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Study the mammalian acute toxicity of sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) upconversion nanomaterials

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Abstract

The potential toxicity and biocompatibility of sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) upconversion nanoparticles are of great importance for their biomedical applications. In this work, the acute toxicity of sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) upconversion nanomaterials toxicity was evaluated. Rats received intravenous injection of 10 mg/kg of $NaYF_4$: Er^{3+}, Yb^{3+} doped upconversion nanoparticles once dose and were observed at two different times (24 hours and 14 days post injection) for acute toxicity compared with control group. The results of hematological, blood biochemical analyses indicated that $NaYF_4$: Er^{3+}, Yb^{3+} doped upconversion nanoparticles treated rats survived for 14 days without any evident of toxic effects. Histopathological analysis of major organs including liver had no obvious signs of abnormality after intravenous injection of rats by $NaYF_4$: Er^{3+}, Yb^{3+} doped upconversion nanoparticles.

Keywords: $NaYF_4$: Er^{3+}, Yb^{3+} doped upconversion nanoparticles & acute toxicity.

1. Introduction

Nanoparticles (NPs) are particles with sizes ranging from 1 to 100 nm that entirely includes various features in comparison with their external bulk. In addition, the large surface area to volume ratio allows them to have specific physical, optical, mechanical and chemical characters [1].

Recently, many academic groups have been involved in research concerning nanoparticles due to their minute sizes, customized surface, multifunctional properties, and affinity to water. These are attractive markers that bring biomaterials and drugs to site-specific environments [2, 3].

To reflect long term safety, Kirchner et al. (2005) observed three essential categories of nanoparticle toxicity after working with living cells [4].

(1) Chemical toxicity of substances from which they have been produced.

(2) Their small size: nanoparticles may attach to cellular membranes and pass through the cells.

(3) Their shape: Such as, carbon nanotubes can rapidly penetrate cell membrane. By each, it is recently considered that particle size is essential for the particle toxicity [5].

Fundamental researches in nanotoxicology showed that the DNA has possessed a specific challenge when processing potential toxicological risks detected by nanomaterials [6, 7].

As a matter of fact to determine nanoparticle toxicity, in-vitro models are not enough alone to find accurate disorders to humans [8]. In-vivo researches are necessary to describe the mechanisms, pathways and penetration methods of nanoparticles in a complex multi cellular organism [9].

The toxicity of upconversion nanoparticles (UCNPs) is a serious problem that is not yet determined. The investigation of cytotoxicity depending on mitochondrial metabolic activity did not overcome all the obstacles up till now. The drawback of this fundamental research is that there is no apparent differentiation between cells that are actively dividing and those that are quiescent. Intravenous administration of UCNP did not have an accurate effect on the results of histology and hematology at the imaging dose, as well as on body weight and behavior. However, high doses of UCNPs lead to dangerous side effects, illustrating that the toxicity of UCNPs is dose-dependent [10]. Above all, the

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observation of traditional hematological and biochemical parameters were more utilized to better detection of the adverse health effects of UCNPs [11]. Moreover, researches did not observe marked prominent adverse event on experimental mice compared to control mice. Estimation of serum biochemistry parameters illustrated more quantitatively the effect of UCNPs on injected mice, especially those with potential hepatic disorders and renal dysfunctions [12]. The present study aimed to investigate the possible acute toxicity of sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) one of the upconversion nanoparticles after 14 days of treatments.

2. Materials and Methods

Chemicals:

Sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) upconversion nanomaterials: were prepared in the chemistry laboratory of National Institute of Laser Enhanced Sciences (NILES) and used after characterization by X-ray diffraction (XRD) and Transmission electron microscope (TEM).

Animals:

Adult male albino rats (twenty four) from the animal house of the National Organization for Drug Control and Research (NODCAR), Giza, Egypt, weighing 150 - 200 g, were used. Animal procedures followed the recommendations of the Ethics Committee of the NODCAR Giza, Egypt and the United States National Institutes of Health Guide for Care and Use of Laboratory Animals.

Experimental **design:**

Rats were divided into 2 main experimental groups, 12 rats of each. (6 rats of each interval) Control group (Normal saline treated group), the 2nd group (sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) upconversion nanoparticles treated group). Rats received 10 mg/kg intravenous injection of $NaYF_4$: Er^{3+}, Yb^{3+} upconversion nanoparticles once [13] and data were observed for acute toxicity at two intervals, at 24 hours and at day 14 post injection and were compared to control groups.

Blood Samples:

At the end of the experiment, blood samples were collected after light anesthesia using diethyl ether, by the orbital sinus technique. Blood samples were left to clot in clean dry test tubes and then were centrifuged at 3000 rpm for 10 minutes at 4 ºC. Serum was separated in eppendorff`s tubes then frozen at -20 ºC for the biochemical analyses.

Tissue collection:

After collection of blood samples from rats, liver was removed and washed with ice-cold saline solution (0.9%NaCl), weighed and stored at -80º C. for making liver tissue homogenate, the rest of each liver was fixed in formaldehyde buffer (10%) for histopathological evaluation.

Investigations:

For the determination of the liver function by Spectrum kit, based on the method of Henry R J et al. [14].

Serum creatinine and blood urea were determined using spectrum kit [15,16].

Nitrites and nitrate was determined according to the method of Papadoyannis et al., (1999) by HPLC [17].

HPLC determination

Brain tissues were weighed and homogenized in 10% (w/v) 75% methanol of HPLC grade. The homogenized tissue was centrifuged and the supernatant was used for HPLC-UV analysis. The HPLC device used was Agilent HP 1100 series (USA). It included a column oven, quaternary pump, Rheodyne injector, 20-µL loop, and variable wavelength UV detector. The energy carriers, monoamines, nitric oxide (NO) standards, used by high-performance liquid chromatography (HPLC) techniques, were also purchased from Sigma (St. Louis, MO, USA), with high purity, and all were of HPLC grade.

Preparation of the standard solution

Sodium nitrite and sodium nitrate used for the reference standard preparation with stock concentration 1mg/ml. A standard mixture of nitrite and nitrate was used to determine the retention times and separation of the peaks. Nitrite and nitrate concentrations were equal in the mixture solution.

HPLC analysis

Samples were analyzed on an Agilent HP 1100 series HPLC apparatus (USA). The analytical column was anion exchange PRP-X100 Hamilton, 150 x 4.1 mm, 10 µm. The mobile phase was a mixture of 0.1 M NaCl - methanol, at a volume ratio 45:55. The flow rate of 2 mL/min, wavelength adjusted to 230 nm.

Histopathological examinations:

Liver was collected at each time point and fixed with formalin. The fixed liver was embedded in paraffin, sliced at a thickness of 5µm and then placed onto glass slides. After hematoxylin–eosin (H&E) staining, the slides were investigated and photographed on an optical microscope **(Optech microscope, Germany).**

Statistical analysis:

Statistical analysis of the obtained data was performed by Statistical Analysis Systems Institute. Significant differences among means were evaluated using Duncan's Multiple Range Test. In the present study, data were statistically analyzed using SPSS 18.0 software (SPSS, Chicago, IL, USA) and are expressed as the mean ± SE. One way analysis of variance (ANOVA) was used for comparison among multiple groups. The difference was considered significant if p value < 0.05.

3. Results and Discussion:

Physicochemical characterization and long-term toxicity studies of upconversion nanoparticles still need to be performed before introducing them for wide spread use in drug screening, bioassays or bio-imaging [18].

Nevertheless, upconversion nanoparticles discovered since mid-1960s and widely used in optical devices. Moreover, rare earth-doped upconversion nanoparticles have been manufactured and are becoming clearer in biological sciences. Upconversion nanoparticles still need to be wide spread use in bioassays and bioimaging. So in the present study, we discuss the challenges of ensuring the biosafety of one type of upconversion nanoparticles, sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) in vivo.

It is well known that the majority of information on UCNPs is obtained from in vitro studies on cell cultures, and a few number of in vivo toxicity studies have been reported [13].

Sodium yttrium fluoride ($NaYF_4$) nanocrystals co-doped with the rare earth ions such as: erbium(Er^{+3}) and ytterbium (Yb^{+3}) were synthesized to modulate more upconversion nanoparticles safety. Fluoride is the best host matrix for doping lanthanides (Ln) to achieve upconversion nanoparticle emission. Sodium yttrium fluoride ($NaYF_4$) matrices able to be a better material due to highest upconversion rate between most discovered UCNP hosts [19].

To make these nanoparticles exhibited the same crystalline phase and their size and shape did not obviously change with this doping, they were analyzed by XRD and TEM respectively. To prepare small size Ln-doped upconversion nanoparticle with maintaining their luminescent intensity, need synthetic procedures are to be developed through adjusting reaction parameters, selection of host matrix and doping ions and appropriate surface coating. The synthetic procedure was used such as hydrothermal methods which is the best and cheapest methods.

Toxicity of upconversion nanoparticles performed in vivo was assessed by animal studies. The present work showed that healthy rats injected with sodium yttrium fluoride, erbium and ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) with dosages of 10 mg/kg of body weight exhibited no signs of abnormal behavior or mortality during the whole time of experiment. This agree with Liqin Xian and his colleagues 2010 as they investigated the long-term in-vivo distribution and toxicity of another type of UCNPs, ($NaYF_4$: Er^{3+}, Yb^{3+}) coated with the polyacrylic acid (PAA-UCNP). They found that mice remained alive for 115 days after the intravenous injection of 15 mg/kg of $NaYF_4$: Er^{3+}, Yb^{3+} (PAA-UCNPs) with no detected adverse health effects appearing in their bodies [12].

In the present study, complete blood counts, serum liver enzymes and renal functions parameters were assessed, the investigations were observed and the p values that were calculated by comparing the sodium yttrium fluoride: erbium, ytterbium doped ($NaYF_4$: Er^{3+}, Yb^{3+}) upconversion nonmaterials treatment groups (UCNP groups) and the control groups. According to the p values, no statistically significant differences between the treated groups and the control groups, all were within the normal range. For one example of the hematological parameters for complete blood counts table (1): The mean value of serum Hemoglobin (Hb) level in UCNP group experimental animals 1st interval: (1st day post injection of selected dose), was significantly decreased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 11.84 ± 0.58[a] gm/dl in UCNP compared to 12.85 ± 0.34[a] gm/dl in control group and the mean value of serum Hemoglobin (Hb) level in UCNP group experimental animals 2nd interval: (After 14 days post injection of selected dose), was significantly decreased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 13.14 ± 0.3 [a] gm/dl in UCNP compared to 13.42 ± 0.28 [a] gm/dl in control group, another example for the immunological parameters for complete blood counts: The mean value of serum WBCs level in UCNP group experimental animals 1st interval was significantly increased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 7 ± 0.15 [a] × 10^3 cells/cu. mm compared to 6.71 ± 0.17 [a] × 10^3 cells/cu. mm in control group and The mean value of serum WBCs level in UCNP group experimental animals 2nd interval was significantly increased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 7 ± 0.21 [a] × 10^3 cells/cu. mm compared to 6.99 ± 0.08 [a] × 10^3 cells/cu. mm in control group as shown in table (1).

The present study is also agreed with Liu S and Han MY 2010 [20] who suggest that serum biochemical analysis is usually used to determine whether the function of vital organs is damaged or not. For example, liver function parameters and kidney index were measured. So that the results showed that ALT, AST and ALP remain unchanged after consecutive administration for 7 and 14 days. The BUN levels in nanoparticles treatment groups were

significantly elevated at day 7, while they came back to the normal level at day 14. For example one parameter of serum liver enzymes such as table (2): ALT: The mean value of serum ALT level in UC group in experimental animals 1st interval: was significantly increased ($p<0.05$) compared to control groups. The recorded mean value was 31.23 ± 1.38 [a] U/L in UCNP compared to 29.18 ± 1.29 [a] U/L in control group and the mean value of serum ALT level in UCNP group in experimental animals 2nd interval was significantly increased ($p<0.05$) compared to control group. The recorded mean value was 29.75 ± 1.87 [c] U/L in UCNP compared to 29.54 ± 1.86 [c] U/L in control groups as shown in table (2) for serum liver enzymes. Renal functions investigations showed normal change with no dangerous effect on the animal. For example the mean value of serum creatinine level in UCNP group in experimental animals 1st interval was significantly increased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 0.85 ± 0.03 [a] mmol/L in UCNP compared to 0.79 ± 0.02 [a] mmol/L in control group and the mean value of serum creatinine level in UCNP group in experimental animals 2nd interval was significantly increased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 0.86 ± 0.03 [a] mmol/L in UCNP group compared to 0.79 ± 0.03 [a] mmol/L in control groups as shown in table (3)

Table (1): Effect of sodium yttrium fluoride: erbium, ytterbium upconversion nanoparticles on complete blood count after a single dose of treatment in adult male rats.

Intervals	Parameters	Groups	
		Control	UC
1st interval	Hb	12.85 ± 0.34[a]	11.84 ± 0.58[a]
	RBCs	5.29 ± 0.14 [a]	4.68 ± 0.28 [b]
	Platelets	752 ± 11.21 [a]	751 ± 23.89 [a]
	WBCs	6.71 ± 0.17 [a]	7 ± 0.15 [a]
2nd interval	Hb	13.42 ± 0.28 [a]	13.14 ± 0.3 [a]
	RBCs	5.26 ± 0.16 [a]	5.35 ± 0.15 [a]
	Platelets	743 ± 21.68 [a]	740 ± 14.21 [a]
	WBCs	6.99 ± 0.08 [a]	7 ± 0.21 [a]

Data represents the mean ± SEM.
a ,b means having different superscript letters in the same row differ significantly ($P<0.05$).

Table (2): Effect of sodium yttrium fluoride: erbium, ytterbium upconversion nanoparticles on liver functions after a single dose of treatment in adult male rats.

Intervals	Parameters	Groups	
		Control	UC
1st interval	ALT	29.18 ± 1.29 [a]	31.23 ± 1.38 [a]
	AST	32.01 ± 0.8 [a]	33.29 ± 0.83 [a]
	ALP	43.73 ± 1.4 [a]	46.8 ± 1.16 [a]
2nd interval	ALT	29.54 ± 1.86 [c]	29.75 ± 1.87 [c]
	AST	30.6 ± 0.98 [b]	32.77 ± 0.81 [b]
	ALP	42.77 ± 0.97 [a]	44.27 ± 1 [a]

Data represents the mean ± SEM.
a, b, c means having different superscript letters in the same row differ significantly ($P<0.05$).

Table (3): Effect of sodium yttrium fluoride: erbium, ytterbium upconversion nanoparticles on kidney functions after a single dose of treatment in adult male rats.

Intervals	Parameters	Groups	
		Control	UC
1st interval	Creat	0.79 ± 0.02 [a]	0.85 ± 0.03 [a]
	Urea	30.82 ± 1.22 [a]	28.97 ±1.15 [a]
2nd interval	Creat	0.79 ± 0.03 [a]	0.86 ± 0.03 [a]
	Urea	30.51 ± 0.74 [a]	32.64 ±0.79 [a]

Data represents the mean ± SEM.
a means having different superscript letters in the same row differ significantly ($P<0.05$).

Oxidative stress assays:

The levels of nitric oxide (NO) in sodium yttrium fluoride: erbium, ytterbium doped upconversion nanoparticles -treated groups were not significantly different from control ones, the mean value of Nitric Oxide (NO) level in UC group in experimental animals 1st interval was significantly increased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 0.49 ± 0.01^{a} nmol/g in UC compared to 0.48 ± 0.01^{a} nmol/g in control group and the mean value of NO level in UC group in experimental animals, 2nd interval was significantly decreased ($p<0.05$) compared to control group but within the normal range. The recorded mean value was 0.39 ± 0.01^{ab} nmol/g in UCNP compared to 0.4 ± 0.01^{a} nmol/g in control groups as shown in table (4). This result is agreed with Mingzhu Zhou et.al, 2019 who reported that the oxidative stress is an important cause of injury or inflammation for certain organs and concluded that upconversion nanoparticles just induce slight fluctuations of GSH and MDA levels in certain organs [21].

Histopathological Results:

The biodistribution of Sodium yttrium fluoride ($NaYF_4$) erbium (Er^{+3}) and ytterbium (Yb^{+3}) doped nanoparticles in different organs of treated rats was also investigated after intravenous injection. To assess the acute toxicity of $NaYF_4$: Er^{3+}, Yb^{3+} upconversion nanoparticles on rats at two different times 24 hours and 14 days post intravenous injection after one dosage.

The analysis was performed on the liver tissues to investigate signs of potential toxicity or accumulation of sodium yttrium fluoride: erbium, ytterbium doped upconversion nonmaterial ($NaYF_4$: Er^{3+}, Yb^{3+}) at doses of 10 mg/kg for 1day and after 14 days post injection of a single dose. Hepatocytes were arranged in rows that radiate out from the central vein, and no inflammatory infiltrates of hepatocytes were observed in liver samples. There was no change in the morphology of hepatocytes and central vein in the experimental and control groups. The main parenchymal tissue of liver structure was easy to distinguish and there was no sign of inflammations. Furthermore, normal hepatocyte structure and function and no central vein fibrosis or other abnormal phenomena was observed in the liver tissues for experimental groups, as shown in figure (1).

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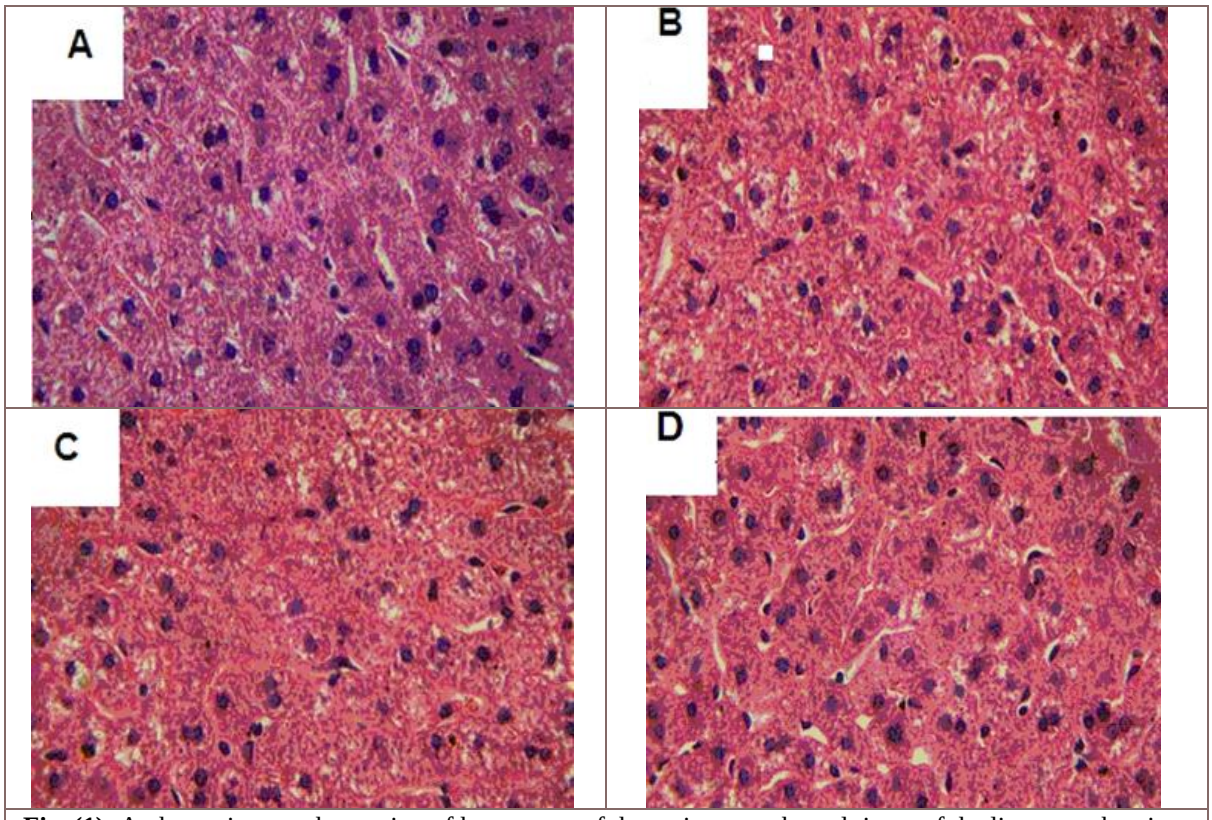

Fig. (1): A photomicrography section of hepatocyte of the main parenchymal tissue of the liver rats showing: **Experimental animals 1st interval which indicates for one day recovery:** Showed the control group (A) and upconversion treated group (B), which showed normal hepatocyte structure and function. **Experimental animals 2nd interval which indicates for two weeks recovery:** Showed the control group (C) and upconversion treated group (D) which showed normal hepatocyte structure and function.

Table (4): Effect of sodium yttrium fluoride: erbium, ytterbium doped upconversion nanoparticles on nitric oxide after a single dose of treatment in adult male rats.

Intervals		Parameters	Groups	
			Control	UC
1st interval	NO		0.48 ± 0.01 a	0.49 ± 0.01 a
2nd interval	NO		0.4 ± 0.01 a	0.39 ± 0.01ab

Data represents the mean ± SEM.
a, b means having different superscript letters in the same row differ significantly (P<0.05).

The only adverse observation in the first interval (1 day recovery) some of UCNP appeared in liver tissue but they disappeared after 14 days recovery (2nd interval). This result agrees with Haase and Schafer, (2011) study when they found hugely accumulation of UCNP in different animal organs 30 minutes after injection. These amounts decreased at 24 hours after injection. Moreover, no detectable UCNP were found at day 7 after injection [22]

Conclusion

Our results showed that generally, there was no significant difference between the studied groups, also, results on rats revealed that there was no obvious sign of abnormality on their major organs including the liver. This may reflect the safety of Sodium yttrium fluoride ($NaYF_4$) erbium (Er^{+3}) and ytterbium (Yb^{+3}) doped to be used in biological application like cancer treatment and bioimaging.

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