Cheap, Suitable, Predictable and Manageable Nanoparticles for Drug Delivery: Quantum Dots

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Abstract: Recently ZnO quantum dots are reported to be very promising for drug delivery. It has also been reported that adsorptive material can deliver drug molecules by simple adsorption and they release the drug at site of action by subsequent desorption. This has been shown for carbon nanotubes and some other hydrophobic molecules for transdermal applications in the literature. Therefore it was aimed to find the effect of ZnO quantum dots on transdermal penetrations of selected model drug molecules (ketoprofen and dexketoperofen). Drug coated ZnO quantum dots were found to increase transdermal penetration of ketoprofen and dexketoprofen through rat skin.

Keywords: Dexketoprofen, ketoprofen, kuantum dots, penetration, transdermal, ZnO.

INTRODUCTION

Nanotechnology is a rapidly developing field in especially engineering and medical sciences. The most common problem with these kinds of nanotechnology based particles so called nanoparticles, is to predict their behavior in biological mediums and to get rid of them after finishing their jobs, after released all drug molecules. Their release properties are strongly influenced by the medium and environmental conditions. When nanoparticles enter the body, they are simultaneously surrounded by phagocytic cells and travels all together and drug release starts to take place. Many nanoparticles can even enter the cell nucleus (i.e. carbon materials, carbon nanotubes) [1]. As long as *in vitro* drug release experiments are performed in artificial mediums with lack of phagocytic cells it is really difficult to predict *in vivo* releases. It is also truth that, when nanoparticles enter inside of the cell it triggers some irritation reactions and many chemicals release to the medium which can alter the conditions. Another problem is to get rid of the nanoparticles after end of the release. Recently it has been proposed that carbon materials can be used for drug delivery. Although carbon nanotubes (CNTs) are one of the most studied nanomaterials in material sciences and physics but not in medical sciences and pharmacy. Recent study results indicate that the most and safe body site for nanoparticle applications is to skin. If CNTs are able to penetrate through skin layers or if they can be able to provide drug molecules on to the skin surface they can be used to deliver active substances for therapeutic purposes but exploration of their pharmaceutical applications remains at a very early stage [2]. It has been also shown that single-walled carbon nanotubes (SWNTs) and multiwalled carbon nanotubes (MWNTs) can be internalized by living cells and pass across the biological membranes in cell culture studies [1]. The internalization of carbon nanotubes by corneocytes has been shown in the literature [3]. It has been first shown in the literature that SWNTs and MWNTs can be used to deliver drug molecules through deeper skin layers [3]. The application of iontophoresis using carbon nanotube electrode having adsorbed drug molecules on their surface has been shown and molecules successfully transferred through deeper skin layers [4]. Carbon nanotubes have been also used to increase dermal penetration of drugs [5, 6]. The penetration of indomethacin through full thickness of rat skin was enhanced when indomethacin adsorbed CNTs were used (flux values were 0.119±0.037 μg/h for indomethacin alone; 0.330±0.052 μg/h for indomethacin with MWCNTs and 0.347±0.106 indomethacin with double walled carbon nanotubes (DWCNTs, n=3, ±SD) [5]. The penetration enhancement was higher with DWCNTs and MWCNTs however the mechanism was still unknown. The CNTs may act to facilitate presentation of the drug to the lipophilic membrane and/or they facilitate penetration through the skin accompanying the drug into the dermal tissue. Similar results were obtained when pig ear skin was used. Penetration of indomethacin was found to be much higher when indomethacin molecules were introduced to the skin surface with CNTs [5]. The main problem with CNTs is the biocompatibility. Although latest literature results suggest dermal application of CNTs do not create any negative biocompatibility issue [5, 6] but it still remain as a question.

Quantum dots can also be used for diagnosis and monitoring cell trafficking [7]. Recently it has been proposed that quantum dots can be used for drug delivery. Zhang *et al.* have synthesized highly uniform quantum dot-doped chitosan nanobeads for traceable siRNA delivery [8] and most recently Jia *et al.* have combined PEI-coated carbon nanotubes with quantum dots for antisense oligodinucletide delivery [9]. These innovative approaches have opened up exciting opportunities in targeted DNA and RNA delivery. For example, after being treated with quantum dots – oligonucleotides, cells with differential expression levels of the pro-

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tein of interest, which correlates with quantum dots fluorescence, can be isolated using fluorescence-activated cell sorting; and, if multicolor quantum dots are used, it will allow the screening of siRNA sequences and the monitoring of downstream cell behaviors in a multiplexed manner.

One of the more interesting properties of such nanoparticles so called quantum dots has been indicated in the literature as antimicrobial effect [10]. Antibacterial effect naturally comes from metals and metal oxides, naturally occurring antibacterial substances, carbon-based nanomaterials, and surfactants in the structure [11]. Very interestingly some nanoparticles made of metal oxides are stable under harsh processing conditions and have selective toxicity to bacteria when exhibiting a minimal effect on human and animal cells [12-14]. For example, ZnO nanoparticles are reported to be nontoxic and biocompatible, have been utilized as drug carriers, cosmetics ingredients, and medical filling materials [15, 16]. Recently, ZnO nanoparticles were found to have an antibacterial activity against *E. coli* O157:H7 and enterotoxigenic *E. coli* [12, 17, 18]. ZnO nanoparticles have also some advantages over Ag NPs, such as a low production cost and UV-blocking properties [19]. ZnO nanoparticles deposited cotton fabrics reported to show quite strong antibacterial activity against S. aureus [20]. ZnO nanoparticles are believed to destruct lipids and proteins of the bacterial cell membrane, resulting in a leakage of intracellular contents and eventually the death of bacterial cells can be seen [17,21]. In addition, generation of hydrogen peroxide and Zn^{+2} ions were suggested to have a key role for antibacterial effect [22]. ZnO quantum dots are also small nanoparticles and possess antimicrobial activities against L. monocytogenes and S. Enteritidis in liquid egg white and culture media, and *E. coli* O157:H7 in culture media [23]. The inhibitory effect was found to be concentration dependent and the higher the concentration of ZnO resulted in higher the antibacterial effect.

ZnO and TiO_2 quantum dots were shown to be fluorescent and used for the colorectal cancer area imaging [24]. This results show the affinity of ZnO quantum dots to the cancer cells. The electrostatic nature of nanoparticles is another important factor. Electrostatic interactions between positively charged nanomaterials and target cells are believed to play an important role for adhesion to the cellular wall and uptake [25]. Comparing to normal eukaryotic cells whose outer part consists of neutral charged zwitterionic phospholipids [26], cancer cells frequently maintain a high concentration of anionic phospholipids on their outer surface and this makes outer part negatively charged [27-29]. In addition, it has been shown that intracellular pH increases with cell cycle progression and proliferation [30, 31], which could affect electrostatically-driven interactions with charged particles at the cell membrane surface. It is very interesting that while polycationic polymer particles and cationic fullerenes cause substantial disruption of biomembranes, their neutral or negatively charged counterparts fail to cause measurable effect [32]. While nanoparticles with higher positive charge may be desirable for higher toxicity to cancer cells, very high positive charge may not be suitable for *in vivo* cancer treatment due to rapid serum clearance [33], but if it can be presented at the cell surface of cancer tissue, effective treatment may be accomplished. ZnO nanoparticles are also reported to have a positive charge on their surface [34].

The surface modification of ZnO quantum dots is also possible and as a conclusion ZnO quantum dots appeared to be the most suitable material for drug transport having higher surface area and being an adsorptive material and natural selectivity to cancer cells. Therefore it was aimed to prepare ZnO quantum dots and to study their drug molecule carrying properties.

MATERIALS AND METHODS

Materials

Zinc chloride was purchased from Riedel de Haen Seelze, Hannover Germany. Nitric acid was form Merck KGaA, Darmstadt, Germany. Methanol and petroleum ether was obtained from J.T. Baker, New Jersey, USA. Ketoprofen was obtained from Fargem Pharmaceutical Research and Development Center of Industry and Trade Co., Ltd., Duzce, Turkey. Dexketoprofen was from Huangshi Shixing Pharmaceutical Co., Ltd., Hubei, China. Other chemicals and reagent were of analytical grade.

Methods

Preparation of ZnO Quantum Dots

ZnO quantum dots were prepared using an adapted procedure based on the literature [35]. Zinc chloride (13.4 mmol) was dissolved in HNO_3 (26.8 mmol) and 5 mL methanol was added and dried at 80°C. Dried sample was dissolved in 125 mL of methanol. Sodium hydroxide (23 mmol) dissolved in 65 mL of methanol at 60°C and added in 10 min to the zinc nitrate solution under vigorous stirring. Temperature was kept at 60°C and after 5 min, the solution became translucent. After reacting for 1.5 hours, the quantum dots started to precipitate and the solution became turbid. The heater and stirrer were removed after 2 h and 15 min and the nanoparticles were allowed to precipitate for an additional 2 h. Precipitate and mother liquor were separated, and the precipitate was washed twice with 20 mL of methanol.

Coating ZnO Quantum Dots with Drugs

ZnO quantum dots (400 mg) were dispersed in methanol (100 mL) and dexketoprofen (400 mg) was added and dissolved. Petroleum ether (100 mL) was added slowly to the ZnO quantum dot and drug mixture. Dexketoprofen came out and then coated ZnO quantum dots were obtained. Similarly ZnO quantum dots (400 mg) dispersion in methanol (100 mL) was prepared and ketoprofen was dissolved (400 mg). Cold water was then added slowly and ketoprofen coated ZnO quantum dots were obtained. Samples were dried in the oven at 40°C over night.

Determination of Characteristics of ZnO Quantum Dots

A transmission electron microscope (TEM, Fei Tecnai G2 Spirit Biotwin, Tokyo, Japan) was used. Briefly, ZnO quantum dots were dispersed in methyl alcohol and kept in an ultrasonic water bath for approximately 3 min. The suspension was placed onto a microscope plate and dried for 24 h

under vacuum. The physical appearances of ZnO were than determined. The physical appearance of ZnO quantum dots was investigated under atomic force microscope (AFM, Nanomagnetic Instruments Ltd., Oxford, UK.). Briefly, quantum dots dispersion were sonicated for a minute. Dispersion placed as a droplet on the surface of mica and dried under laminar flow. Tapping/dynamic mode was used for investigation. The force constant of aluminum reflex coated cantilever was Diamond coated tip (DI-NCHR-20, 204-477 kHz, 10-130 N/m, Nano Censors, Neuchatel Switzerland). Particle size of the quantum dots were determined using TEM and zeta potentials were calculated using Malvern Zetasizer (Worcestershire, UK).

Penetration Experiments

Passive penetration experiments were performed with Franz-type diffusion cells (receptor volume 2.5 mL, donor volume 1.5 mL, cross sectional area is 1 cm^2 for diffusion, made by Caliskan Glass, Ankara, Turkey) and full-thickness rat skin. Rat skins were obtained from the Pharmacology Department from control group of other experiments; the skins were gently removed from the underlying tissues and kept in a deep freezer until used. Diffusion experiments were performed at 34°C. Aqueous solutions containing dexketoprofen or ketoprofen or dexketoprofen or ketoprofen coated ZnO quantum dots were applied to the donor chamber and samples were collected at different time points from the receiver chamber (pH 7.4 isotonic PBS) and replenished with fresh solution at same temperature. Samples were then analyzed using spectrophotometer. Analyses were performed at 265 nm using validated method (r^2=0.999, method was validated and found to be linear, specific, sensitive, reproducible).

RESULTS AND DISCUSSION

Prepared ZnO quantum dots were found to be fluorescent when analyzed under UV lamp as it has been stated in the literature [36]. (Fig. **1**) shows the fluorescent properties of ZnO quantum dots. Light emitting properties of ZnO quantum dots are completely depend on the size. Smaller particle size gives bright yellow light emission. The particle size determination was initially performed using a particle sizer but scattered results were obtained because of fluorescent nature of the samples. Zeta potentials of samples were also measured. Zeta potentials of ZnO quantum dots were found to be -1.557±0.109 for naked quantum dots, -20.467±1.348 for ketoprofen coated quantum dots and -0.214±0.171 for dexketoprofen coated quantum dots (mean±standard error of the mean (SEM), n=3). These results indicate that surface of the quantum dots were occupied with drug molecules.

The particle size was also found to be increased after drug loading. The physical appearance and particle sizes of the prepared quantum dots were investigated under TEM (Fig. **2**). It was clearly seen in the figure that quantum dots aggregate after drying and very tiny particles can be found around aggregated mass. Particles were found bigger after drug loading. Initially particle size was determined smaller than 10 nm, but after drying particles were aggregated and size range was found to be increased.

Fig. (1). Physical appearance of prepared ZnO quantum dots under UV lamp (345 nm).

Particles were also investigated using AFM. (Fig. **3**) shows typical ZnO quantum dots under AFM. ZnO quantum dots were found to be aggregated as it was seen under TEM and therefore bigger clusters and joined particles were observed.

Recent literature findings suggest that a material used for drug delivery may adsorb parent drug molecule and subsequent desorption actively delivers the drug molecule to the site of action [5, 6]. Such material like carbon nanotubes (CNTs) were found to be suitable material for drug transport through the skin having higher surface area and being an adsorptive material. Moreover, higher penetration has been shown to be possible when drug adsorbed CNTs were used for transdermal administration [5, 6]. Transdermal administration has got some advantages over conventional routes such as having little hepatic first pass effect etc. Skin is the biggest organ in the body. The ultra-structure of the skin and the epidermis is different at molecular level according to body site, gender and species which makes molecular diffusion different. The tortuous epidermal lipid layers limit drug permeation (the size limitation is reported to be 50.4nm [37]. The skin is practically impermeable to typical particles or even to colloidal components with the exception of major opening namely pores, shunts or lesions on the skin and of some hydrophilic pathways in the stratum corneum. The radius of negatively charged hydrophilic transepidermal pores has been calculated with the range of 13–27 nm [38]. Obviously, skin pores wider than 30 nm are not compatible with the protection role of the skin; because of rapid evaporation or loosing water can be a dramatic problem if skin has got that large pore. However, the transepidermal pathway and pores and their distributions depend on the size and shape of the clusters in the stratum corneum. In some places, a narrow average openings (50.4 nm water evaporation pathways) exist but in other places much wider pores (100 nm inter corneocyte pathways) claimed to be exist [38]. A few micrometer wide follicular shunts on clean human skin are open all the time. The hydrophilic path between the skin cell clusters, can act as a transcutaneous shunt, which is typically wider than 30 nm and almost permanently open. Transepidermal shunts thus cover a broad spectrum of widths, encompassing anything between a relatively wide inter cluster gap (width 5 μm), a hair follicle (width 5 μm) and a cutaneous

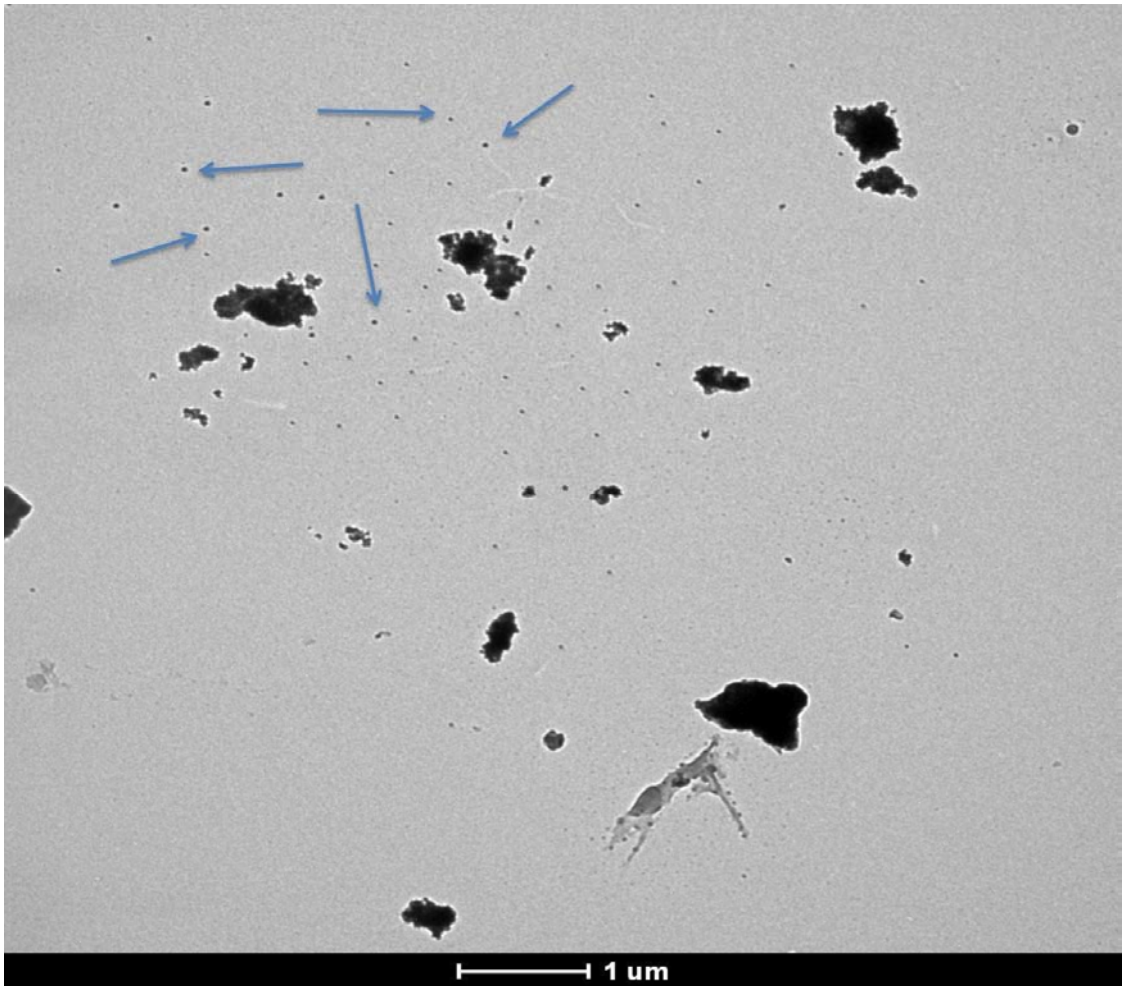

Fig. (2). Physical appearance of prepared ZnO quantum dots under TEM without drug loading. Arrows show independent quantum dots among aggregated quantum dots.

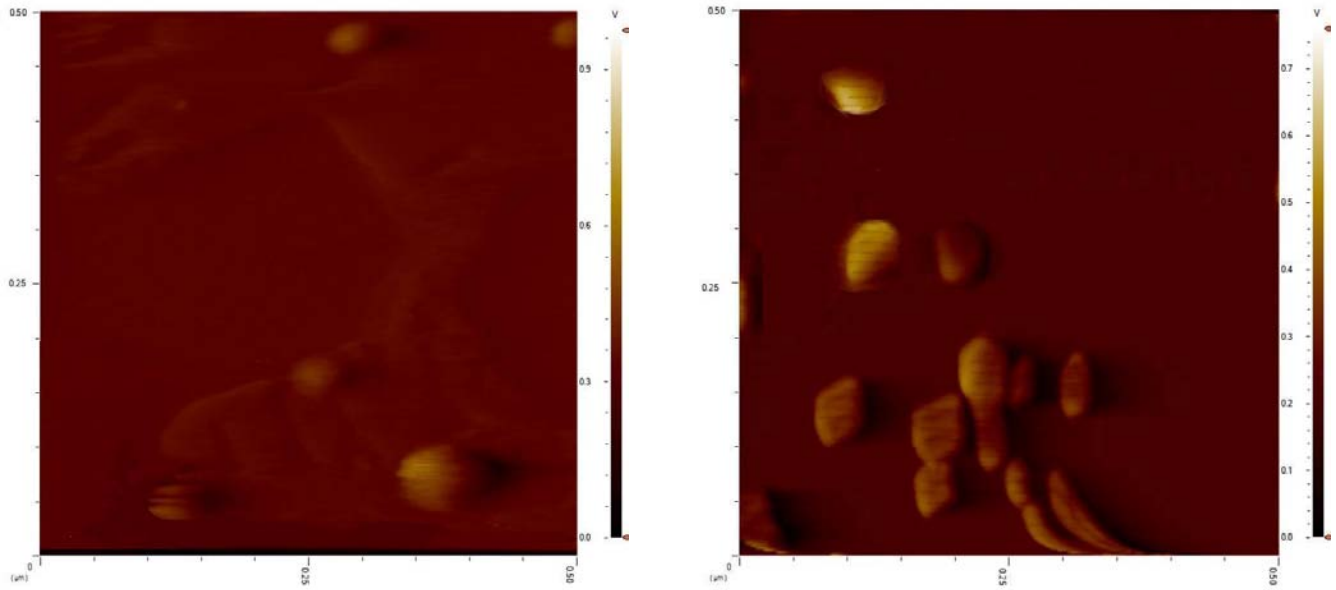

Fig. (3). Physical appearance of prepared ZnO quantum dots under AFM.

gland (width 50 μm) [38]. Penetration of nanosized materials through the skin layers can be achieved by several complex mechanisms [39-44]. They can enter through the pores or through the lipid bilayers or they can alter the barrier function of the lipids in the membrane (the fluidity of the membrane can be altered or molecules may remain among the lipids in the membrane bilayer and they can alter the composition of the membrane) or penetrant can be bound to the material of interest and these can then penetrate together. The hydrogen bonding acceptor or donor ability plays an important role [45].

It has been shown in the literature that CNTs are suitable for drug transport since they consist of an adsorptive material with a high surface area [5, 6]. The CNTs investigated so far did not found to be penetrated through the skin layers, and their penetration enhancement is via adsorption and subsequent desorption (i.e. depot effect) [5] or may be alteration of thermodynamic activity of the molecule plays a role [46]. CNTs have reported to be useful to increase transdermal penetration for especially hydrophobic drugs. Quantum dots are also small crystals having quite large surface area. Therefore quantum dots are coated with drug molecules and subjected to transdermal penetration experiments. (Fig. **4**) shows the penetration properties of ketoprofen and dexketoprofen through rat skin.

Higher penetrations were clearly seen with ZnO quantum dots. ZnO quantum dots are not soluble in water; they only provide higher surface area. As it has been stated in the literature [5,6] quantum dots with higher surface areas resulted in higher penetrations. Similarly permeability coefficients (as cm^{-1}) were higher with quantum dots (log $kp_{Dexketoprofen}$= -3.351±0.048; log $kp_{Ketoprofen}$= -2.666±0.032; log $kp_{Dexketoprofen+QD}$= -2.748±0.012; log $kp_{Ketoprofen+QD}$= -2.532±0.032 (mean±SEM, n=3)).

All experiments have been performed and current knowledge show us that the transdermal application will be the best approach because the outmost layer of the skin (stratum corneum) is already constituted from dead cells which are not capable to actively internalized any molecule, active endocytosis is not possible.

ZnO is considered to be generally recognized as safe substance by the Food and Drug Administration Office (FDA). Safe substance commonly refers to materials in the micron to larger size. When it is reduced to the nanoscale it may possible for them to develop new actions of toxicity. Therefore, a detailed evaluation of nanomaterial toxicity in both *in vitro* and *in vivo* systems is needed. One common approach to increase biocompatibility and reduce particle aggregation is to coat nanoparticles with polymers to make them less toxic and more suitable for drug delivery applications [47]. The possibility of functionalization of ZnO quantum dots have been shown and functionalized, biocompatible ZnO quantum dots have been prepared [48]. More interestingly, recent literature results indicate that ZnO quantum dots can be used for the treatment of cancer and ZnO quantum dots based delivery system may be more suitable [47, 48]. Although ZnO quantum dots are very promising for drug delivery, the more and detailed studies are still needed.

CONCLUSION

All these data and results represented and discussed here show that ZnO quantum dots can be used to deliver active drug molecules through skin successfully. Moreover, although all these are at the development stage, ZnO quatum dots can be also used as it is. Quantum dots have quite large surface area to adsorb drug molecules and subsequently they can release the drug. Functionalization of quantum dots and more developments are still available to apply. These applications will develop these systems and more opportunities for different applications will also be possible. Quantum dots are found to be suitable for drug transport being an adsorptive material and having high surface area. Their penetration enhancement found to be possible via adsorption and subsequent desorption (i.e. depot effect).

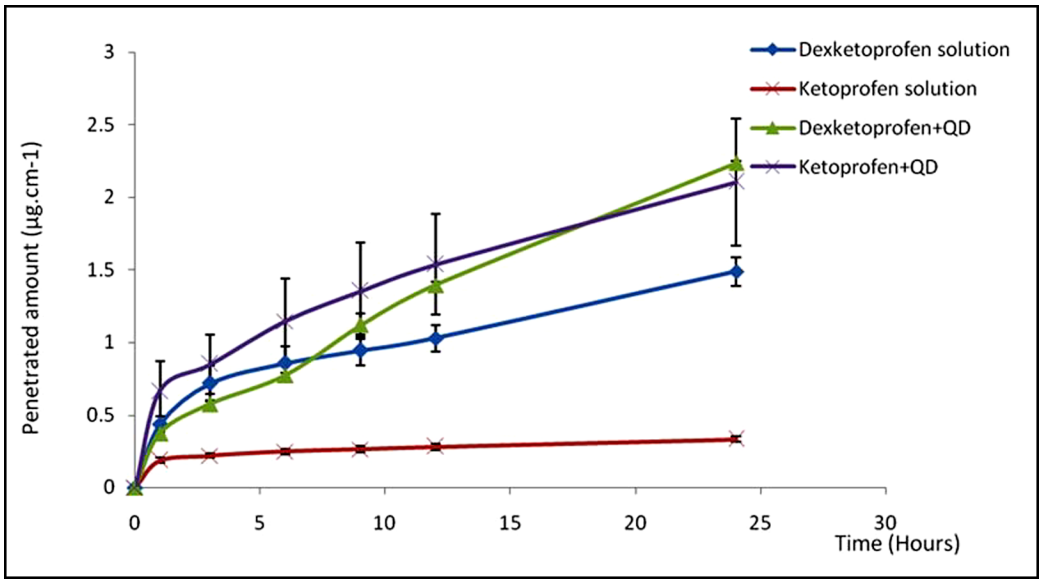

Fig. (4). Penetration properties of ketoprofen and dexketoprofen through rat skin with and without ZnO quantum dots (Error bars represent standard error of the mean - SEM, n=3).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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PATIENT CONSENT

Declared none.

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