2016-09-02

MICROVESICLE FORMULATION CONTAINING SODIUM 3 ,7 - DIHYDROXY-12- KETO-5 - CHOLANATE ENHANCES ORAL ABSORPTION OF CEFOTAXIME

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UDK 615 (497.11)

ISSN 2217-8767 (Online)

ARHIV ZA FARMACIJU

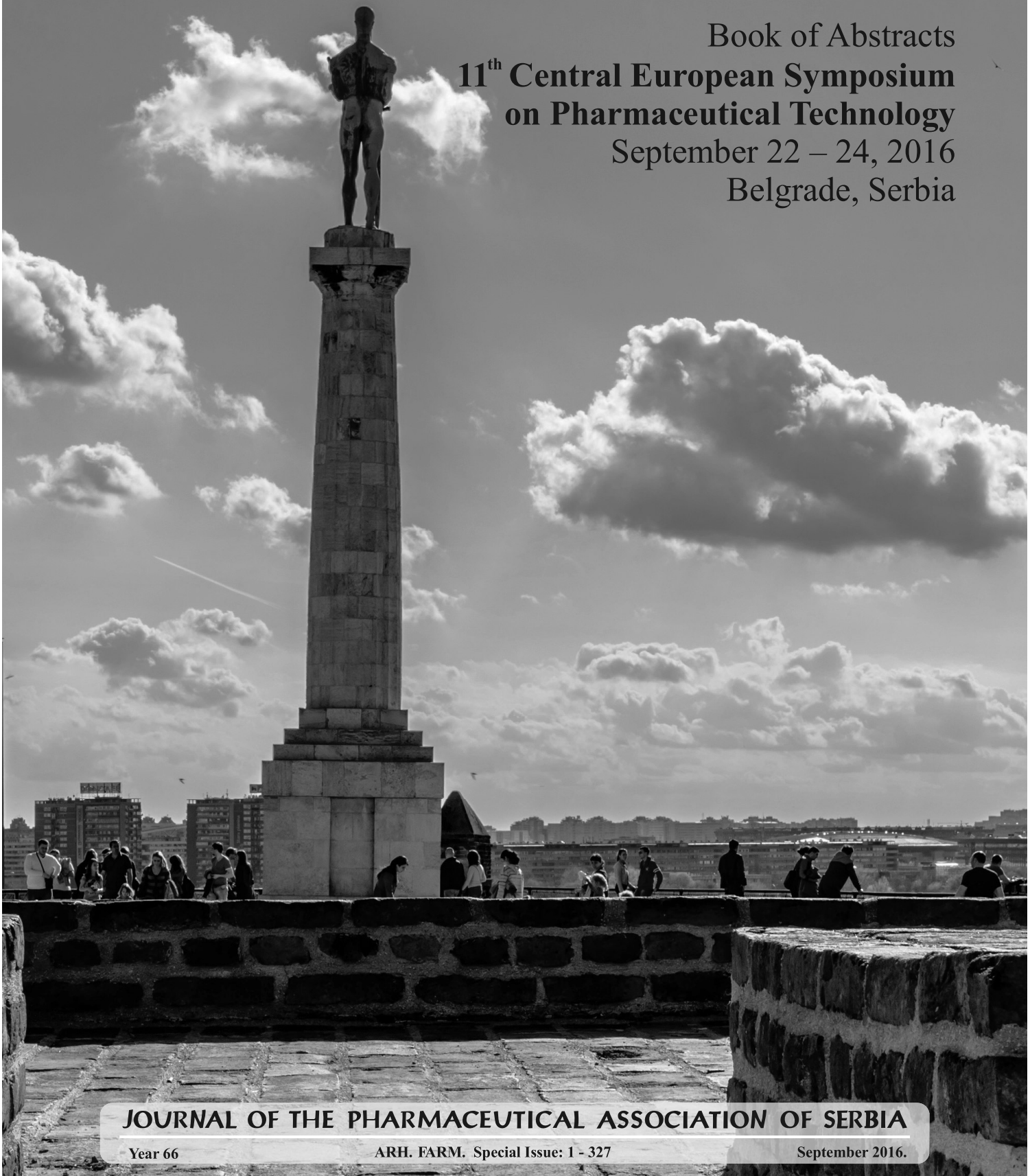
Special Issue

Book of Abstracts

11th Central European Symposium on Pharmaceutical Technology

September 22 – 24, 2016

Belgrade, Serbia



JOURNAL OF THE PHARMACEUTICAL ASSOCIATION OF SERBIA

Year 66 ARH. FARM. Special Issue: 1 - 327 September 2016.

ARHIV ZA FARMACIJU

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SAVEZ FARMACEUTSKIH UDRUŽENJA SRBIJE / PHARMACEUTICAL ASSOCIATION OF SERBIA

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Arh. farm. 2016;66 / Special Issue

PP86

MICROVESICLE FORMULATION CONTAINING SODIUM 3α,7α-DIHYDROXY-12-KETO-5β-CHOLANATE ENHANCES ORAL ABSORPTION OF CEFOTAXIME

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INTRODUCTION

Cefotaxime sodium (CEF) is a water-soluble semi-synthetic cephalosporin, which exhibits a potent activity against various bacteria. CEF is not appreciably absorbed from the gastrointestinal tract and is therefore only available in an injection form, as the sodium salt. Bioavailability of CEF after oral administration is less than 5%. CEF is class III based upon the biopharmaceutical classification system. The low oral bioavailability is mostly due to its instability in the harsh environment of the stomach and intestine. Studies have shown that CEF solution exhibits maximum stability in the pH range of 4.3-6.5. Degradation appears to be rapid at pH 1.5. It was reported that the β-lactam moiety undergoes hydrolysis at lower pH while at higher pH~8, the side chain undergoes hydrolysis (1).

Bile salt derivatives have shown significant ability to enhance the bioavailability of various drug compounds. The semisynthetic sodium 3α,7α-dihydroxy-12-keto-5β-cholanate (MKC) has been shown to improve the absorption and blood brain barrier penetration of morphine and quinidine. Attempts have been made to increase CEF absorption in combination with sodium cholate/deoxy-cholate and in liposome encapsulation (2).

The aim of this study was to investigate the pharmacokinetics of CEF after oral application in the new formulation of 3α,7α-dihydroxy-12-keto-5β-cholanate (MKC) microvesicles (MV) in rats.

MATERIALS AND METHODS

CEF loaded-microvesicles, with or without MKC, were prepared by the rotary film evaporation method, as previously described (3). The particle size of micro-vesicles was measured by laser diffraction technique using a Mastersizer X, and the result were vesicles size 0.385 ± 0.071μm with MKC and 0.396 ± 0.058μm without MKC. In order to determine entrapment efficiency of CEF-loaded microvesicles, samples were centrifuged at 30,000 rpm for 5 min using an ultra-filter. The filtrate containing free CEF was analyzed by HPLC. The entrapment efficacy was for CEF loaded-MV with MKC 54.29 ± 11.69% and for CEF loaded-MV without MKC 47.61 ± 12.72%.

Wistar rats were divided into 6 groups and CEF (15 mg/kg) was administered orally: 1. alone in saline; 2. in saline with MKC (2 mg/kg) (CEF+MKC), 3. in saline with microvesicles (CEF+MV), 4. encapsulated in microvesicles (CEFinMV) with saline solution, 5. in saline with MKC microvesicles (CEF+MKCMV), 6. encapsulated in MKC microvesicles (CEFinMKCMV) with saline solution. Blood samples were taken before the gavage and 10, 20, 30, 40, 60, 90, 120, 150, 180 and 240 minutes after the gavage. Plasma samples were analyzed for CEF by HPLC method (4).

Results were analyzed by SPSS 17.0 software and data were further analyzed by

WinNonLin 4.1 software, using a non-compartmental model.

RESULTS AND DISCUSSION

After the oral administration of CEF solution with MKC, Cmax and AUC were significantly higher than after the administration of CEF solution alone (2-fold). After the administration of CEF encapsulated in MV without MKC, Cmax and AUC were significantly higher than after administration CEF solution alone (1.5 and 2-fold, respectively). After the administration of CEF encapsulated in microvesicles with MKC, Cmax and AUC were significantly higher than after administration of CEF solution alone (12 and 9-fold, respectively) which shows that administered as this formulation CEF has significantly higher bioavailability, reaching inhibitory concentration for most bacteria. Besides, Cmax and AUC after the administration of CEF encapsulated in microvesicles with MKC were significantly higher than after the administration of CEF in MV without MKC (5-fold). There were no significant differences in other pharmacokinetic parameters.

MKC, like other bile salts, may incorporate CEF into micelles which can increase its permeability through the mucosal membrane. MKC may also enhance penetration of CEF via the paracellular route by exerting a mucolytic effect and binding calcium ions causing tigh junctions to open. Bile salts can improve the bioavailability of drugs by enhancing the affinity for transporters like H^+/peptide symporter (PEPT1) and increase beta-lactam antibiotic transepithelial flux and availability.

The mechanism of the 9-fold increase in CEF bioavailability resulting from the administration of the microvesicles formulated with MKC in our study may involve multiple factors such as: 1. The direct MKC absorption enhancement properties; 2. The formulation in microvesicles and increased intestinal uptake by endocytosis via both Payer's patches and intestinal enterocytes; 3. The increased stability in the intestinal tract and consequently availability for the absorption when microvesicles are formulated with MKC.

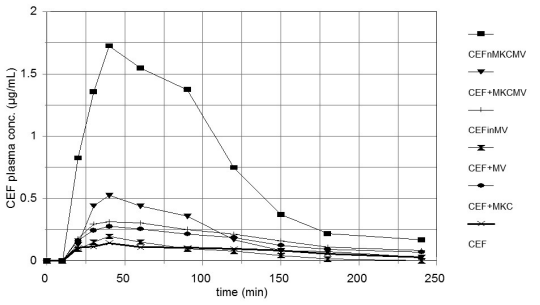

Fig. 1. Cefotaxime concentrations in rat plasma after oral administration of CEF alone; together with MKC (CEF+MKC), mixed with microvesicles (CEF+MV), encapsulated in microvesicles (CEFinMV), mixed with MKC microvesicles (CEF+MKCMV), encapsulated in MKC microvesicles (CEFinMKCMV).

CONCLUSIONS

Encapsulation in MKC microvesicles increased CEF oral bioavailability and it is superior in comparison to CEF solution and CEF encapsulated in microvesicles without MKC. This suggests that the encapsulation of CEF in microvesicles with MKC can extend CEF application from parenteral only to oral as well.

ACKNOWLEDGEMENT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 690876.

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