**Research Article** 

# Multifunctional properties of acetaminophen immobilized polymer nanohybrid composites



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### Abstract

The present work describes the acid functionalization of single-walled carbon nanotubes (SWCNTs) with *N*-acetyl-*p*-amino phenol methacrylate (APM) of structural, thermal, morphological electrochemical and biological properties. The target nanohybrid composites were obtained by the condensation reaction between SWCNT, *N*-acetyl-*p*-amino phenol and methacrylic anhydride. The *N*-acetyl-*p*-aminophenol methacrylate [APM] was successfully immobilized with SWCNTs by free radical polymerization technique (FRP). The uniform dispersion on SWCNTs was achieved by functionalization of APM on the SWCNT surface, and the stability confirms up to 8 months. The stability enhancement is due to strong interaction of the SWCNTs carboxylic group with the amide moieties of the polymer. The morphological studies were performed by FE-SEM and HR-TEM, which shows distinct morphological architecture based on the arrangement of nanotubes into the polymer. The synthesized nanocomposites were characterized through various spectroscopic measurements. The anti-cancer studies, results obtained by this process are ideal, and showed optimal percentage of cancer cell death upon a 48 h cell line analysis.

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### **Graphic abstract**



Keywords Functionalization of polymers · Nanocomposites · Raman spectroscopy · Biocompatibility

### **1** Introduction

Carbon nanotubes (CNTs) have received wide attention in the last two decades, because of their distinctive physical, electrical, mechanical and liquid crystal properties [1]. However, SWCNTs with their extraordinary chemical and thermal stability [2] prove to be highly promising materials by providing a better nanoplatform for enhanced biomedical applications including those of drug delivery [3], medical imaging, nanosensors and cancer targeting [4, 5]. Furthermore, the incorporation of functional groups on SWCNTs surface by covalent approach creates a facile nanomaterial with increased biological properties and its application has been explored extensively [6]. However, the major intrinsic drawback of carbon nanotubes (CNTs) lies on their poor solubility in most of the common organic solvents due to their hydrophobicity and difficult to dispersed because of their strong van der Waal forces between inter-tubes. Particularly, Changes on CNTs surface, which includes functionality, surface charge, reactivity and stability can leads to good dispersibility. In order to overcome these issues dispersion of carbon nanotubes and their surface has been modified via non-covalent, covalent and/or electrostatic interactions in various organic, inorganic and hybrid polymers [7, 8]. The functionalized single walled-carbon nanotubes

SN Applied Sciences A SPRINGER NATURE journal (*f*-SWCNTs) exhibit a greater promise for novel drug delivery systems, as they posses high surface area and provide multiple attachment sites for functional groups and other molecules, which may allow creating the polyvalent derivatisation [9]. Other hand, the acetaminophen is an analgesic based non-steroidal anti-inflammatory drug (NSAID), and is commonly known as paracetamol. It has effective, cheap and extensively accessible drug and also found to possess good anti-inflammatory properties [10].

The stable dispersion of CNTs [11] achieved by biopolymers and they were utilized for biomedical applications such as tissue engineering and drug delivery system. Jenny et al, reported the hydrogen bonding between methacrylic acid and amide functionality of acetaminophen have been synthesized via thermally initiated free radical polymerization [12]. This common drug, which is both the analgesic and anti-pyretic crystallizes into its most stable monoclinic form and a less stable thermodynamically favorable orthorhombic form [13, 14]. Chen et al. [15], have reported, high performance electrochemical sensing behavior of acetaminophen on SWCNTs and graphene sheet based hybrid films. In addition, the advantage of SWCNTs in cancer therapy is a backbone to form supra-molecular complexes with polycyclic aromatic molecules through  $\pi$ - $\pi$  stacking [16, 17]. Acetaminophens are used to reduce bacterial and viral fever and certain other disorders. Acetaminophen could be determined by titrimetry, spectrophotometry and liquid chromatography [18, 19]. Actually, the significant possibility for intake of high concentration of acetaminophen can be caused severe adverse effect, which includes, analgesic, liver and kidney damages that are portentous to human health even in toddlers too. Therefore, establishment of this type of drug is responsive for the determination in human life. Our preliminary study is to develop to reduce their toxicity level [20]. Recently, the acetaminophen based carbon nanotubes with graphene oxide composite have been reported as an electrochemical sensors [21, 22]. Chun et al. have prepared carbon coated Fe<sub>3</sub>O<sub>4</sub> nanoflowers composite and tested for acetaminophen release studies. It has been used as an antipyretic and analgesic drug for relieving pain, which is associated with cancer, arthritis and inflammation [23]. Biopolymers are promising agent has a wide attention on biopolymers assisted CNTs engineering [24]. High concentration of CNTs dispersion and stabilization can be achieved by various polysaccharides [25-27]. Acetaminophen is a class of biopolymer, which is largely used for SWCNTs stabilization for biological application. The sensitivity of positively charged amino group in the acetaminophen molecular chain to the surface of SWCNTs, enables a variety of biological applications in tissue engineering and drug delivery [28, 29]. In the present work, we report the facile functionalization of single-walled carbon nanotubes with poly (N-acetyl-p-aminophenol methacrylate) and its novel analgesic drug derived from acetaminophen to gain a stable dispersion. The potent antiproliferative activity was carried out on MCF-7 cell line and observed that the shape of the f-SWCNTs would allow to entering the cells and bind effectively on surface of the cell line in order to reduces their cytotoxic level and inhibit the cancer cell growth. [30].

### 2 Experimental

### 2.1 Materials

Methyl methacrylate (MMA) was purchased from Aldrich and passed through an  $Al_2O_3$  column to remove the impurities for further use. Dimethylformamide (DMF), Dimethyl sulfoxide (DMSO), triethylamine (Et<sub>3</sub>N), tetrahydrofuran (THF) and hexane were dried and distilled as per standard protocols before use. MCF 7 cell lines were procured from National Centre for Cell Science, Pune, India. 3-Minimal essential media (MEM), Fetal Bovine serum (FBS), Antibiotic and antimycotic solution, 0.25% Trypsin–EDTA, (4,5-dimethyl thiazol-2-yl)-2,5-(diphenyl tetrazolium bromide) (MTT), SWCNTs (70–80%), *N*-acetyl-*p*-aminophenol, sodium hydroxide 98% and benzoyl peroxide (BPO) were obtained from Sigma-Aldrich (USA).

### 2.2 Methods

The <sup>1</sup>H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using DMSO and CDCl<sub>3</sub> as an internal solvent. UV-Visible absorption spectra were measured on a JASCO UV-Visible 530 spectrometer. The Field Emission Scanning Electron Microscopy (FE-SEM) was performed using a FEI Quanta 200 Scanning Electron Microscopy operating at 15 kV. High Resolution Transmission Electron Microscope (HR-TEM) was obtained on FEI 300 kV, Technai G2 S Twin. Raman spectroscopy was performed on Nanophoton using wavelength 532 nm laser source. FT-IR spectroscopy was performed using ABB MB3000. Probe sonicator, VCX 750 (750 W), 20 kHz, 60% amplidude, was used for sonication purpose. Thermal properties were carried out by using TG analysis (Model Q50); the cyclic voltammetry analysis was carried out using CHI 600D electrochemical work station using platinum electrode as a working electrode, Ag/AgCl as a reference electrode, platinum wire as a counter electrode and 0.1 M of TBAPF6 was used as the supporting electrolyte. The CV and LSV scan rate 0.000001 to 5000 V/s potentiostate was used in the experiments. The optical polarizing microscopy (OPM) was performed using Olympus BX50 with magnification of 100X.

# 2.3 Synthesis of *N*-acetyl-*p*-aminophenol methacrylate (APM)

N-(4-hydroxyphenyl)acetamide (1 g, 6.6 mmol) and methacrylic anhydride (1.2 g, 6.6 mmol) in dry THF (25 mL) were stirred at room temperature about 10 min until complete dissolution. The reaction mixture was allowed to cool to 0 °C, and an aqueous solution of NaOH (12 mmol) was added slowly for 10 min with constant stirring. The reaction mixture was allowed to stir at 25 °C for 6 h. The reaction mixture was filtered and washed with water to remove the precipitate and the solution was extracted with ethyl acetate to obtain the solid product. The acetaminophen based monomer derivative was synthesized using methacrylic anhydride in basic medium. The obtained product was further purified by column chromatography using silica gel and ethyl acetate/hexane as an eluent to obtain the pure product as a slight yellow solid (70% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) = 2.2 (s, 3H), 3.0 (s, 3H), 5.8 (s, 1H), 7.4 (s, 1H). FT-IR (cm<sup>-1</sup>): 3311(–NH stretching); 1662(C=O stretching); 1584(C-O, aromatic stretching); and 1594(C=C stretching).

### 2.4 Synthesis of *f*-SWCNT-poly(*N*-acetyl-*p*-aminophenol methacrylate) (FSPA)

The FSPA was prepared by the following procedure; a mixture of SWCNTs-COOH (10 mg) and *N*-acetyl-*p*-aminophenol methacrylate (0.2 g) in DMF (20 ml) were sonicated for 3 h, in order to obtain a uniform dispersion.  $N_2$  gas was purged into the system for a period of 30 min., to eliminate the moisture from the system.

BPO was dissolved in 5 ml of DMF and slowly added to the reaction mixture by using glass syringe needle and allowed to stir at 70 °C for a period of 24 h. The above procedure was repeated to prepare the pristine SWCNT-poly(*N*-acetyl-*p*-aminophenol methacrylate) [PSPA]. A detailed synthetic route is given in scheme 1 (ESI scheme S1). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>,  $\delta$ , ppm): 2.4(s, -CH<sub>3</sub>), 2.7 (m, -C=O), 7.2 (m, -Ar), 7.8(s, -NH); FT-IR (cm<sup>-1</sup>): 3431(-NH); 1664(C=O); 1584(C-O, aromatic stretching); 1590(C=C). Raman (bands in cm<sup>-1</sup>): 1324(D); 1570(G); 178.

### 2.5 Cell culture

The MCF-7 cell line was grown at 37 °C in 5% carbon dioxide atmosphere in MEM supplemented with 10% fetal bovine serum and 1% antibiotic and antimycotic solution. For experimental purpose, cells grown up to 80–90% confluence, were harvested using 0.25% trypsin–EDTA and plated at desired density and allowed to re-equilibrate for 24 h before any further treatment. Non cancerous cell lines were also cultured and exposed to nano-hybrid to test their cytotoxicity.

### 2.6 Anti-cancer studies

The cytotoxic effects of polymer materials (PSPA and FSPA) were determined by using MTT assay. Briefly,  $2 \times 10^5$  cells were seeded in sterile 24 well plates with different concentration of samples and incubated for 48 h. Triplicate measurements were made for each concentration of polymer composite (PSPA and FSPA) samples. After treatment, 100 µl of MTT (1 mg/mL of PBS) solution were added in each well and incubated dark at 37 °C for 3 h. Finally, Formazan crystals were dissolved with DMSO and transferred in 96 well plates were read at 540 nm by using ELIZA multiwell reader. The cell viability was calculated by using the standard formula: Optical density (OD) of treated sample/OD of Control × 100.

# 3 Results and discussion

# 3.1 FT-IR spectra of acetaminophen based nanocomposites

The synthesized materials APM, FSPA and PSPA were confirmed by FT-IR spectroscopy and shown in Fig. 1a–c shows the characteristics vibration bands about 1731 cm<sup>-1</sup> is due to the carbonyl stretching (–C=O) group, 3311 cm<sup>-1</sup> is for amine (–NH), the –C=C stretching appears at 1662 cm<sup>-1</sup>, and the –C–O stretching peaks at 1320 cm<sup>-1</sup>. The acetaminophen based monomer derivative was synthesized before proceeding to encapsulation formation of the composites. In the case of pure APM, the presence of –NH stretching peak appeared at 3311 cm<sup>-1</sup>.

The amide moiety of the monomer as well as polymer nanocomposite appeared at the same region. A shift was observed in the –NH stretching, when compared to FSPA (3320 cm<sup>-1</sup>). This provides a clear evidence for carboxylic

Scheme 1 Synthesis of poly(*N*-acetyl-*p*-aminophenol methacrylate) immobilized with *f*-SWCNTs via multiple hydrogen bonding interaction



f-SWCNT-poly(N-acetyl-p-aminophenol methacrylate)

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Fig. 1 FT-IR spectra of a APM, b PSPA, c FSPA

acid functionalized SWCNTs completely immobilized with N-acetyl-p-aminophenol methacrylate, whereas PSPA does not interact well with SWCNTs due to absence of -COOH group. The presences of *allylic carbon* signals at around 1350 cm<sup>-1</sup> in the composites confirm the presence of polymer in the SWCNTs. The presence of acetyl and carboxylic carbonyl stretching are clearly differentiated from the spectra, where acetyl carbonyl appears at lower frequency absorption around 1690 and 1730  $cm^{-1}$ .

### 3.2 Confocal Raman study

green (4) respectively

The confocal Raman spectroscopy was performed on FSPA as given in Fig. 2. Raman spectroscopy is well established in determining nanomaterial, especially for 1-D nanostructure of carbon nanotubes and their electronic properties. It reveals the affluent information about carbon nanotubes, such as structure, defects and diameter [31-33].

Raman scattering in SWCNTs is subjected to resonant process. The disorder band (D-band) at 1324  $\text{cm}^{-1}$ , 1329 cm<sup>-1</sup>, 1334 cm<sup>-1</sup> and 1340 cm<sup>-1</sup> scan region for green, pink, orange and blue respectively, and is sensitive to any structural defect in the graphitic  $sp^2$  network [34].

However, the presence of tangential mode (G-band) at 1570 cm<sup>-1</sup>, 1576 cm<sup>-1</sup>, 1580 cm<sup>-1</sup> and 1584 cm<sup>-1</sup> and G'bands 2520 cm<sup>-1</sup>, 2524 cm<sup>-1</sup>, 2530 cm<sup>-1</sup> and 2532 cm<sup>-1</sup> respectively for green, pink, orange and blue at different scan region were analyzed for FSPA. In addition, a higher shift was observed in the radial breathing mode (RBMs) at 178  $cm^{-1}$ , which may be due to the amide moiety of analgesic based polymer completely immobilized on nanotubes surface. The Raman image for FSPA is given in Fig. 2a. The different scan region of Raman image shows uniform distribution of SWCNTs into polymer network. From the Raman spectra of PSPA as shown in Fig. 3, the most intense band at (1585 cm<sup>-1</sup>, 1584 cm<sup>-1</sup>, 1586 cm<sup>-1</sup> and 1588 cm<sup>-1</sup>) corresponds to tangential band revealed the G-bands in the PSPA. However, Raman image Fig. 3a shows, nanotubes that are aggregated into polymer network. The G-bands are less intense with broad peak for PSPA, compared to FSPA, It clearly revealed that pristine SWCNTs doesn't immobilize to the polymer due to absence of -COOH group on CNTs surface.

### 3.3 NMR and UV-vis spectroscopy studies

The <sup>1</sup>H-NMR spectra of APM, PSPA and FSPA were shown in Fig. 4. The peaks are noticed at 5.8 and 6.2 ppm indicates the presence of ene protons in the monomer. The existence of ene protons appears slightly in the nanocomposite



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sample and hence their intensity is also greatly reduced, which confirms the formation of polymer grown on SWC-NTs surfaces. The peaks 7.8 (s, –NH) and 2.7 (–C=O) groups clearly reveals the hydrogen bonding between COOH-SWCNTs and FSPA composite.

Compared to pristine SWCNTs, functionalized SWCNTs produced more adsorption of polymer units due to the presence of hydrophilic groups on the walls. The presence of polymeric methylene groups (2.4 ppm) is also clearly visible in the spectra, which confirms the formation of the composites as shown in Fig. 4. UV–*vis* spectra of polymer nanocomposite APM, PSPA and FSPA were shown in ESI Fig. S9. The absorption peak at 365 nm is attributed to the presence of N-phenyl acetyl group in the monomer (APM). Similarly, a peak appeared in the same region for composite too.

The dispersion of FSPA composite was stable up to 8 months. This stability confirms the immobilization of polymer units on the SWCNTs walls. The intensity of the peak in the composite is reduced, which may be

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### 3.4 Thermal properties

The thermal stability of all the synthesized material was measured using thermo gravimetric analyzer (TGA). The FSPA of thermograms show two-stage degradation temperatures. The initial stage degradation was observed at 215 °C corresponds to degradation of amide linkage of the polymer. The second degradation was observed at 336 °C which may be due to the degradation of organic components. Besides this, a major weight loss was appeared at 455 °C corresponding to the decomposition of CNTs based composites and the material was thermally stable up to 455 °C. Thermal stability drastically increased (185-215 °C, 266-336 °C and 438-455 °C), which is further confirmed that the amide moiety of the polymer were completely immobilized on carboxylic acid functionalized SWCNTs. In addition, thermograms show (see Fig. 5) two stage degradation (164 °C and 271 °C), which may be due to the methacrylate functional group decomposition.

The enhanced thermal stability observed for FSPA compared to PSPA materials influenced by the interaction of polymer and functionalized SWCNTs, as shown in Fig. 5. In addition, DSC thermograms conducted on APM and PSPA show melting temperature at 110 °C and 121 °C as shown in ESI (Fig. S3).



Fig. 5 TGA trace of a APM, b PSPA and c FSPA

### 3.5 Cyclic voltammetry of polymer nanocomposite

Cyclic voltammetry (CV) of the polymer nanocomposites (FSPA, PSPA and APM) were performed in dimethylformamide (DMF) solution state using platinum disc electrode as a working electrode, Ag/AgCl as a reference electrode, platinum wire as a counter electrode and tetrabutyl ammonium hexafluorophosphate (0.1 M TBAPF6) was used as the supporting electrolyte. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energy levels of the synthesized materials were found to be semiconducting in nature (ESI Fig. S1, S2) [35]. The HOMO and LUMO values were calculated using the following Eq. (1) [36].

$$HOMO = -[E_{ox} + 4.71], LUMO = -[E_{red} + 4.71] \text{ and } E_g^{ec}$$
$$= [LUMO-HOMO]$$
(1)

The oxidation peak of FSPA was observed at 1.55 eV corresponds to HOMO value of – 6.26 eV and the reduction peak of – 0.95 eV corresponds to LUMO value at – 3.76 eV and the bandgap energy was 2.5 eV. Acetaminophen based amines and amides are oxidized in ErCi mechanism process [44, 45]. In this work, we have observed the amide functionalized acetaminophen was oxidized at 1.49 eV and reduction at – 0.86 eV. The HOMO and LUMO values are slightly reduced and the band gap energy level was drastically increased when compared to *p*-SWCNT, SWCNT-COOH, PSPA and APM (see ESI) [37, 38], which indicates that all the synthesized materials exhibit as semiconducting behavior.

#### 3.6 Morphological studies of FSPA

The *f*-SWCNT-polymer composite materials morphology changes on heating were observed through the OPM analysis. The obtained results shows that the clear dispersion takes place in the polymer composite (FSPA) and polymer units are grow as a palm tree structures as shown in optical microscopic images (ESI Fig. S7). In the PSPA composite materials, pristine SWCNTs were found to be agglomerated on the polymer end surface and it do not interact well with their polymer units as shown in ESI Fig. S6. Surface morphology of the FSPA was studied using FE-SEM analysis. It was observed in the FE-SEM micrograph of polymer composite had smooth flower like structure and small microsphere of polymers grown on the SWCNTs surface (Fig. 6 and ESI Fig. S4).

The figures show flower like morphology, where polymers wrapped on the side wall of the nanotubes and exhibit as nanoflowers, which is better agreement with **Fig. 6** FE-SEM images of *f*-SWCNT-polymer composites **a** 1 µm and **b** 500 nm



**Fig. 7** HR-TEM mages of *f*-SWCNT-poly(*N*-acetyl-*p*-aminophenol methacrylate), **a** 20 nm, **b** 50 nm, **c** 100 nm and **d** 20 nm

optical microscopic images. The images are clearly shows the tube width of 10 nm even after polymer wrapping, confirms the regular encapsulation of the repeating units in the wall. The HR-TEM images of nanocomposite (FSPA) produce fine tube like structure. Thus, the polymer spherical grown on the ends of the nanotube surface of the SWC-NTs, is clearly observed in Fig. 7 (ESI Fig. S5).

The detailed morphological nanostructure is comprehensively characterized by HR-TEM and it exists as typical hierarchical structure with diameter, approximately around 5 nm. The morphological characteristic data for these nanocomposites [39] supports the existence of strong interaction between polymer and SWCNTs to improve its uniform dispersion in DMF (see Fig. 8) and also



Fig. 8 Stability of composite materials

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Fig. 9 Contrast microscope images of APM, a control, b 24 h, c 48 h, PSPA of d control, e 24 h, f 48 h and FSPA of g control, h 24 h, i 48 h in MCF-7 cancer cell lines

supports the interaction [40] of polymer and SWCNTs in the dispersion of nanocomposite. [41] However interesting morphological features were observed in the sense, small nanospheres of polymer were found to be well grown on functionalized nanotube surfaces.

### 3.7 Anti-cancer studies in MCF cell lines

The anticancer activity of the synthesized SWCNT-polymer composite was tested against cancer cells (MCF-7) with various concentrations of samples as described in the supporting information. The anticancer activities are monitored for three samples namely APM, PSPA and FSPA polymer composites samples. The results obtained for these three samples IC<sub>50</sub> values depicted in ESI Fig. S8. Compared to control polymer sample (APM), the *f*-SWCNT-polymer composite (FSPA) showed higher percentage of cell viability, which shows that the toxicity of CNT gets reduced essentially because of the  $\pi$ - $\pi$  stacking of bioactive polymer namely *p*-aminophen. The spiro arrangement of FSPA helps to reduce the cancer cell growth [42, 43] and retain more living cells (resistant) in non-cancerous cells in practice. The carboxylic group functionalized

with SWCNTs are interacted with the amide moieties of the acetaminophen (FSPA) through multiple hydrogen interactions, and clearly show that the cancer cells were inhibited and lower half maximal inhibitory concentration  $IC_{50}$  is higher percentage in normal cell viability. This may indicated that the polymer functionalized SWCNTs has more biocompatible in normal cells. The *f*-SWCNTs being act as nanosyringes and able to penetrate through plasma membrane via a passive and energy-independent "pierce-through" mechanism. In addition, *f*-SWCNTs of different size and their functional groups (–COOH, –NH, and –OH) might have different routes to enter cells and reduced the cancer cells and enhanced their cell viability.

The numbers of living cells in SWCNT-polymer composite (FSPA) are evidently shown in Fig. 9a–i, as compared to other samples (APM, PSPA) even after 48 h of cell culture. The efficient way to improve the dispersion of SWC-NTs is by the surface functionalization, which helps in preventing of nanotubes aggregation and also reduces their toxicity level. The functionalization is more reactive and an enriched propensity with chemical species such as, functional groups –COOH, –NH and OH. The biostability enhancement is due to strong multiple hydrogen interaction of the SWCNTs carboxylic group with the amide moieties of the acetaminophen (FSPA) that could leads to good solubility, dispersibility and inhibited the cancer cell line against MCF-7 at optimum level. The proposed nanocomposite material could be used for anticancer treatment after further studies.

## **4** Conclusion

The nano-hybrid materials were prepared by functionalization of poly(*N*-acetyl-*p*-aminophenol methacrylate) on SWCNTs, through the hydrogen bonding interactions. The structure of the materials was confirmed by <sup>1</sup>H NMR, FT-IR and Raman. The TGA thermograms show high thermal stability and two-stage decomposition temperature pattern. The pot-life of FSPA was stable for long duration, the distinct morphology of the dispersions was confirmed by FE-SEM and HR-TEM and the width of the nanotubes are ~ 5 nm. The proposed polymer (FSPA) composites could be a potential material for anti-cancer treatment.

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