Biocompatible nanoemulsions as a tool for preclinical testing of CW-02-79, a pyrazoloquinolinone modulator of sigma-2 receptors: preformulation and formulation studies

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Conclusion

Athough the formulation with 30% of the oil phase had satisfying physicochemical properties, its relatively high viscosity can restrict syringeability and injectability. On the other hand, owing to satisfying solubilization capacity for CW-02-79 as well as small and uniform droplet size and low viscosity, NE prepared with 20% oil phase represents a promising carrier worth exploring further to support the preclinical progress of CW-02-79.

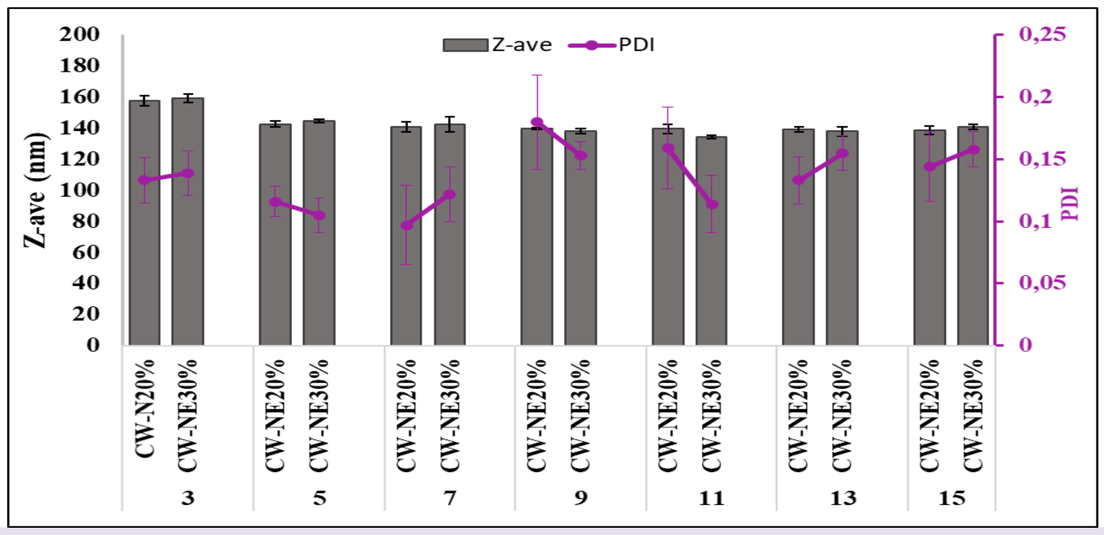
Introduction

Recently, we hypothesized that novel patent-protected ligand of the pyrazoloquinolinone chemotype (CW-02-79) with a substantial binding affinity for sigma-2 receptors in the brain may have a distinct pharmacological profile useful for the treatment of psychiatric and neurodegenerative disorders. However, very low water solubility hinders its administration and reliable efficacy and safety in vitro/in vivo evaluation. Therefore, this study aimed to develop biocompatible nanoemulsions (NEs), as carrier for CW-02-79, using high pressure homogenization (HPH) method. Firstly, preformulation studies were performed to obtain insight into the key properties of CW-02-79 required for further stages of formulation development. During NE preparation, the influence of formulation /process parameters was investigated to obtain NEs with small and uniform particle size suitable for parenteral administration.

Results and disscusion

Substance CW-02-79 appeared as a yellow powder, with broad particle size distribution. Results of the solubility study revealed the highest solubility of CW-02-79 in a MCT-castor mixture (1:1, w/w) which was chosen as the oil phase for NE development. The developed NEs exhibited size in the nanometer range nm), narrow size distribution (<0.15) and relativery high surface charge (>-30 mV), irrespective of the oil content, indicating good stability of the system.

Figure 4. The impact of the number of homogenization cycles on droplet size (Z-ave) and polydispersity index (PDI)



Methods

After the preformulation evaluation of CW-02-79 (e.g., solubility, physical state), NEs were prepared by varying the content of the oil phase (20%/30%, w/w) and process parameters (number of homogenization cycles), using hot HPH at 800 bar and 50°C. The tested formulations were characterized regarding the droplet size (Z-ave), size distribution, zeta potential (ZP), pH and electrical conducitivity.

- **Preformulation evaluation of CW-02-79**

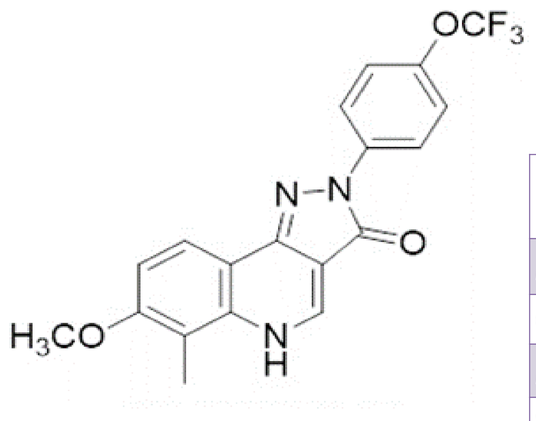


Figure 1. Chemical structure of CW-02-79

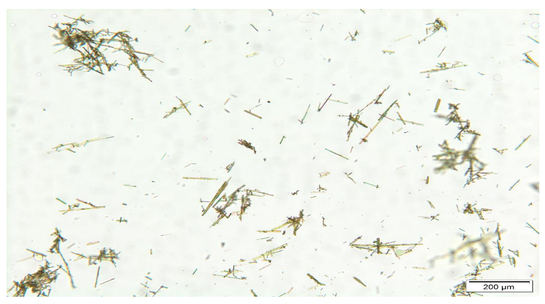


Figure 2. Representative polarization micrograph of CW-02-79

Table 1. Solubility of CW-02-79 in the investigated solvents

Excipients	Solubility (mg/ml)
MCT	0.499±0.043
Castor oil	0.280±0.074
MCT:castor oil 1:1 w/w	2.184±0.302
Soybean oil	0.659±0.043
MCT:soybean oil 1:1 w/w	0.414±0.043
Fish oil	0.342±0.015
0.1 M hydrochloride acid	0.123±0.016
Phosphate buffer (pH 7.4)	0.118±0.007
Isopropanol	5.746±0.458
Methanol	0.939±0.135
Ultrapure water	0.117±0.007
Dimethyl sulfoxide	>30

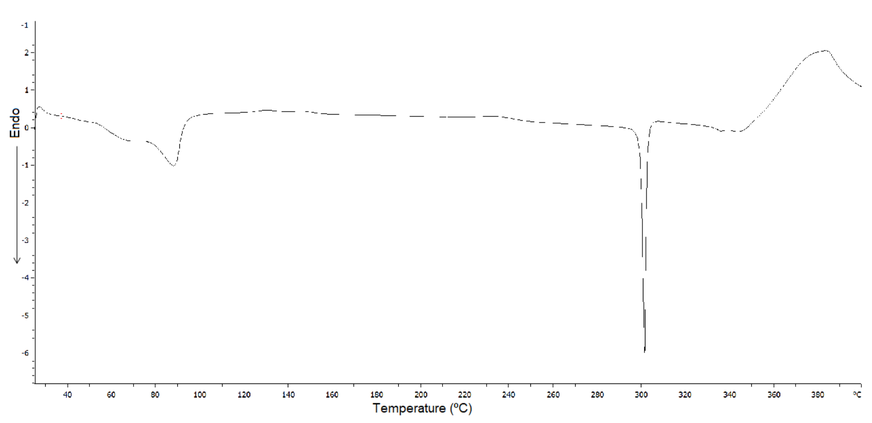


Figure 3. DSC thermogram of CW-02-79

Table 2. The physicochemical parameters of the tested CW-02-79-loaded nanoemulsions (mean ± SD, n=3)

Parameters	CW-NE20%	CW-NE30%
Z-ave ± SD (nm)	139.7±0.7	142.4±5.0
PDI ± SD	0.097±0.032	0.122±0.022
ZP ± SD (mV)	-50.9±0.9	-53.6±0.9
pH	5.71±0.02	5.56±0
Electrical conductivity (µS/cm)	114.1±0.2	143.1±1.6

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