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Development and Investigation of Emulsion Form for Antiepileptic Drug Carbamazepine

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This study was directed to obtain a carbamazepine nanoemulsion for intravenous administration which consists of medium-chain trigycerides (Myritol) used as oil phase and Tween 80 as emulsifier. The spontaneous emulsification method with additional sonication was used to prepare different formulation containing 0.5 mg/ml carbamazepine. The nanoemulsions were evaluated concerning droplet size, zeta potential and drug content. Preliminary studies of anticonvulsant activity for resulting formulation were carried out.

Keywords: Carbamazepine, Nanoemulsion, Anticonvulsant activity, Epilepsy, Parenteral formulation, Drug solubilization.

PACS numbers: 83.80.Iz, 83.80.Qr, 87.19.xm

1. INTRODUCTION

Carbamazepine (CBZ), 5H-dibenz(b,f)asepine-5-carboxamide is one of the widely used drugs in medical practice for the treatment of patients with epilepsy. However, very poor water solubility of drug (0.061 mg/ml) leads to its slow absorption from the gastrointestinal tract [1], which significantly reduces bioavailability and the overall effectiveness of therapy. Also still there is no dosage form of CBZ for parenteral administration, which is extremely important in emergency assistance in case such as coma, swallowing problems and others. In this regard there is a very actual problem to producing a water-soluble CBZ formulation. One of the most suitable solutions to solve this problem is to create a different kind of emulsions. Emulsion formulations offer an appealing alternative for the administration of poorly water soluble drugs due to their effectiveness for drug solubilization, potential for improved efficacy and anticipated patient acceptance and compliance due to the reduced side effects [2]. At present time there is an urgent problem in choosing the conditions for the simultaneous achievement of stability and inclusion of high percentage of drug in the emulsion.

2. MATERIALS AND METHODS

We used the following devices: ultrasonic bath (Sonorex TK-52, Germany), magnetic stirrer Ika RH basic (Ika Labortechnik, Germany), pH meter (Mettler Toledo, Germany), spectrophotometer (Shimadzu UV-1700, Japan), the chromatographic separation system of the high pressure (Beckman-Coulter, USA), a rotary evaporator (Heidolph, Germany).

The particle size distribution was determined by the autocorrelation spectrometer «DelsaNano» (Beckman-Coulter, USA).

The convulsions test induced by maximal electroshock, was carried out on the unit Rodent Shocker RS type 221 (Harvard Apparatus, GmbH) by the application of electrical stimulation (0.3 ms, 24-25 mA, voltage 700 V - for mice C57Bl/6 and weighing 20-22 g) through cranial electrodes.

For preparing emulsions we used the following reagents: carbamazepine (Sigma-Aldrich, Germany), Myritol 312 (Fluka, Switzerland), Tween 80 (Sigma-Aldrich, Germany), sodium deoxycholate (Sigma-Aldrich Germany), pharmacology grade DMSO (Fluka, Switzerland). HPLC grade tetrahydrofuran and ethanol were purchased from Sigma-Aldrich Germany

3. RESULTS AND DISCUSSION

To achieve the above goal, the investigation was carried out in several stages: optimization of qualitative and quantitative composition of CBZ emulsion, study of physicochemical parameters resulting dispersions (particle size, zeta potential, morphology, aggregation stability) and research of anticonvulsant activity for obtained CBZ formulations.

The method of spontaneous emulsification previously described by Kelman et al. [3] with additional sonication step was used to prepare different formulation containing 0.5 mg/ml CBZ. It has been proposed to add the sodium deoxycholate to the emulsion because of its good structure-forming properties and charge generation on interfacial surface of dispersions.

CBZ concentration in emulsions was measured by two different methods: spectrophotometric method and high performance liquid chromatography (HPLC), and the values obtained by both methods were identical.

No precipitation was observed in the prepared samples, which can be explained by the fact that CBZ is well included in the dispersed phase. The sample showed good stability for one month at a temperature of 4 °C; however, the value of the zeta potential was not high enough and was – 23 mV. The particle size and its

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distribution were obtained using size analyzer and represented in Figure 1. In order to get rid of substances unincorporated into droplets, the sample obtained using centrifugation at 10,000 rpm for 15 minutes at 25 ºC.

Figure 1 shows that the sample is present in a fraction of particles with an average diameter of 96 nm.

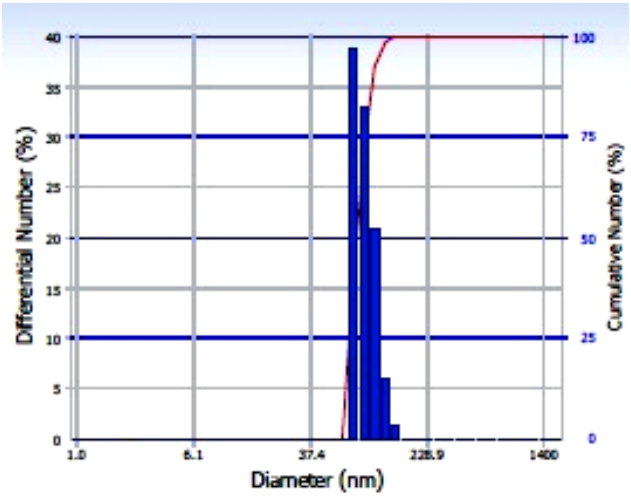

Fig. 1 – The particle size distribution for CBZ emulsion

In maximum electroshock test we used following scoring system, where "0 points" correspond to the absence of seizures, "1 point" – clonic convulsions, "2 points" – the tone of the upper limbs and clonic spasms of the hind limbs, "3 points" – tonic extension of hind limbs and "four points" – the death of animals. The results of the study are shown in Table 1.

Table 1 – Anticonvulsant activity for CBZ emulsion form comparison with carbamazepine in the substance model convulsions induced by maximal electroshock in mice of the C57Bl/6

Group/dose	Convulsions, points	The number of surviving animals, %
The control group	3.72 ± 0.19	28.6
Carbamazepine substance 20 mg/kg	1.75 ± 0.48	100
Emulsion of carbamazepine, 10 mg/kg	3.00 ± 0.0	100

4. CONCLUSION

These studies revealed anticonvulsant carbamazepine emulsion forms in a dose of 10 mg/kg, but at the same time there were some side effects, suggesting the need for additional experiments to determine the causes of the latter.

Thus, in this paper we propose a technique to obtain stable emulsions CBZ and revealed their anticonvulsant activity.

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