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Experimental and theoretical Studies of Anti-HIV Medication Azidothymidine (AZT) Interactions with Non-functionalized and Functionalized Nanotubes

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Abstract

The current paper experimentally and theoretically investigates Anti-HIV medication Azidothymidine (AZT) interactions with Non-functionalized single-walled nanotube (5, 5) (NT) and functionalized nanotube NTCOOH. All calculations were done using a B3LYP hybrid density function and the basic function 6-31G(d,p)in the gas and solution phase and polarization of the continuum model (PCM) was used for solvent effects, also covalent and non-covalent capture of the medicine was studied on the SWNT. The computational results of bond interactions were studied through the NH, using pure Anti-HIV medication Azidothymidine (AZT) and its interaction with String and Ultrasonic methods with the nanotubes as well as taking advantage of FTIR and XRD spectroscopy methods. Two covalent and two non-covalent configurations were studied in solution phase.Binding energy in non-covalent capture depends on the group on the CNT. The most powerful complex from non-covalent configuration is created when there is an interaction between Zidovudine and SWNT through the NH group. Molecular quantum descriptors likehardness and chemical potential and AIM studies show the nature and absorption of medicine on SWNT. A comparison between FT-IR spectrum of Azidothymidine (AZT) and medication combination with sonicated functionalized nanotubes shows that the peak has reduced significantly at3462cm-1 that may indicate the interaction between acidic factor and the combination of Azidothymidine N-H. Acidic functionalized nanotubes peak is clearly observed in FT-IR spectrum of medication combination with functionalized nanotubes in absence of waves that is overlapped with the combination of Azidothymidine N-H peak. In these circumstances, there was no possibility of interaction between medication combination and functionalized nanotubes. In XRD spectrum, Azidothymidine peaks have been sharp prior to being sonicated with carbon nanotubes, but peaks have been reduced in sharpness after interactions with carbon nanotubes in non-functionalized mode and functionalized nanotubes.

Keywords: FTIR spectroscopy, XRD spectroscopy, HIV, Zidovudine, Azidothymidine, functionalized nanotubes, Carbon nanotubes in non-functionalized mode.

1.INTRODUCTION

Medicine delivery is one of the most important branches of Nano medicine. It is predicted that 80 percent of the future global market for nano-medicine belongs to nano technology that 64 percent covers medicine delivery. Iran, according to the 20-year development visions has to allocate 10 percent of the global market of Nanotechnology in 2015, that close attention to the areas of medicine delivery is one of the approaches. Medicine delivery technology focused on delivering medicine to the correct location in the body at the right time with the right treatment effects. Conventional medicine delivery systems have virtually no control over time, place and there would be no medicine release, but in these medicine delivery systems medicine releases at a steady pace within the specified time. In this method, the medicine's toxic effects reduces due to maintaining a constant medicine concentration released in the blood, while in the conventional medicine use, at first, medicine concentration is high (immediately after consumption) and after a period of time it is less than the effective level (extreme fluctuations in medicine concentration in the blood) that may lack necessary effectiveness (Burchell, 1999). Basically, a wide range of molecules can bind in nano-clustersand easily move toward cells. Generally nano-clusters do not have high toxicity and are harmless at low doses; however at high concentrations cause loss of cell and its effects in the body must be studied. Ruth Duncan, an England Cardiff University researcher, believes there are many reasons.That indicate that nanoparticles may be useful in the pharmaceutical system but the mechanism to get into the cells is not clear; she adds, there have been unsuccessful researches to deliver spherical nano carbon anti-cancer medicines and radiation nucleotides into the cell. Moreover, cellular receptors can also be placed on carbon nanotubes for medicine delivery, which recognizes specific cells to effect on. Therefore, the healthy cells will not be exposed to these medicines. The medicine effectiveness increases because concentrates on defected cells as well as a large amount of medicine is placed on a small surface of carbon nanotubes (Bianco and Prato, 2003). Carbon nanotubes interaction with biologically living cells has become possible since the biocompatibility of carbon nanotubes with biological aquatic environment is provided. Experiments show that carbon nanotubes can interact with the membrane and penetrate into the cytoplasm, without having to pass through the cellular pores. Studies showed that functionalized nanotubes can easily intracellular transport plasmid DNA (Kam et al., 2005). Acquired immune deficiency syndrome (AIDS) is the biggest challenge of the 21st century. Human immunodeficiency virus (HIV) is a virus with low proliferation rate that is HIV disease agent. HIV is a virus that leads to immune deficiency by impairing and destruction of immune function of coordinator cells of the human body. It may take 6 months to 10 years or even more after the entry of HIV into the body to the incidence of the HIV, The person although seemingly healthy, but may spread the virus to others. HIV mainly transmitted through unprotected sexual intercourse, contaminated blood transfusion, infected needle stick, mother to child during pregnancy, childbirth or breastfeeding. Some body fluid such as saliva and tear are not able to transmit HIV. Prevention of HIV is carried out by safe sex and needle-exchange programs (Weiss, 1993; Sepkowitz, 2001; Douek et al., 2009). Zidovudine is a medicine that is widely used in the fighting against HIV. Its combination with nanotubes is a promising way to overcome the increasing cellular uptake and is internalized by functionalized carbon nanotubes, respectively (Pignatello et al., 2004). . The aim of this study was to experimental and theoretical evaluation Anti-HIV medication Azidothymidine (AZT) interactions with non-functionalized and functionalized nanotubes.

2. MATERIALS AND METHODS

The materials used in this study include: Non-functional chiral nanotube and carboxylic nanotube (Sigma-Aldrich Corporation), Zidovudine (Pars Darou Pharmaceutical Co.), Nano filter, and double distilled water.

Instruments used include:

- FTIR Infrared Spectrometer: FT-IR5000 model, Galexy- series models with wave length range 200-400cm^{-1}

- X-ray Diffraction: PANNULYTICAL X ray model with y=0/15405 Cu-kanm radiation in the area 2&=10-90 with 0.03 degrees of accuracy
- Heater stirrer model L-71
- Ultrasonic bath model PARSONIC 7500S with a frequency of 28 ±5HZ and the ultrasonic power of 100 W 220VAC Max.

2.1 *COMPUTATIONAL DETAILS*

Density functional theory (DFT) was used in the current study to evaluate the interactions and all calculations were performed using Gaussian 09 software. Calculations were performed using the B3LYP level of theory and basis set 6-31G (d, p) molecule drugs (Zidovudine), single walled carbon nanotubes (CNT) and functionalized nanotubes (f-CNT) for all configurations. All configurations have been tested. All configurations in the gas-solvent phase (water) were applied with the Polarizable Continuum Modulation (PCM) method. This section examines the interaction of single-walled carbon nanotubes (5,5) with the medication Zidovudine. This section applies ZIDO goes for the medication Zidovudine, CNT goes for pure carbon nanotubes and f-CNT goes for functionalized carbon nanotubes with COOH (Gallo et al., 2007; Monajjemi et al., 2014).

2.2.*PREPARATION OF SOLUTION METHOD*

Zidovudine was provided from Pars Darou Pharmaceutical Co. by Kerman University of Medical Sciences. It is necessary to interact on the active ingredient so the purification of the medicine was firstly carried out. According to the Zidovudine solubility of 25mg/ml in water at 25°C first the medicine was dissolved in an appropriate amount of distilled water with classical methods and then insoluble contents were separated and the solution was dried in vacuum oven.

3.RESULTS AND DISCUSSION

3.1.*Structures* optimization

For the calculation of the interaction of Zidovudine with functionalized carbon nanotubes (5,5) the optimal structure of each is separately required. Zidovudine, carbon nanotubes (5,5)and functionalized nanotubes in the gas phase and solvent phase are individually optimized. Five configurations were considered to investigate the interaction of nanotubes with Zidovudine. optimized configuration structure include CNT-ZIDO 1, CNT-ZIDO 2, CNT-ZIDO3, f-CNT-ZIDO1 and f-CNT-ZIDO2 in gas and solvent (water) phase, in each of these configurations Zidovudine interacts from Deoxy thymidine ring with π-π interaction; RCH_2 OH groups oxygen and van der Waals interactions from the N3 group with natural carbon nanotubes (CNT), and also has covalent binding from alcohol group and deoxy thymidine ring. Table 1 shows the absolute energy values for these configurations. Binding energy (BE) for each Complex and to determine their relative stability, taking into account the interaction of nanotubes with medication is calculated as follows:

Equation 1: $BE = E_{CNT-ZIDO} - (E_{CNT} + E_{ZIDO})$

Where,$E_{CNT-ZIDO}$ is the electron energy of the whole medication placed on pure nanotube or functionalized nanotube, E_{CNT} and E_{ZIDO} are the total carbon nanotubes optimized electron energy and the total optimized medicine electron energy, respectively. BE can be obtained for configurations with van der Waals interactions and relative stability of this configuration to be determined using the above formula and energy values in Table 1, so that the more negative BE, the configuration is more stable (Mealey et al., 2015; Srivastava et al., 2013).BE Values, for configuration CNT-ZIDO 1, CNT-ZIDO 2 and CNT-ZIDO 3, for a gaseous state is 5.80295 kJ / mol-, -9.01984 kJ / mol, -3.90596 kJ /

mol, respectively. According to energies calculated in Table 1 and BE values, the most stable configuration in the gas phase for van der Waals interactions is CNT-ZIDO 2. By changing the solvent or by changing the dielectric environment sustainability trends will be similar to the values for the configuration CNT-ZIDO1PCM, CNT-ZIDO2PCM and CNT-ZIDO3PCM, as 2.3214 kJ / mol-, -4.7959 kJ / mol, -0.6010 kJ / mol, respectively.But by comparing values for two phases we observe that interaction is weaker in the solvent phase with lower interaction energy levels. According to Table (1) it seems that f-CNT-ZIDO1 configuration in the solvent phase has more stability than that of f-CNT-ZIDO2, so that the f-CNT-ZIDO2 configuration lacks an optimal structure.

Table 1- Absolute energy values related to medicine and nanotubes and different configurations according to Harter in the gas phase and solvent phase.

	E	BE	HOMO	LUMO	E gap
		GAS			
ZIDO	-963.5187801		5.65133	.32194	29392
CNT	-3428.46649		4.77509	3.73262	42476
CNT-ZIDO1	-4391.987482	80295	4.85972	3.81534	44381
CNT-ZIDO2	-4391.988709	01984	4.75387	3.71003	43837
CNT-ZIDO3	-4391.986759	90596	4.62434	3.53179	92546
FCNT	-3617.605573		4.69182	3.36798	91431
FCNTZIDO1	-4504.662065		4.61019	3.29587	13493
FCNTZIDO2	-4504.699969		4.78298	3.46458	14582
		PCM			
ZIDO-PCM	3.538022		-6.5120	-1.0825	5.4295
CNT-PCM	-3428.470560		-4.6559	-3.6270	1.0289
NT-ZIDO1PCM	-4392.009467	2.3214	-4.6652	-3.6360	1.0291
NT-ZIDO2PCM	-4392.010411	4.7959	-4.6597	-3.6306	1.0291
NT-ZIDO3PCM	-4392.008811	0.6010	-4.6532	-3.6251	1.0281
FCNT-PCM	-3617.614438		-4.5884	-3.2695	1.3189
NTZIDO1-PCM	-4504.685053		-4.5941	-3.2765	1.3176
NTZIDO2-PCM	-		-	-	-

3.2.Review the overall reactive descriptors

To evaluate the overall reactive descriptors, first the overall descriptors; Electrophilicity ω, electronic chemical potential μ, η hardness and softness S of reactive molecules is calculated and then the data is compared. The calculation of all reactive descriptors is possible using density functional theory such as Electrophilicity ω, electronic chemical potential μ, η hardness and softness S. The following equation was used to calculate the quantum molecular descriptors that Table 2 shows all configuration values.

$\mu = -\frac{(I+A)}{2}$(2)$\chi = -\mu$(3)

$\eta = \frac{(I-A)}{2}$(4)

$\omega = \frac{\mu^2}{2\eta}$(5)

$E_{gap} = E_{LUMO} - E_{HOMO}$ (6)

Where, in the above equations, μ is the chemical potential and χ is negative chemical potential that represents

Electronegativity. η or hardness can be estimated from Koopman theory because$I = -E_{HOMO}$is the ionization energy and $A = -E_{LUMO}$is the amount of molecule Electron Affinity [47, 74-71].HOMO and LUMO energy difference isobtained from Eq. (6) that is called energy gap (Egap). The more energy gap the more stable structure will be. E_gap represents less reactivity or instability of complex (de Leon et al., 2008). According to Table (2) pure ZidovudineE_gap in the gaseous phase is 5.3294 eV, which is more compared to the CNT-ZIDO 1, CNT-ZIDO 2, f-CNTZIDO1 and f-CNTZIDO2 configurations; it seems that the position of Zidovudine on carbon nanotubes increases reactivity, with exposure to solvent phase E_gap amount of Zidovudine increases to9.649 kJ / mol, which states Zidovudine structure stability increase and reduced reactivity.The E_gap for CNT-ZIDO 1, CNT-ZIDO 2, f-CNTZIDO1 and f-CNTZIDO2 configurations in the gas phase is 1.0444 eV, 1.0438 eV,1.0925eV, 0.9135 eV, 0.9146 eV, respectively. These values show, f-CNTZIDO1 and f-CNTZIDO2 configurations are more responsive than the van der Waals three configurations. But compared to ZIDO, it seems that configurations are more active. According to the data in Table 2, Zidovudine ω in the gas phase is equal to 2.98 and Electrophilicity reduces by changing the dielectric environment and will be almost constant at about 2.66, the value for the CNT-ZIDO 1, CNT -ZIDO 2, CNT-ZIDO 3, f-CNT-ZIDO1 and f-CNT-ZIDO2 configurations is 18.01, 17.16, 15.22, 11.89 and 12.90, respectively in the gas phase, which reactivity increases with increasing ω for configurations. The increased reactivity for configuration is as follows:

$$CNT - ZIDO\ 1 > CNT - ZIDO\ 2 > CNT - ZIDO\ 3 > f - CNT - ZIDO2 > f - CNT - ZIDO1$$

Table 2 the values of molecular descriptors differ in different dielectrics that all values are expressed in eV

	I	A	μ	η	χ	ω
			GAS			
ZIDO	6.6513	1.3219	-3.9866	2.6647	3.9866	2.98
CNT	4.7751	3.7326	-4.2539	0.5212	4.2539	17.36
CNT-ZIDO1	4.8597	3.8153	-4.3375	0.5222	4.3375	18.01
CNT-ZIDO2	4.7539	3.7100	-4.2319	0.5219	4.2319	17.16
CNT-ZIDO3	4.6243	3.5318	-4.0781	0.5463	4.0781	15.22
FCNT	4.6918	3.3680	-4.0299	0.6619	4.0299	12.27
FCNTZIDO1	4.6102	3.2959	-3.9530	0.6572	3.9530	11.89
FCNTZIDO2	4.7830	3.4646	-4.1238	0.6592	4.1238	12.90
			PCM			
ZIDO-PCM	6.5120	1.0825	-3.7972	2.7148	3.7972	2.66
CNT-PCM	4.6559	3.6270	-4.1415	0.5144	4.1415	16.67
CNT-ZIDO1PCM	4.6652	3.6360	-4.1506	0.5146	4.1506	16.74
CNT-ZIDO2PCM	4.6597	3.6306	-4.1451	0.5146	4.1451	16.70
CNT-ZIDO3PCM	4.6532	3.6251	-4.1392	0.5140	4.1392	16.67
FCNT-PCM	4.5884	3.2695	-3.9289	0.6595	3.9289	11.70
FCNTZIDO1-PCM	4.5941	3.2765	-3.9353	0.6588	3.9353	11.75
FCNTZIDO2-PCM	-	-	-	-	-	-

It seems that the Zidovudine place on carbon nanotubes increases reactivity. E_gap data show that f-CNT-ZIDO1,

unlike other complexes; is more stable, with more electron affinity and less ionization energy than other configurations when exposed to solvent phase.As mentioned, we functionalize carbon nanotubes to reduce toxicity of and prevent the accumulation. Now, if we consider it toxic with ω limit of pure carbon nanotubes that is 17.36 in the gas phase and 16.67 in the solvent phase we can go on that toxicity is reduced with the functionalization of nanotubes (ω = 11.89) and stability increased (E_gap = 0.9135) compared to than non-functionalized carbon nanotubes. So f-CNT-ZIDO1 in the gas phase is more volatile than three covalent complexes, but the ω value for CNT-ZIDO 2 configuration is less than the amount of nanotubes, which indicates decreased toxicity of configuration as a result of covalent bond. On the other hand, f-CNT-ZIDO1, being in solvent phase is more stable than three other Van der Waals complexes with little changes in reactivity compared to the other complexes.As discussed, in the f-CNT-ZIDO1 configuration the ω is less than the natural carbon nanotubes and is about functionalized nanotubes, which is equal to 11.75. This means that, for drug delivery by the nanotubes, the best way is to connect the drug to functionalized nanotubes.Accordingly, the solvent can have a direct impact on the stability and toxicity of configurations and affect the proper configuration for drug delivery on the nanotube.

3.3.FT-IR SPECTRUM

A FT-IR spectrum was obtained from the resulting dried solution (Fig. 1). Compounds of medicine, nanotube, and water was prepared from purified medicine with optimized ratio of 5 to 1 with non-functionalized nanotubes and carboxylic functionalized nanotube in water solvent mixtures under the same conditions (temperature 25°C, ambient pressure) and dried control samples were made from each mixture after stirring with a stirrer and then FT-IR spectra were prepared (Fig. 2, 3). Samples were sonicated for an hour and a half. Then, the solvent was evaporated and FT-IR spectrums were taken of them Figure (4 and 5).FT-IR spectra was obtained from non-functionalized nanotubes and functionalized nanotube (Fig. 6, 7).

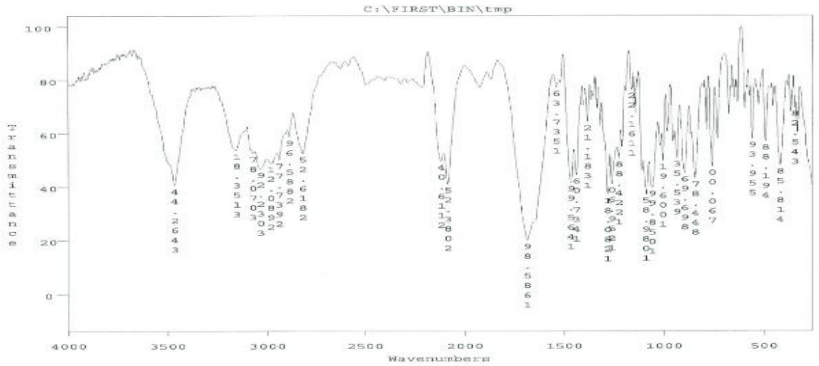

Fig. 1-Zidovudine FT-IR spectrum

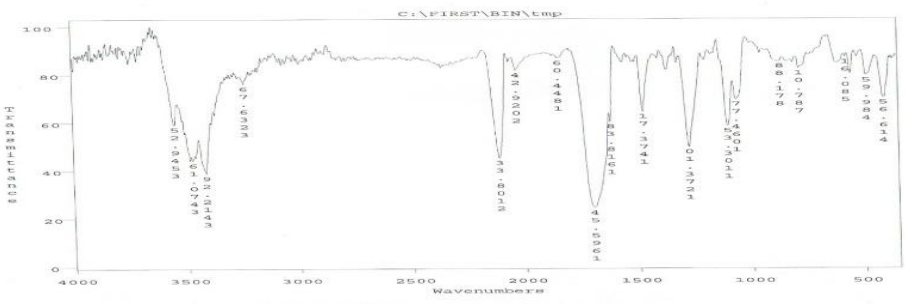

Fig. 2-Functionalized nanotubes with the stirrer Zidovudine FT-IR spectrum

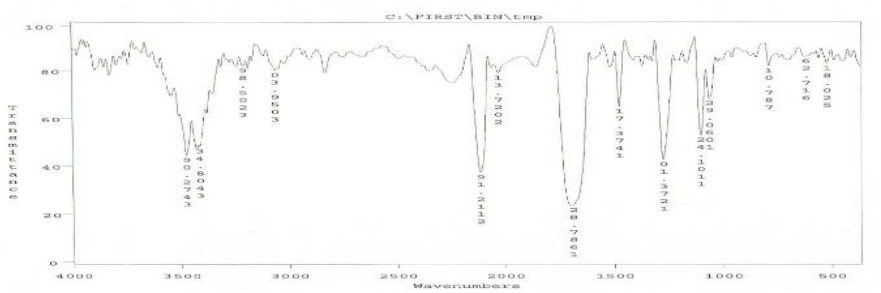

Fig. 3-Non-functionalized nanotubes with the stirrer Zidovudine FT-IR spectrum

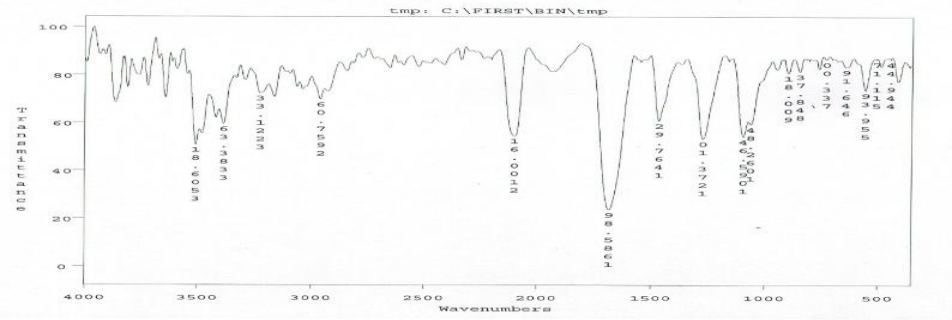

Fig. 4-Non-functionalized nanotubes with the sonicated Zidovudine FT-IR spectrum

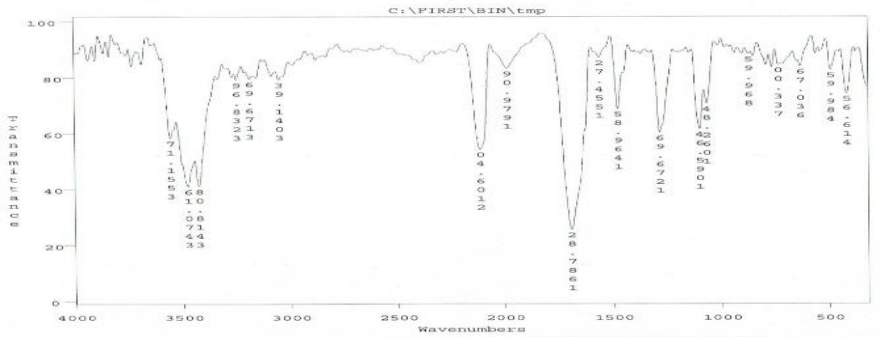

Fig. 5-Functionalized nanotubes with the sonicated Zidovudine FT-IR spectrum

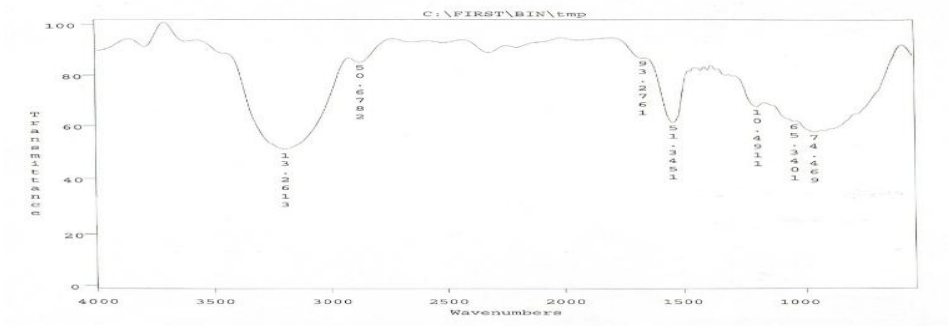

Fig. 6-Functionalized nanotubes FT-IR spectrum

3.4. XRD SPECTRA METHOD OF PREPARATION

First, XRD spectra were obtained from non-functionalized nanotubes and functionalized nanotube (Fig. 11, 12). XRD spectra were also obtained from solutions (medicine non-functionalized and water) and (functionalized medicine nanotubes and water) after sonicated (Fig. 9, 10)

3.5.NANOTUBES SPECTRA

A comparison of FT-IR spectra of Zidovudine medicine (Fig. 1) and combination of medicine with sonicated

functionalized nanotubes (Fig. 5) shows that peak in 3462cm-1 area decreased significantly, indicating interaction of acidic factor and N-H Zidovudine compound. Flatten peaks in the spectral region between 3000 and 3400 cm-1 confirmed the presence of the carboxylic acid functionalized nanotubes. The result confirms the interaction of Anti-HIV Zidovudine medicine and functionalized nanotubes using ultrasonic waves. The FT-IR spectra in the combination of medicine and functionalized nanotubes stirred without the presence wave (Fig. 2).Functionalized nanotubes acidic peak is clearly seen overlapping with Zidovudine compound N-H peak that in these circumstances there is no possibility of interacting between medicine and functionalized nanotubes. A comparison of the FT-IR spectra of medicine combined with non- functionalized nanotubes in sonicated condition (Fig. 4) and normal stirring (Fig. 3) shows no changes in product range in both circumstances, and the presence of peak in 3200-3400 area due to the presence of Zidovudine N-H indicates no interaction. XRD analysis of pure Zidovudine shows the crystal structure of the medicine (Fig. 8). XRD spectra of non- functionalized nanotubes in sonicated with Zidovudine and XRD spectra of functionalized nanotubes in sonicated with Zidovudine show a similar peak pattern with little change in intensity (Fig. 9, 10). As can be seen in Zidovudine spectrum prior to sonication with carbon nanotubes peaks have been sharp prior to being sonicated with carbon nanotubes, but peaks have been reduced in sharpness after interactions with carbon nanotubes in non-functionalized mode and functionalized nanotubes. Carbon nanotubes in non-functionalized mode Zidovudine spectrum shows the minimum reduction in sharpness and differences with pure Zidovudine, however the differences in peaks intensity is higher in Zidovudine spectrum and functionalized carbon nanotubes that is a result of higher interactions between the two and the evenly distributed medication .Comparison between Zidovudine XRD spectrum and functionalized nanotubes sonicated with Zidovudine XRD spectrum, Zidovudine XRD spectrum and non- functionalized nanotubes sonicated with Zidovudine XRD spectrum, and Zidovudine functionalized nanotubes XRD spectrum and sonicated with Zidovudine non-functionalized nanotubes XRD spectrum were shown in fig. 13, 14 and 15, respectively.

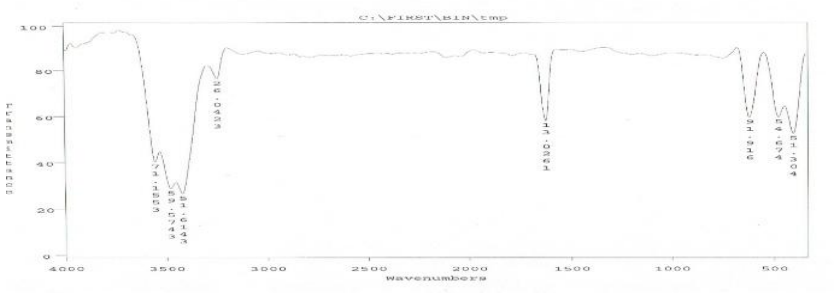

Fig. 7-Non-functionalized nanotubes FT-IR spectrum

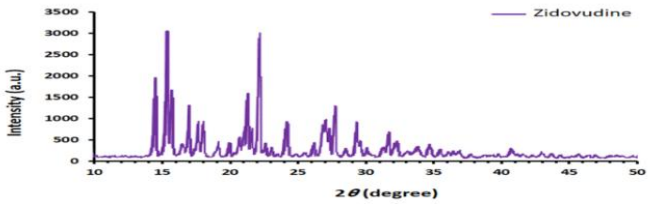

Fig. 8-Zidovudine XRD spectrum

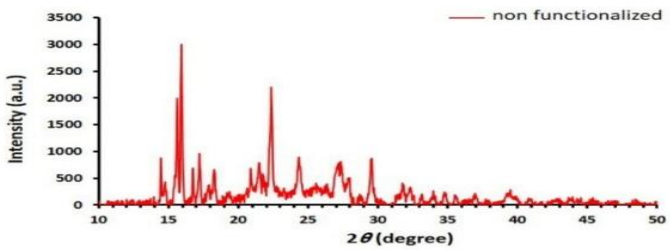

Fig. 9- Non-functionalized nanotubes with the sonicated Zidovudine XRD spectrum

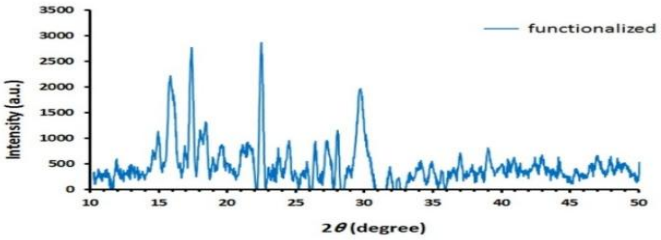

Fig. 10- Functionalized nanotubes with the sonicated Zidovudine XRD spectrum

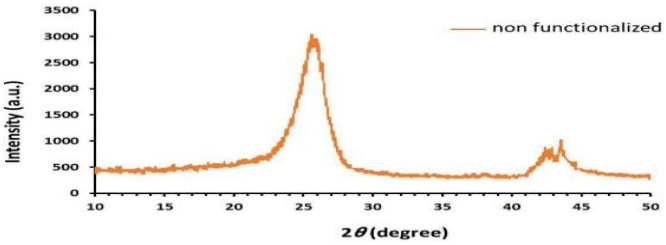

Fig. 11- Non-functionalized nanotubes XRD spectrum

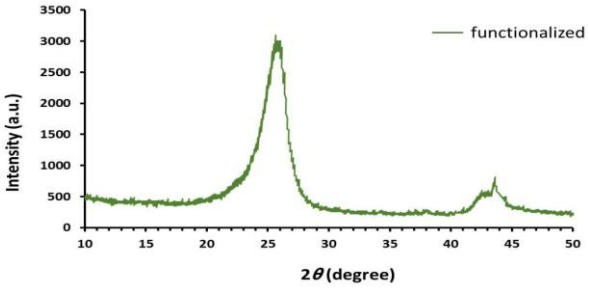

Fig. 12- Functionalized nanotubes XRD spectrum

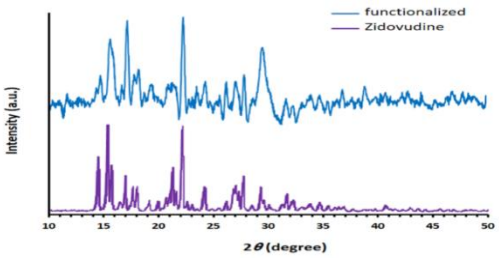

Fig. 13- Comparison between Zidovudine XRD spectrum and functionalized nanotubes sonicated with Zidovudine XRD spectrum

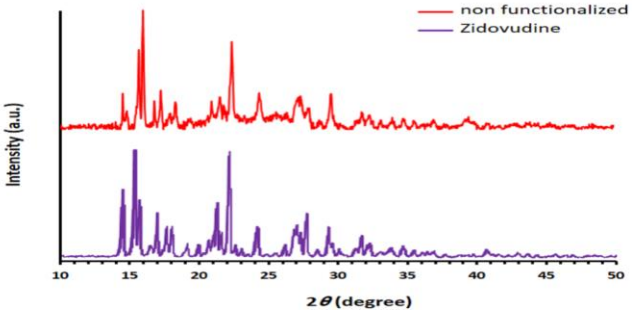

Fig. 14- Comparison between Zidovudine XRD spectrum and non- functionalized nanotubes sonicated with Zidovudine XRD spectrum

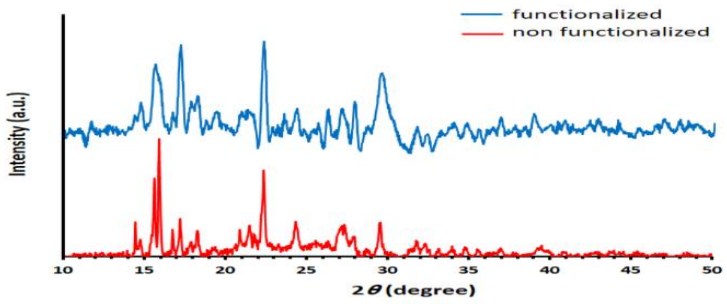

Fig. 15-Comparison between Zidovudine functionalized nanotubes XRD spectrum and sonicated with Zidovudine non-functionalized nanotubes XRD spectrum

3.CONCLUSION

We can conclude that configurations that use non-functionalized carbon nanotubes show direct effect of the solvent and the interaction between the nanotubes and Zidovudine is under the effect of solvent. On the other hand the interaction between functionalized nanotubes and Zidovudine in a covalent bond of Zidovudine and functional groups on the nanotubes shows that the best type of Zidovudine and nanotubes bond is covalent. It should be noted as a conclusion that the presence of 2 ketones in the Pyrimidine – 2 structures in $f-CNT-ZIDO1$ covalent structure leads to increased electron affinity of nitrogen in NH group in the ring with more acidic property than other hydrogen contents. Generally, it can be predicted that the binding of medication occurs through NH group of Pyrimidine ring-2, 4 Dionne.

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