that the OX-SWCNTs are able to keep the CP molecules more tightly and for a long time as compared with the non-OX-SWCNTs. The values of drug release were, respectively, 52 and 86 per cent for oxidised and non-OX-SWCNTs when the pH changes from 9.4 to 5.4 at 37°C. These values changed from 60 to 88 per cent for the oxidised and non-oxidised SWCNTs at 60°C.

On the other hand, although the trend of TC at both temperatures is not obviously ascending or descending, it is clear that the drug release could change the TC values. Because of stronger binding of CP in oxidised SWCNTs, higher values of TC were observed and this result proved the important role of the CP in the TC parameter.

Therefore, it can be concluded that the thermal properties of the medical nanofluid are one of the most effective parameters for higher drug release. In this research, the metallic characteristics of CP and the special thermal properties of SWCNTs intensify the drug release and thermal properties of medical nanofluids.

Thus, the TC value could be one of the important parameters of heating mediators for cancer therapy (hyperthermia). When the tumour region is irradiated, higher CNTs would be absorbed significantly as compared with the surrounding fluid. So, the CNTs can heat up more and cause severe damage (thermal ablation) to the adjacent cells. Hence, the ETCE is effective for two reasons: (i) increase in thermal ablation and (ii) increase in the efficiency of drug release because of further enhancement of the local temperature.

4. Conclusion: Medical nanofluids with better thermophysical characteristics were designed and synthesised based on DSPE-PEG2000, DSPG wrapped pristine SWCNTs and OX-SWCNTs. This complex was conjugated with an anticancer drug, CP, that has potential applicability in the treatment of malignant tumours.

The results highlight the improvement in the thermal properties of medical nanofluids by use of SWCNTs and CP nanoparticles. In addition, the increase in temperature and a decrease in pH towards the acidic range improve the thermal property of the medical nanofluid and, as a result, increase the drug release of CP. On the other hand, the stronger binding forces between the oxidised SWCNTs and CP assist in maintaining the state of the complex. This might help in improving the circulation half-life of the complex in the blood vessels, thereby leading to an effective EPR mechanism.

Overall, the TC as an important engineering property of medical nanofluids was found to be an effective parameter for optimising the drug release in the target tumour, which could also possibly reduce the side effects of CP.

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