Pharmacological Studies on Tetracyclines and Tetracycline Nanoemulsion Formulas.

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The study was done to compare the pharmacokinetic and pharmacodynamics of 50 mg/kg b.wt tetracycline hydrochloride (TC-hcl) and tetracycline nanoemulsion (TC-nm) formulas in rabbits and detection of their effect on standard and field bacterial strains. After oral TC concentration in plasma started to be detected at 0.25 h, reach the maximum at (0.5 h TC-hcl) and 1 h.(TC-nm) and decline at 12 hours. Following a single i.v administration a volume of distribution V2 (0.292±0.111 L/kg) in TC-nm than for TC-hcl (0.216 ± 0.183L/kg) and was slowly cleared (0.393±0.183 L/h/kg) in TC-nm than in TC-hcl (0.415±0.311 L/h/kg). After oral administration a rapidly absorbed with significant slowly absorption half-life t1/2 α (0.550±0.090 h and 0.176±0.058 h.) and elimination half-life t1/2 β (4.215±1.661 h. and 1.58±1.447 h.) with higher calculated Cmax of (4.215±1.661 μg/ml and 1.58±1.447 μg/ml) achieved at prolonged calculated tmax (0.759±0.149h. and 0.356±0.305 h.) in TC-nm than in TC-hcl, respectively.

The value of TC-hcl and TC-nm MIC was the same for Staph. Aureus 6538, Staph. Epidermidis 12228, E.coli 8739 were 0.14, 0.8 and 0.12 μg , respectively, and interpreted as sensitive. Field sensitive Corynebacterium, E.coli, S. typhimurium, S. enteriditis and Staph. leutus isolates MIC value was 1.4, 8, 2, 1.6 and 2 μg for , respectively. Tetracycline resistant 2 Staph. scuiri (18 and 16µg) and 2 Staph. xylosis (18 and 6µg).

Keywords: Pharmacokinetics, pharmacodynamics, Tetracycline, nanoemulsions, MIC, Rabbits.
selectivity, enhanced activity against intracellular pathogens, protection of antibiotic drugs against hydrolytic activity of enzymes, decreased toxicity, enhanced penetrability, and thereby increased residence time of the drug in macrophages [10,11].

Tetracycline hydrochloride–loaded particles was reported to be efferent against *H. pylori* [12], *P. aeruginosa* [13], *E. coli* strains in pigs [14], Salmonella spp. *E. coli*0157:H7 (VT-), *P. aeruginosa*, *Staph. aureus* and *L. monocytogenes* [15].

The synthesized tetracycline-loaded calcium phosphate nanoparticle (Tet-CPNP) bactericidal activity of nano-particulate tetracycline was investigated by agar plating, spectrophotometry, and phase contrast-fluorescence-atomic force microscopy and flow cytometry techniques. Efficiency of tetracycline loading in CPNP was about 20% and the minimum inhibitory concentration (MIC) was in the range of 20–40 μg/ml on multiple antibiotic resistant bacteria like *E. coli, S. kentuckey* and *Shigella flexneri*, whereas MIC of free tetracycline was in the range of 150–180 μg/ml [16].

The integration of PK (bioavailability and clearance) and PD (MIC) indices allows predicting efficacy and potency of a drug in the early phase of drug development and supports post-marketing surveillance [17, 18].

Therefore this study was planned to evaluate the Pharmacokinetics and antibacterial activity of prepared tetracycline nanoemulsion formulas as compared with tetracycline and in vitro.

**Materials and Methods**

**Tetracycline**

**Tetracycline-loaded nanoemulsion (TC-nm)**

Prepared and characterized TC-nm was supplied by Amer et al. [30].

**Tetracycline hydrochloride (TC-hcl)**

TC-hcl was obtained as pure powder 100% from El-Nasr pharmaceutical chemicals Co. (Abu Zaabal, Egypt).

**Pharmacokinetics**

**Rabbits**

Male New Zealand white rabbits, weighing 3.25-3.75 kg were obtained from animal house Faculty of Veterinary Medicine Cairo University. Rabbits were allowed for acclimatization for 15 days before being used. Animals were housed singly in stainless steel cages in a separate animal room at an environmental temperature of 20-24°C and will ventilation and a 12 hour light/dark cycle. Rabbits were fed on antibacterial free balanced commercial pelleted ration free from antibacterial drugs. Rabbits were given ration and drinking water ad libitum.

**Groups and administration**

Sixteen (16), white male New Zealand rabbits were randomly divided into 2 groups, 8 animals/group. Animals of group 1 given TC-nm and animals of group 2 given Tc-hcl. Single dose of 50 mg/kg body weight (BW) from each preparation will be given for each rabbit using oral and intravenous (i.v) route, with 14 day interval to insure complete drug clearance from rabbits body [30,32,33]. Blood samples were collected at different time intervals at 0.083 (5 min), 0.15 (0.15 min), 0.5 (30 min), 1, 2, 4, 6, 8, 10, 12 and 24 hours after each dose administration. Individual non-coagulated blood samples were collected from ear vein through i.v catheter for separation of plasma [34, 35]. The collected plasma was stored at -80 ºC till determination of tetracycline using microbiological technique.

**Antibiotic assay**

Blood samples were centrifuged at approximately 1500 rpm. The plasma was collected and either tested immediately or stored frozen at -80°C in individual vials until assayed. Each sample was induplicate assayed for the presence of tetracycline using the plate disk method as previously described [36]. Cultures of *Bacillus cereus varmycoides* ATCC 1177815 (Difco Laboratories, Detroit, Michigan) freshly prepared were used as the test organism in antibiotic assays. All tests were done in duplicate, including standard controls. The minimum level of sensitivity of the assay was 0.02 µg/ mL of serum and compared with standard curve. Samples with drug levels lower than 0.02 µg/ mL were recorded as undetected.

**Pharmacokinetic modeling**

Compartmental analysis is a widely used technique to quantitatively evaluate and predict the in vivo fate of a drug by modeling the concentration–time data with a suitable. PK compartment model. Pharmacokinetic values were calculated using PKsolver program [37] and values were expressed as mean ± SD. The actual maximum concentration in plasma (Cmax) and time to maximum concentration (tmax) were determined from the concentration–time relationship for each rabbit. The duration of time that the plasma concentration of tetracycline exceeded 0.12 µg/mL was determined for each rabbit. This concentration cut point was selected...
based on data from rabbit where the in vitro MIC for *Bacillus cereus varmycoides* ATCC 1177815 0.07µg/ [38].

A two compartment open model was applied to data obtained following IV injection and pharmacokinetic values calculated using standard equations [39]. A two compartment model provided the best model fit based on residual analysis when compared to 1 or 3 compartment models. Bioavailability (F) of tetracycline after oral injection was calculated as a percentage using a standard equation [40] as: 

\[ F = \frac{{AUC_{oral} \times 100}}{{AUC_{IV}}} \]

**Potentiometric Assays**

Antibacterial activity and MIC determination

**Bacterial strains**

Field and standard bacterial isolates were obtained and used for testing their susceptibility to tetracyclines. Standard strains *Staph. Aureus* 6538, *Staph. Epidermidis* 12228, *Ecoli* 8739. Field bacterial strains including tetracycline sensitive strains including *Corynebacterium, E. coli*, *S. typhimurium* *Staph Leutus* and *S. enteritidis* [41,42]. Coagulase negative staph ylococci tetracycliner esistant include 2 *Staph. xylosis* and 2 *Stap. scueri* [43]. Field resistant strains *Corynebacterium cervicis, E. coli* and *S. typhimurium* were supplied by Dr. M.M. Amer, poultry clinic lab. Fac. Vet. Med. Cairo University).

**Culture and preparation of bacterial inoculum**

Overnight Mueller Hinton broth cultures of all bacterial strains at 37°C were prepared. Bacterial inoculum density for preparation of inoculum suspension was adjusted to be equal that of the 0.5 MacFarland standards was done by picking up of 4:5 colonies from 24 hour culture in 2 ml of Mueller-Hinton broth. To aid comparison compare the test and standard against a white background with a contrasting black line. Suspension contain for determination of tetracyclines were previously used [45-47].

**Minimum inhibitory concentration (MIC)**

Stock solutions of both TC-hcl powder and TC-nm was prepared in concentration of 1000 mg/L in sterile saline. Working solutions of each tested formulas were freshly prepared in concentrations 0.06 - 128 µg/ml. MIC for all bacterial strains was performed using Mueller Hinton agar (Oxoid) plates in Petri dish 9 cm in diameter. for control without antibiotic 2 mL of sterile distilled water in a Petri dish and 2 mL of each dilution antibiotic from the lowest to the highest concentration were added to a series of Petri dishes followed by 18 mL of Mueller-Hinton agar medium. Mixed well and allowed to dry at 35 to 37°C for 30 min, a 1ml of suspension was delivered on to the surface of the agar and allowed the inoculum to be absorbed into the agar before incubation. Inoculated plates were incubated 37°C for 18 h. All tests were done in triplicate. *Bacillus cereus varmycoides* ATCC 1177815 was used as MIC control positive control strain for 0.16µg/ml. MIC endpoint as the lowest concentration of antibiotic in mg/L at which there is no visible growth and interpreted [38, 44].

**Statistical analysis**

Data was presented as mean ± SD. Selected pharmacokinetic values were compared for IV and oral administration of tetracycline using mixed models analysis of variance and a compound symmetry covariance matrix (PROC MIXED, SAS 9.2, SAS Inc, Cary, NC). A P value <0.05 or P < 0.001 was considered significant.

**Results and Discussion**

Since the discovery of Tetracyclines in the 1940s, it used extensively in the prophylaxis and therapy in human and animal infections. Tetracyclines still widely used in veterinary medicine for the treatment of gastrointestinal, respiratory and skin bacterial infections [1-3].

**Pharmacokinetics**

Tetracycline concentration in rabbit plasma was determined following TC-hcl powder and TC-nm administration in a single dose of 50 mg/kg b.wt via oral and IV. Micro-biological assays for determination of tetracyclines were previously used [45-47].

The mean plasma tetracycline concentration–time relationship following a single oral administration of 50 mg/kg of BW (Table 1) TC-hcl concentration in plasma started to be detected at 0.25 h, reach the maximum at 0.5 h followed by decline at 12 hours as 4.26 ± 1.158µg/ml, 7.60±1.102µg/ml and 0.03±0.005µg/ml, respectively. While, TC-nm was determined at 0.25 h and reach the maximum at 1 h and decline to the minimum value at 12 h as 3.77 ± 0.923µg/ml, 7.41±2.184µg/ml and 0.08± 0.008µg/ml, respectively. Similar results were detected in rat [48], in dogs [49], in man [50], in rabbit[30]. The drug had a rapid distribution phase [31, 51]. The non-detected concentration at 24 was reported in dog [27].

Nanoemulsion showed higher concentrations persisted higher than MIC for longer time (more

TABLE 1. Plasma concentration of TC-hcl and TC-nm after oral or i.v administration (50 mg/kg b.wt) in rabbits (N =8, Mean ± SD)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Oral administration</th>
<th>IV administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tetracycline concentration µg/ml (mean ± SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TC-hcl</td>
<td>TC-nm</td>
</tr>
<tr>
<td>0.083</td>
<td>4.26 ± 1.458</td>
<td>ND</td>
</tr>
<tr>
<td>0.25</td>
<td>6.76 ± 1.102</td>
<td>4.32 ± 0.969</td>
</tr>
<tr>
<td>1</td>
<td>2.18 ± 0.368</td>
<td>7.41 ± 2.184*</td>
</tr>
<tr>
<td>2</td>
<td>1.29 ± 0.152</td>
<td>2.45 ± 0.270</td>
</tr>
<tr>
<td>4</td>
<td>0.47 ± 0.079</td>
<td>1.56 ± 0.322**</td>
</tr>
<tr>
<td>6</td>
<td>0.17 ± 0.011</td>
<td>0.61 ± 0.056**</td>
</tr>
<tr>
<td>8</td>
<td>0.10 ± 0.014</td>
<td>0.26 ± 0.034**</td>
</tr>
<tr>
<td>12</td>
<td>0.03 ± 0.005</td>
<td>0.08 ± 0.008**</td>
</tr>
<tr>
<td>24</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: Non-detected. *Significant <0.005 **Significant P < 0.001.

Fig. 1. Semilogarithmic graph depicting the time concentration relationship of TC-hcl or TC-nm after oral administration (50 mg/kg b.wt) in rabbits. (N =8, Mean ± SD)

Fig. 2. Semilogarithmic graph depicting the time concentration relationship of TC-hcl or TC-nm after i.v administration (50 mg/kg b.wt) in rabbits. (N =8, Mean ± SD)
than 10 hours) than that for powder form 6 hours (Table 1, Fig 1) [30].

The pharmacokinetic variables that describe the disposition of tetracycline following a single i.v administration presented in (Table 2). Tetracycline had higher volume of distribution V2 (0.292 ± 0.111 L/kg) in TC-nm and was slowly cleared (0.393 ± 0.183 L/h/kg) than for TC-hcl(0.216 ± 0.183L/kg) and (0.415 ± 0.311 L/h/kg) after i.v administration, respectively. Also, higher k12 0.765 ± 0.361 l/h and slow k21 1.431 ± 0.75 l/h were recorded in TC-nm as compared with those of TC-hcl k12 0.683 ± 0.511 l/h and k21 2.1 ± 1.8 l/h, respectively. These results are in accordance with those reported previously by many animal species in rats [48], female rats and male guinea-pigs [52], adult white Californian rabbits [30,54] and dogs [49]. These findings represented by higher and prolonged tetracycline plasma concentration after TC-nm administration than TC-hcl powder [30].

After oral administration tetracycline was rapidly absorbed with significant slowly absorption half-life t1/2 α (0.550 ± 0.090 h and 0.176 ± 0.058 h.) and elimination half-life t1/2 β (4.215 ± 1.661 h. and 1.58 ± 1.447 h.) with higher calculated Cmax of (4.215 ± 1.661 μg/ml and 1.58 ± 1.447 μg/ml) achieved at prolonged calculated tmax (0.759± 0.149h. and 0.356± 0.305 h.) in TC-nm than in TC-hclpowder treated rabbits, respectively. A significant higher AUC0-tinf (18.67 ±3.07 and 8.80± 9.42 μg/ml.h.) at prolonged MRT (4.796 ±2.781 and 1.58 ± 1.447 h.) in TC-nm than in TC-hclpowder treated rabbits, respectively. Tetracycline pharmacokinetic variables indicated higher bioavailability in nanoemulsion 23.79± 17.31 % than 10 hours) than that for powder form 6 hours (Table 1, Fig 1) [30].

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### TABLE 2. Pharmacokinetic parameters of TC-hcl and TC-nm after oral or i.v administration (50 mg/kg b.wt) in rabbits (N =8, Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Oral administration</th>
<th>IV administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TC-hcl</td>
<td>TC-nm</td>
</tr>
<tr>
<td>k10</td>
<td>1/h</td>
<td>1.917 ± 4.266</td>
<td>0.701 ± 0.102**</td>
</tr>
<tr>
<td>k12</td>
<td>1/h</td>
<td>1.566 ± 6.784</td>
<td>0.379 ± 0.105**</td>
</tr>
<tr>
<td>k21</td>
<td>1/h</td>
<td>0.903 ± 1.338</td>
<td>0.406 ± 0.335**</td>
</tr>
<tr>
<td>t1/2 Alpha</td>
<td>h</td>
<td>0.176 ± 0.058</td>
<td>0.550 ± 0.090**</td>
</tr>
<tr>
<td>t1/2 Beta</td>
<td>h</td>
<td>1.58 ± 1.447</td>
<td>4.215 ± 1.661**</td>
</tr>
<tr>
<td>t1/2 ka</td>
<td>h</td>
<td>0.05 ± 0.027</td>
<td>0.519 ± 0.091**</td>
</tr>
<tr>
<td>V</td>
<td>L/kg</td>
<td>1.26 ± 0.0570</td>
<td>0.216 ± 0.0208**</td>
</tr>
<tr>
<td>CL</td>
<td>L/h/kg</td>
<td>3.77 ± 0.0335</td>
<td>0.301 ± 0.0235**</td>
</tr>
<tr>
<td>V2</td>
<td>L/kg</td>
<td>3.98 ± 0.0548</td>
<td>0.122 ± 0.0463**</td>
</tr>
<tr>
<td>CL2</td>
<td>L/h/kg</td>
<td>4.58 ± 0.1459</td>
<td>0.167 ± 0.0811**</td>
</tr>
<tr>
<td>Tmax</td>
<td>h</td>
<td>0.356 ± 0.305</td>
<td>0.759 ± 0.149**</td>
</tr>
<tr>
<td>Cmax</td>
<td>μg/ml</td>
<td>10.689 ± 21.491</td>
<td>6.326 ± 1.173**</td>
</tr>
<tr>
<td>AUC 0-t</td>
<td>μg/ml.h</td>
<td>8.768 ± 9.397</td>
<td>16.679 ± 1.246*</td>
</tr>
<tr>
<td>AUC 0-inf</td>
<td>μg/ml.h</td>
<td>8.8 ± 9.42</td>
<td>18.67 ± 3.07*</td>
</tr>
<tr>
<td>AUMC</td>
<td>μg/ml.h²</td>
<td>13.17 ± 13.77</td>
<td>97.67 ± 77.24**</td>
</tr>
<tr>
<td>MRT</td>
<td>h</td>
<td>1.277 ± 1.215</td>
<td>4.796 ± 2.781**</td>
</tr>
<tr>
<td>F</td>
<td>%</td>
<td>13.7 ± 15.03</td>
<td>23.79 ± 17.31**</td>
</tr>
<tr>
<td>C0</td>
<td>μg/ml</td>
<td>0.356 ± 0.305</td>
<td>0.759 ± 0.149</td>
</tr>
<tr>
<td>Vss</td>
<td>L/kg</td>
<td>10.689 ± 21.491</td>
<td>6.326 ± 1.173</td>
</tr>
</tbody>
</table>

*Significant <0.005  **Significant P < 0.001
than TC-hcl 13.7 ± 15.03% treated rabbits. TC-nm showed lower volume of distribution VSS 6.326 ± 1.173 L/kg than that for tetracycline 10.689 ± 21.491 L/kg. The recorded serum pharmacokinetic parameters after oral administration of single dose was studied in rabbit [29, 30], in sheep [23]. While tetracycline was detected for 30 hours after oral administration of 40 mg/kg in pigs [55]. These findings were recorded after oral administration represented by higher and prolonged tetracycline plasma concentration for TC-nm administration than TC-hcl. This can be attributed to the nanoemulsion increases drug solubility and bioavailability, reduced patient variability, controlled drug release, and protection from enzymatic degradation [56]. The effect of nanoemulsions clarified by Mishra et al. [57] stated that nanoemulsions exhibited sufficiently high level of stability for them to be proposed as vehicle for drug delivery as it eliminates the side effects in the transdermal route, increases patient compliance, avoids first-pass metabolism, enhance bioavailability and maintains the plasma drug level for a longer period of time. It was reported that the pharmacokinetic parameters of tetracycline are dose dependent where its parameters in man after single oral doses 250 mg resulted in Cmax (2 mg/L), tmax 2-4 h and t1/2 6-11 h [58], doses 300 mg the Cmax (2.5 mg/L), tmax 3 h and t1/2 7.8 h [59] as well as in oral doses of 500 mg Cmax (3-5 mg/L), tmax 2 h and t1/2 8.5 h [60].

Pharmacodynamics

To evaluate the efficiency of antibiotic there are two factors, the 1st is the measure of potency of the antibiotic for the pathogen in question MIC and MBC, the 2nd is relationship between the concentration time profile and potency of the antibiotic [61-63]. Results were interpreted according to CLISI [44] where, MIC µG/ML value interpretive standards for Staphylococcus spp and Enterobacteriaceae are ≤ 4: sensitive, 8: intermediate and ≥ 16 µG/ML: resistant.

The result of MIC to determined and compare the antibacterial activity of TC-hcl powder and TC-nm on different Gram positive and Gram negative bacterial strains are presented in (Table 3). MIC for both TC-hcl and TC-nm are the same for Staph. Aureus 6538, Staph. Epidermidis 12228 and E. coli 8739 (Stander strains) were the similar 0.14, 0.8 and 0.12 µg, respectively, and interpreted as sensitive [44]. This result agree with MIC for reference E. coli and S. aureus strains were 1-2 mg/L and 0.06 - 0.5 mg/L, respectively [38]. Field sensitive isolates had MIC values of 1.4, 8, 2, 1.6 and 2 µg for Corynebacterium, E. coli, S. typhimurium, S. enteriditis and Staph. leutus, respectively, interpretation showed all were sensitive expect E. coli was intermediate. S. Enteritidis was sensitive to oxytetracycline [63]. E.coli resistance tetracycline was reported in vitro and confirmed genetically by detection of gens tet(A) and tet(B) [41]. Tetracycline resistant Staph.scuiri-1, Staph. xylosis-1, Staph. scuiri-2 and Staph. xylosis-2 showed equal values of MIC 18, 18, 16 and 6 µg, respectively, all still resistant except Staph. xylosis-2 that interpreted as intermediate. This result was previously reported in vitro and resistance tetK was also detected [41, 42]. Tetracycline bacterial resistance was previously determined [1, 4]. Our results still in the suggested MIC of tetracycline

## TABLE 3. MIC values of tested Gram –ve and Gram +ve bacterial strains to both TC-hcl and TC-nm formula.

<table>
<thead>
<tr>
<th>Source</th>
<th>Bacterial strain</th>
<th>TC-nm µg/ml</th>
<th>Interpretation</th>
<th>TC-hcl µg/ml</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard strains</td>
<td>Staph. Aureus 6538</td>
<td>0.14</td>
<td>S</td>
<td>0.14</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Staph. Epidermidis 12228</td>
<td>0.8</td>
<td>S</td>
<td>0.8</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Ecol 8739</td>
<td>0.12</td>
<td>S</td>
<td>0.14</td>
<td>S</td>
</tr>
<tr>
<td>Field isolates</td>
<td>Corynebacterium</td>
<td>1.4</td>
<td>S</td>
<td>1.6</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>E coli</td>
<td>8</td>
<td>I</td>
<td>8</td>
<td>I</td>
</tr>
<tr>
<td>S. typhimurium</td>
<td>2</td>
<td>S</td>
<td>2</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>S. enteriditis</td>
<td>1.6</td>
<td>S</td>
<td>1.4</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Staph Leutus</td>
<td>2</td>
<td>S</td>
<td>2.2</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Field strains</td>
<td>Staph scuiri-1</td>
<td>18</td>
<td>R</td>
<td>18</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Staph Xylosis-1</td>
<td>18</td>
<td>R</td>
<td>18</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>staph scuiri-2</td>
<td>16</td>
<td>R</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>staph Xylosis-2</td>
<td>6</td>
<td>I</td>
<td>6</td>
<td>I</td>
</tr>
</tbody>
</table>

rangeto Enterobacteriaceae, Staphylococci are 0.25-128 and 0.06-128 mg/L [38].

MIC value of tetracycline against *Staph. aureus*, Shigella spp. and *E. coli* were found to be 0.5, 1.0 and >64.0 mg/ml, respectively [62]. The obtained results showed no difference in MIC values of the bacterial strain between the activity of TC-hcl and TC-nm. This indicated that the nanoemulsion formulation reported to be efferent against many bacterial strains [12-16]. The active tetracycline in oil phase of oil-in-water nano-emulsion is protected from hydrolysis and oxidation [64,65]. While Vatsraj et al. [66] reported the solubility and the bioavailability of elartrhomyacin has increased in the formulated nanoemulsion system. Nanoemulsion as a drug delivery system improve bioavailability and pharmacokinetic activity of tetracycline [5-11,30,67].

In conclusion: the obtained results indicated that the nanoemulsion formulation of tetracycline hydrochloride improves pharmacokinetic parameters than usual formula and not affect the antibacterial efficacy. Therefore, the pharmacokinetic/pharmacodynamics pattern of nanoemulsion formulation must be applied intensively as system for drug delivery in veterinary medicine.

**Ethical approval**

The research plan was approved from Cairo University institutional animal care and use committee (CU-IACUC) with approval number CU-II-F-99-18.

**Conflict of Interest**

The authors have no conflict of interests to declare regarding the publication of this paper. Also, the authors declare that the work was self-funded.

**Authors’ Contributions**

A.M.A, S.A E. and M.M.A designed and planned this study. M.S.S, S.A E. and M.M.A performs experimental work, collects samples and all laboratory tests. All authors shared samples collection, performing the tests, manuscript writing, drafted, revised the manuscript and approved the final manuscript.

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**References**


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دراسات دوائية على صبغ التتراسيكلين والمستحلب النانومترى للتيتراسيكلين

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أجريت هذه الدراسة لمقارنة مسار الحركى والديناميكى الدوائي لصبغ التتراسيكلين الفئران عن طريق الفم والحقن وصبغ التتراسيكلين المصنوع تحت الشكل النانومتري البديل عن النوع الريدي في الفئران وإعداد تقديرات عن تركز الدواء في الدم عند الساعة ١٠٠ ووصول إلى الحد الأقصى عند نصف ساعة في الصبغ التتراسيكلين وساعة في المستحلب النانومترى. 

بين الحسم الريدي للتيتراسيكلين على معدات الانتشار (٧) (٢٠٨) ± ٠.١١١ تتر / كجم في المستحلب النانومترى للتيتراسيكلين (TC-nm) وتم تنفيذ البلازما من المستحلب ببطء (٢١٦) ± ٠.١٨٣ تتر / كجم في الفئران (TC-hcl) وتم استخدام أنواع أخرى من النشاطات الببتيدية والبكتيريا والميكروبات. يتم تحديد هذه النشاطات ببيانات الانتشار وتقديرها على أنها حساسة. تشير النتائج أن مستحلب تتراسيكلين يحسن قراءات الحركى الدوائي عن الصبغة العادية ولا يؤثر على الفعالية المضادة للبكتيريا. ولذلك، من الممكن تطبيق هذا النمط من صياغة مستحلبات النانو كنظام لإيصال الدواء بشكل أكثر في الطب البيطري.