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Eplerenone nanoemulsions for treatment of hypertension. Part II: Physical stability assessment and in vivo study

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ABSTRACT

The aim of the present complimentary study was to investigate physical stability of eplerenone (EP) loaded nanoemulsions and to evaluate their pharmacokinetic profiles after subcutaneous application to Sprague Dawley rats. Nanoemulsions were prepared by using high shear homogenization and ultrasonication techniques. All formulations were having 0.1% EP. They were obtained in 150.6 nm–205.8 nm size range. Physical stability of nanoemulsions was monitored storing them at different thermal conditions for 120 days. Droplet size was confirmed to be affected by storage temperature when it slightly changed at 4 ± 2 °C and 25 ± 2 °C. 40 ± 2 °C was found not to be suitable as a storage condition in general. Pharmacokinetic study on physically stable formulations demonstrated that subcutaneously applied eplerenone solution showed that $AUC_{0\rightarrow\infty}$ and C_{max} were 1.62 and 2.05 folds higher than eplerenone solution after oral administration. Additionally, $AUC_{0\rightarrow\infty}$ and C_{max} were significantly increased in the case of nanoemulsions prepared with Brij® 35 and Tween® 80. Relative bioavailability of the drug was found to be remarkably increased after administration of formulations stabilized with Tween® 80. Results suggested that eplerenone loaded nanoemulsions may provide an alternative application way for efficient management of hypertension attacks.

1. Introduction

Management of hypertension can be possible by using several remedies such as beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone antagonists. These remedies can be administrated to patients as a combination therapy or monotherapy [1,2]. Eplerenone (EP) is an aldosterone antagonist drug which is commonly used for hypertension and chronic heart failure [3,4]. EP selectively binds to mineralocorticoid receptors. Thus, it is also called as mineralocorticoid receptor antagonist. EP has a less affinity to androgenic receptors and glucocorticoid receptors due to its selectivity on mineralocorticoid receptors. Therefore, it reduces the risk of gynecomastia, menstrual irregularities and sexual dysfunction. Although the adverse effects of EP are rarely seen, hyperkalemia is one of remarkable side effects that may result in arrhythmias [5,6].

EP is a class II drug according to the biopharmaceutical classification system (BCS) which means EP has a low aqueous solubility and high permeability [7]. Low soluble drugs are potential candidates for lipid based drug delivery systems which are suitable carriers for increasing drug bioavailability and achieving more efficient therapy [8,9]. Nanoemulsions (NEs) have been used for purposes of parenteral nutrition and drug delivery for many years [10,11]. In recent years, NEs have been significantly interested by several research groups and pharmaceutical industry due to their ease of production, high biocompatibility and suitability for targeting and modifying release profiles of actives [9–11].

A preliminary study was attempted for optimization of EP loaded NEs to achieve better therapeutic performance of the drug in hypertensive attacks or crisis [12]. In this complementary study, physical stability of NEs at different thermal conditions and pharmacokinetic properties of EP loaded NEs were investigated.

2. Materials and methods

2.1. Materials

Eplerenone (EP) was kindly donated by Neutec Pharmaceuticals

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Table 1
Constituents (%), encapsulation efficiency (EE) and loading capacity (LC) of the NE formulations.

Formulation	Constituents (%)							EE (%)	LC (%)
	EP	OE	Water	Surfactants					
				Brij® 35	Tween® 80	TegoCare® 450	Poloxamer® 407		
B1	0.1	5	93	2	–	–	–	96.63 ± 0.81	2.14 ± 0.01
B3	0.1	7	91	2	–	–	–	98.51 ± 0.61	2.15 ± 0.01
T1	0.1	5	93	–	2	–	–	93.49 ± 0.37	1.96 ± 0.02
T2	0.1	8	90	–	2	–	–	93.62 ± 0.28	2.13 ± 0.04
TC1	0.1	5	93	–	–	2	–	88.65 ± 0.49	1.97 ± 0.01
TC3	0.1	8	91	–	–	1	–	85.67 ± 0.32	1.95 ± 0.03
P1	0.1	5	93	–	–	–	2	84.47 ± 0.52	1.95 ± 0.01

Aqueous phase contains 2.5% (w/w) glycerol.

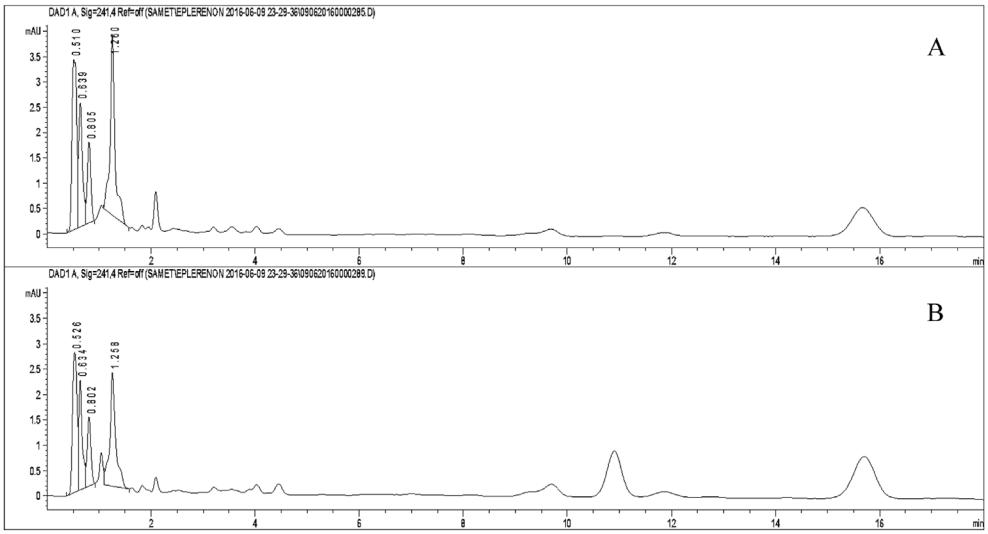

Fig. 1. Blank (A) and EP spiked (B) plasma chromatograms.

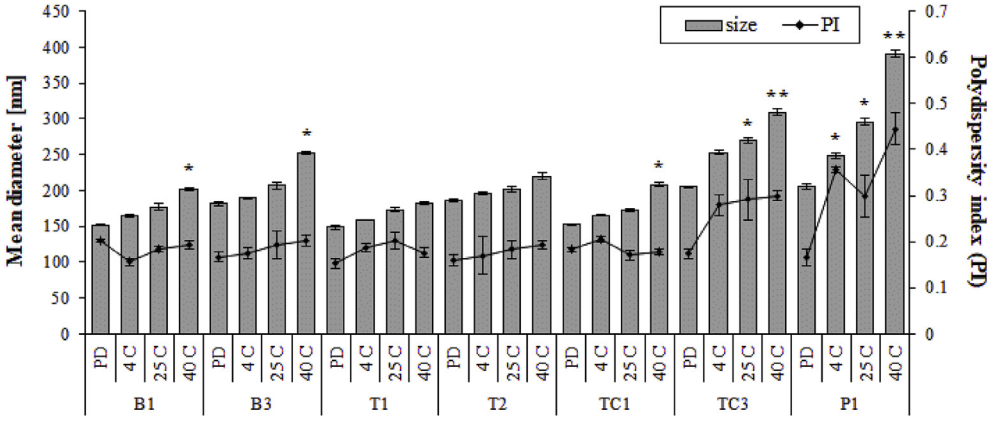

Fig. 2. Mean diameter (nm) and polydispersity index (PI) of NEs during 120 days of storage at various temperatures (PD: production date) (* and ** indicate significant enlargement of droplet radius $p < 0.05$ and $p < 0.01$, respectively).

(Turkey), CremerCOOR® OE (oleyl erucate) (OE) was donated by Cremer Oleo GmbH & Co. KG (Germany). Brij® 35, Tween® 80 and Poloxamer® 407 were supplied by Sigma-Aldrich (Germany). Tego Care® 450 was supplied by Evonik (Germany). Other chemicals used in this study were of analytical grade.

2.2. Methods

2.2.1. Preparation of NEs

NEs were prepared by using high shear homogenization and ultrasonication methods [9,12]. OE, Brij® 35, Tween® 80, Tego Care® 450 and Poloxamer® 407 were used as the liquid lipid and surfactants (Table 1). EP was dissolved in OE at 80 ± 2 °C. An aqueous surfactant solution (containing glycerol at 2.5% (w/w) to provide isotonicity) at the same temperature was added to the oil phase using a high shear