Egypt. J. Vet. Sci. **Vol. 50,** No. 1, pp. 1-11 (2019)

Pharmacological Studies on Tetracycline and Tetracycline Nanoemulsion Formulas.

Mohamed S. Saber[*], Aziza M. Amer[**], Shymaa A. ElBadawy[**], Mohamed M. Amer[***]

[*]PhD Student in Pharmacology ,Veteterinary Service Division, Ministry of Defense, [**]Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University, [***]Department of Poultry Diseases, Faculty of Veterinary Medicine, Cairo University, Cairo, Egypt.

THE study was done to compare the pharmacokinetic and pharmacodynamics of 50 mg/kg b.wttetracycline hydrochloride (TC-hcl) and tetracycline nanoemulsion (TC-nm) formulasin rabbits and detection of their effect on stander 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 $t1/2_{alpha}$ (0.550±0.090 h and 0.176±0.058 h.) and elimination half-life $t1/2_{beta}$ (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 resistant2*Staph.scuiri* (18 and 16µg) and 2 *Staph. xylosis* (18 and 6µg).

Keywords: Pharmacokinetics, pharmacodynamics, Tetracycline, nanoemulsions, MIC, Rabbits.

Introduction

Tetracyclineswere discovered in the 1940s and exhibited activity against a wide range of microorganisms including gram-positive and gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites. They are inexpensive antibiotics used extensively in the prophylaxis and therapy of human and animal infections and also as growth promoters [1,2]. Tetracyclinesare widely used in veterinary medicine mainly for the treatment of gastrointestinal, respiratory and skin bacterial infections [3]. Dissemination of tolerance and resistance determinants has limited their tetracyclinesusage [4]. Tetracycline resistance in pathogenic, opportunistic, and commensal bacteria.is often due to the acquisition of new genes, which code for energy-dependent efflux of tetracycline or for a protein that protects bacterial ribosomes from the action of tetracycline [1].

Nanoemulsions are colloidal dispersion systems that are thermodynamically stable, composed of two immiscible liquids mixed along with emulsifying agents (surfactants and co-surfactants) to form a single phaseandhave been investigated as drug delivery systems [5]. Nanoemulsions formulation improve drug delivery system [6-8],entrapment efficiency (EE) and loading efficiency (LE) of the drug [9], pharmacokinetic and biodistribution, target

Corresponding author: Aziza M. Amer, e-mail: aziza.mahrous@gmail.com
DOI: 10.21608/ejvs.2018.6573.1056

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 Shigellaflexneri*, 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 proximately 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 0.12μg/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= AUC oral x 100/ AUC IV.

Parmacodynamics

Antibacterial activity and MIC determination

Bacterial strains

Field and stander 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.scuiri* [43]. Field resistant strains *Corynebacteriumcervicis, 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^{0}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 between 10^7 - 10^8cfu/ml according to the genera and the inoculum was adjusted to 10^4cfu/ml by dilution with Mueller-Hinton broth and dispensed on the surface of the agar.

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^{O}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 dishes 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 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 < 0.001was 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. Tetracyclinesstill 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 followingTC-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 ± 1.458µg/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]. µNanoemulsion showed higher concentrations persisted higher than MIC for longer time (more

TABLE1. Plasma concentration of TC- hcland TC-nm after oral or i.v administration (50 mg/kg b.wt) in rabbits (N =8, Mean ± SD)

Time (h)	Tetracycline concentration µg/ml (mean ± SD)			
	Oral administration		IV administration	
	TC-hcl	TC-nm	TC-hcl	TC-nm
0.083	ND	ND	67.879 ± 6.555	78.566 ± 5.295**
0.25	4.26 ± 1.458	3.77 ± 0.923	63.051 ± 11.280	68.547 ± 7.284**
0.5	7.60 ± 1.102	4.32 ± 0.969	30.664 ± 5.717	28.455 ± 3.377
1	2.18 ± 0.368	7.41 ± 2.184*	25.319 ± 4.922	24.318 ± 5.595
2	1.29 ± 0.152	2.45 ± 0.270	8.754 ± 3.772	8.527 ± 1.736
4	0.47 ± 0.079	1.56 ± 0.322**	1.013 ± 0.260	0.613 ± 0.111*
6	0.17 ± 0.011	0.61 ± 0.056**	0.232 ± 0.039	0.130 ± 0.010**
8	0.10 ± 0.014	0.26 ± 0.034**	0.043 ± 0.004	0.024 ± 0.002*
12	0.03 ± 0.005	0.08 ± 0.008**	0.021 ±0.005	0.015 ± 0.003
24	ND	ND	ND	0.010 ± 0.002**

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

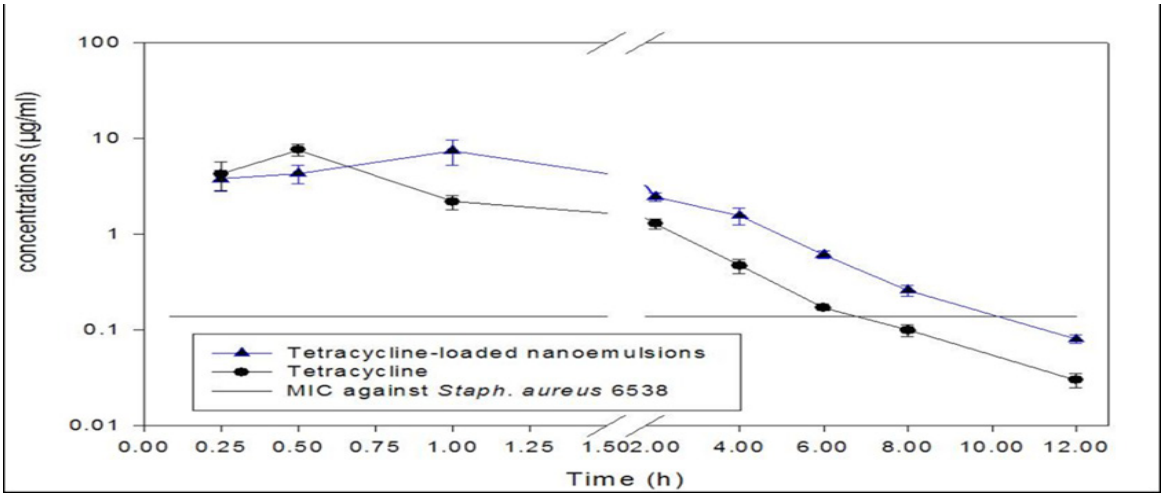

Fig. 1. Semilogarethmic graph depicting the time concentration relationshipof TC-hclor TC-nm after oral administration (50 mg/kg b.wt) in rabbits.(N =8, Mean ± SD)

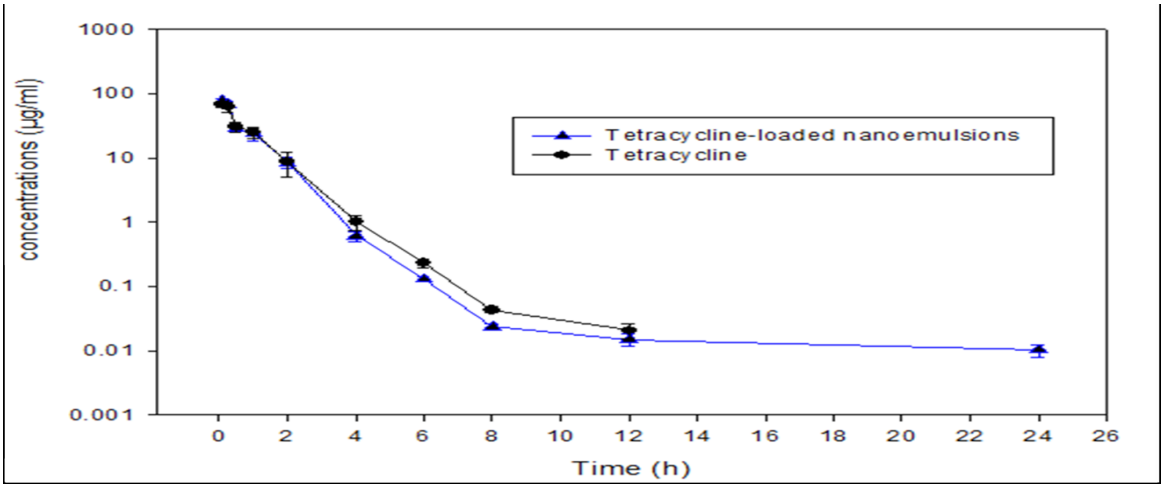

Fig. 2. Semilogarethmic graph depicting the time concentration relationshipof TC-hcl or TC-nm after i.v administration (50 mg/kg b.wt) in rabbits.(N =8, Mean ± SD)

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-nmand 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 1/h and slow k21 1.431 ± 0.75 1/h were recorded in TC- nm as compared with those ofTC-hcl k12 0.683 ± 0.511 1/hand k21 2.1 ± 1.8 1/h., respectively. These results are in accordance with those reported previously by many animal species inrats [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

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

Parameter	Unit	Oral administration		IV administration	
		TC-hcl	TC-nm	TC-hcl	TC-nm
k10	1/h	1.917 ± 4.266	0.701 ± 0.102**	1.199 ± 0.218	1.407 ± 0.198
k12	1/h	1.566 ± 6.784	0.379 ± 0.105**	0.683 ± 0.511	0.765 ± 0.361
k21	1/h	0.903 ± 1.338	0.406 ± 0.335**	2.1 ± 1.8	1.431 ± 0.75
t1/2Alpha	h	0.176 ± 0.058	0.550 ± 0.090**	0.324 ± 0.263	0.25 ± 0.074
t1/2Beta	h	1.58 ± 1.447	4.215 ± 1.661**	1.041 ± 0.277	1.12 ± 0.184
t1/2ka	h	0.05 ± 0.027	0.519 ± 0.091**		
V	L/kg	1.26 ± 0.0570	0.216 ± 0.0208**	0.626 ± 0.09	0.515 ± 0.042*
CL	L.h/kg	3.77 ± 0.0335	0.301 ± 0.0235**	0.736 ± 0.071	0.720 ± 0.082
V2	L/kg	3.98 ± 0.0548	0.122 ± 0.0463**	0.216 ± 0.183	0.292 ± 0.111
CL2	L.h/kg	4.58 ± 0.1459	0.167 ± 0.0811**	0.415 ± 0.311	0.393 ± 0.183
Tmax	h	0.356 ± 0.305	0.759 ± 0.149**		
Cmax	µg/ml	10.689 ± 21.491	6.326 ± 1.173**		
AUC 0-t	µg/ml.h	8.768 ± 9.397	16.679 ± 1.246*	68.51 ± 7.16	70.1 ± 7.2
AUC 0-inf	µg/ml.h	8.8 ± 9.42	18.67 ± 3.07*	68.54 ± 7.16	70.1 ± 7.2
AUMC	µg/ml.h^2	13.17 ± 13.77	97.67 ± 77.24**	79.32 ± 20.06	79.04 ± 13.03
MRT	h	1.277 ± 1.215	4.796 ± 2.781**	1.151 ± 0.238	1.125 ± 0.128
F	%	13.7 ± 15.03	23.79 ± 17.31**		
C0	µg/ml	0.356 ± 0.305	0.759 ± 0.149	81.27 ± 11.25	97.62 ± 8.08
Vss	L/kg	10.689 ± 21.491	6.326 ± 1.173	0.842 ± 0.168	0.807 ± 0.103

*Significant <0.005 **Significant P < 0.001

plasma concentration after TC-nmadministration than TC-hcl powder [30].

After oral administration tetracycline was rapidly absorbed with significant slowly absorption half-life t1/2 $_{alpha}$ (0.550 ± 0.090 h and 0.176 ± 0.058 h.) and elimination half-life t1/2 $_{beta}$ (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-inf. (18.67 ±3.07 and 8.80± 9.42 µg/ml.h.) at prolonged MRT (4.796 ±2.781 and 1.277 ± 1.215 h.) in TC-nm than in TC-hclpowder treated rabbits, respectively. Tetracycline pharmacokinetic variables indicated higher bioavailability in nanoemulsion 23.79± 17.31 %

than TC-hcl13.7 ± 15.03% treated rabbits. TC-nm showed lower volume ofdistribution 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 studiedinrabbit [29, 30], in sheep [23]. While tetracyclinewasdetected for 30 hours after oral dose 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 nanoemulsionincreasesdrug solubility and bioavailability, reduced patient variability, controlled drug release, and protection from enzymatic degradation [56]. The effect of nanomulsionsclarified 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 whereits 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 an 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*showedequal values ofMIC18, 18, 16 and 6ug, respectively, all still resistant except *Staph.xylosis*-2that interpreted as intermediate. This result was previously reported in vitro and resistance tetK was also detected [41,42]. Tetracycline bacterial resistance waspreviouslydetermined [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-hclandtc-nm formula.

Source	Bacterial strain	TC-nm		TC-hcl	
		µg/ml	Interpretation	µg/ml	Interpretation
Standard strains	*Staph. Aureus 6538*	0.14	S	0.14	S
	Staph. Epidermidis 12228	0.8	S	0.8	S
	Ecoli 8739	0.12	S	0.14	S
Field Sensitive isolates	*Corynebacterium*	1.4	S	1.6	S
	E coli	8	I	8	I
	S. typhimurium	2	S	2	S
	S, enteriditis	1.6	S	1.4	S
	Staph Leutus	2	S	2.2	S
Field multidrug resistant strains	*Staph Scuiri-1*	18	R	18	R
	Staph Xylosis-1	18	R	18	R
	staph scuiri-2	16	R	16	R
	staph Xylosis-2	6	I	6	I

S: Sensitive I: Intermediate. R: Resistant.

rangetoEnterobacteriaceae, 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 manybacterial strains [12-16]. The active tetracycline in oil phase of oil-in-water nano-emulsion is protected from hydrolysis and oxidation [64,65]. WhileVatsraj et al. [66] reported the solubility and the bioavailability of clarithromycin 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.

Acknowledgement

TC-nm was prepared in Dept. of Pharmaceutical, faculty of Pharmacy, Cairo University. The experimental work of the research was facilitated and completed in department of pharmacology faculty of veterinary medicine, Cairo University.

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(*Received* 09/12/2018;
accepted 03/01/2019)

دراسات دوائية على صيغ التتراسيكلين والمستحلب النانومتري للتيتراسيكلين

محمد سعيد صابر* ، **عزيزة محروس عامر**** ، **شيماء احمد البدوي**** و **محمد محروس عامر*****
* قسم الادويه – كلية الطب البيطري – الخدمات البيطريه بوزاره الدفاع ، **قسم الادويه – كلية الطب البيطري – جامعه القاهرة و*** قسم امراض الدواجن – كلية الطب البيطري – جامعة القاهرة .

أجريت هذه الدراسة لمقارنة المسار الحركى والديناميكيه الدوائية ليصيغتى للتتراسيكلين و المستحلب النانومتري للتيتراسيكلين بعد اعطاؤه بجرعة واحده مقدارها ٥٠ ميليجرام / كيلوجرام من وزن الجسم عن طريق الفم والحقن الوريدي فى الارانب ودراسه تاثيرهما علي عترات بكتيريه عياريه و حقليه، بدأ تركيز الدواء في البلازما عند ٠,٢٥ ساعة ووصل إلى الحد الأقصى عند نصف ساعه فى التتراسيكلين وساعه فى المستحلب النانومترى ليصل للحد الادنى عند ١٢ ساعه من اعطاء جرعه واحده. اتبع الحقن الوريدى للتتراسيكلين اعلى معدلات الانتشار (V2) ٠,٢٩٢ ± ٠,١١١ لتر / كجم في المستحلب النانومترى للتيتراسيكلين (TC-nm) من ٠,٢١٦ ± ٠,١٨٣ لتر / كجم فى التيتراسيكلين (TC-hcl) وتم تنقيه البلازما من المستحلب ببطء (٠,٣٩٣ ± ٠,١٨٣لتر.ساعة / كجم) عن التيتراسيكلين (٠,٤١٥ ± ٠,٣١١لتر.ساعة / كجم) في التتراسيكلين.

اتبع اعطاء الدواء بالفم امتصاصا سريعا و امتصاص معنوى بطئ نصف عمر $t1/2_{alpha}$ (٠,٥٥٠ ± ٠,٠٩٠ ساعة و ٠,١٧٦ ± ٠,٠٥٨ ساعة) و استخلاص نصف عمر $t1/2_{beta}$ (٤,٢١٥ ± ١,٦٦١ ساعة و ١,٥٨ ± ١,٤٤٧ ساعة) مع ارتفاع 4.215) Cmax ± ١,٦٦١ ميكرو جرام / مللى و ١,٥٨ ± ١,٤٤٧ ميكرو جرام / مللى) منعكسا على قيمهtmax المحسوبة (0.759 ± ٠,١٤٩ ساعة و ٠,٣٥٦ ± ٠,٣٠٥ ساعة) فى المستحلب عن الصيغة العادية فى الارانب المعالجة، على التوالى.

كانت قيم الحد الأدنى للتركيز المثبط للبكتيريا متساويه فى كل من التتراسيكلين العادي والمستحلب النانومتري للمكور العنقودى البرتقالي ٦٥٣٨ و المكور العنقودى البشراوي ١٢٢٢٨ و المكروب القولونى ٨٧٣٩ هى 0.14 و 0.8 و 0.12 ميكروجرام ، على التوالي وتم تقيمها على انها حساسه. اما العترات الحقليه الحساسه من انواع الوتديةو الميكروب القولونى و السلمونيلا التيفوديه و السلمونيلا المعوبه و المكور العنقودى لينتس فكانت قيمها ١و ٤و ٨ و ٢و ١ز٦ و ٢ ، على التوالي. اما القيم فى عتراتى المكور العنقودى سيريس (١٨ و ١٦ مللجرام) وعترتى الزيليوس (١٨ و ٦ ملليجرام) فتاكد مقاومتهم للصيغتى الدواء. تشير النتائج ان صياغه التتراسيكين فى مستحلب نانومترى لم لا تؤثر على فعالية كمضادة للجراثيم.البكتيريه.

في الختام: أشارت النتائج المتحصل عليها إلى أن صيغة مستحلب من هيدروكلوريد التتراسيكلين يحسن قياسات الحراك الدوائي عن الصيغة العادية ولا يؤثر على الفعالية المضادة للبكتريا. ولذلك ، من الممكن تطبيق هذا النمط من صياغة مستحلبات النانو كنظام لإيصال الدواء بشكل في الطب البيطري.