Design of tailor-made biocompatible nanocarrier for novel pyrazoloquinolinone ligand (CW-02-79) based on comprehensive evaluation of critical physicochemical descriptors

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Conclusions

Owing to satisfying solubilization capacity for CW-02-79, physicochemical properties and preliminary stability, the nanoemulsions are the promising carriers worth exploring further to support the preclinical evaluation of CW-02-79.

Introduction

The poor aqueous solubility of the new proprietary ligand of pyrazoloquinolinone chemotype (CW-02-79) with significant binding affinity for sigma-2 receptors in the brain limits the development of conventional parenteral formulations and consequently extensive pharmacological studies during preclinical investigation. Therefore, we aimed to develop a biocompatible nanocarrier tailored to the specific physicochemical properties of CW-02-79 to enhance transport across the blood-brain barrier and achieve optimal distribution in the brain.

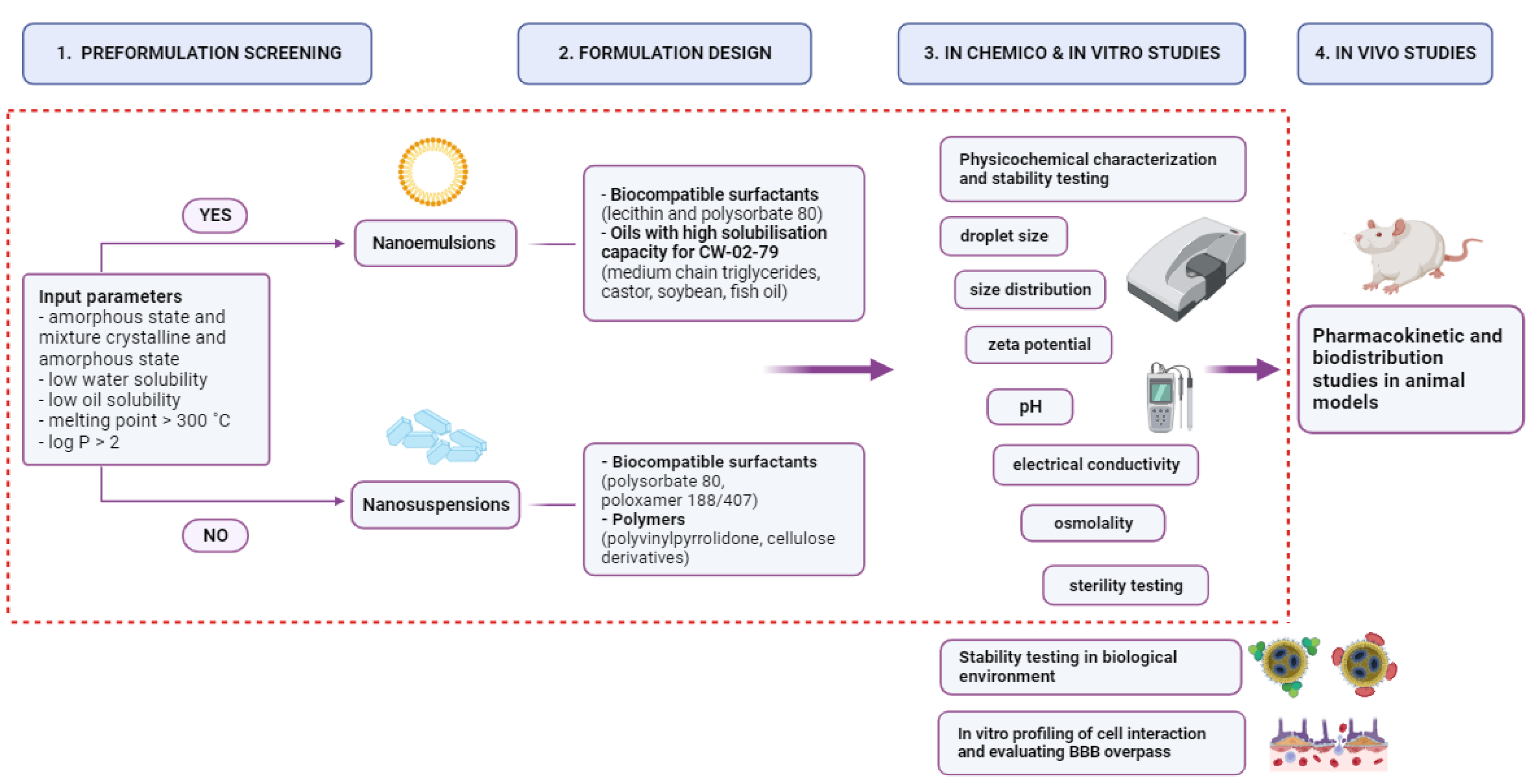
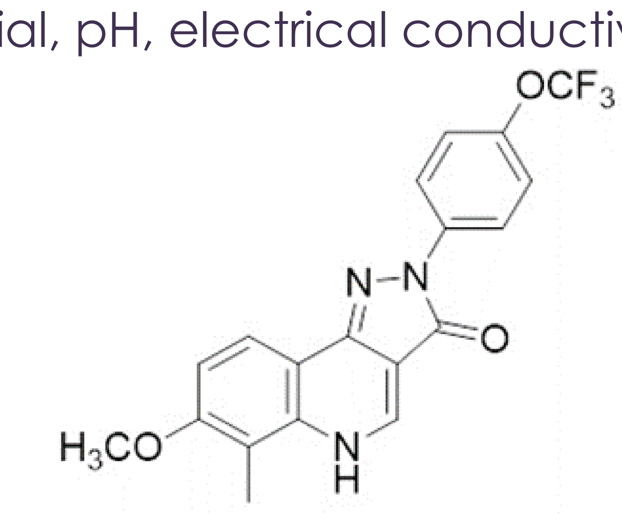


Figure 1. **Proposed protocol for the development and characterization of nanocarriers for innovative ligand/drug candidate**

Methods

Detailed analysis of lipophilicity (using log P and log D determination), solubility in various solvents/excipients (using shake flask method) and crystalline state of CW-02-07 (using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) with melt quenching method and polarization microscopy) was performed. Nanoemulsions selected as promising carriers for CW-02-79 were prepared by the high pressure homogenization method, varying the process and formulation parameters. In addition, the influence of the sterilization process (thermal sterilization/aseptic filtration) on the physicochemical properties of the nanoemulsion was investigated, including droplet size and size distribution, zeta potential, pH, electrical conductivity, and osmolality.



CW-02-079 (14d)

Figure 2. **Chemical structure of CW-02-79**

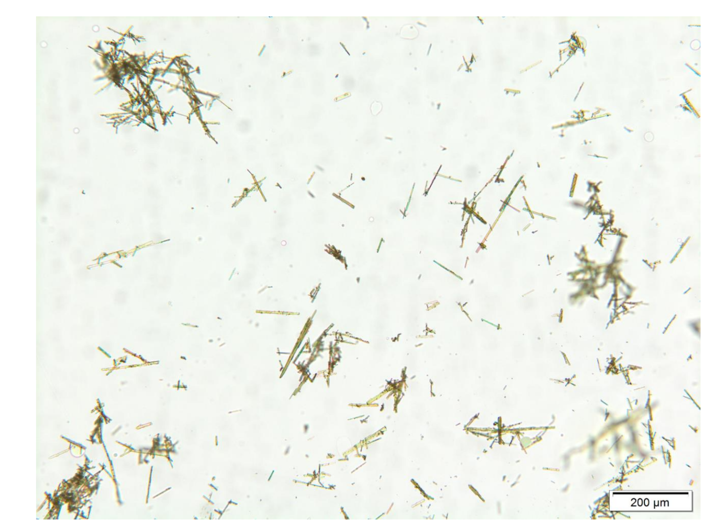


Figure 3. **Representative polarization micrograph of CW-02-79**

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

Excipientis	Solubility (mg/ml)	Excipientis	Solubility (mg/ml)
MCT	0.499±0.043	0,1 M HCl	0.123±0.016
Castor oil	0.280±0.074	Phosphate buffer pH=7.4	0.118±0.007
MCT:castor oil (1:1, w/w)	2.184±0.302	Isopropanol	5.746±0.458
Soybean oil	0.659±0.043	Methanol	0.939±0.135
MCT:soybean oil (1:1, w/w)	0.414±0.043	Ultrapure water	0.117±0.007
Fish oil	0.342±0.015	DMSO	>30

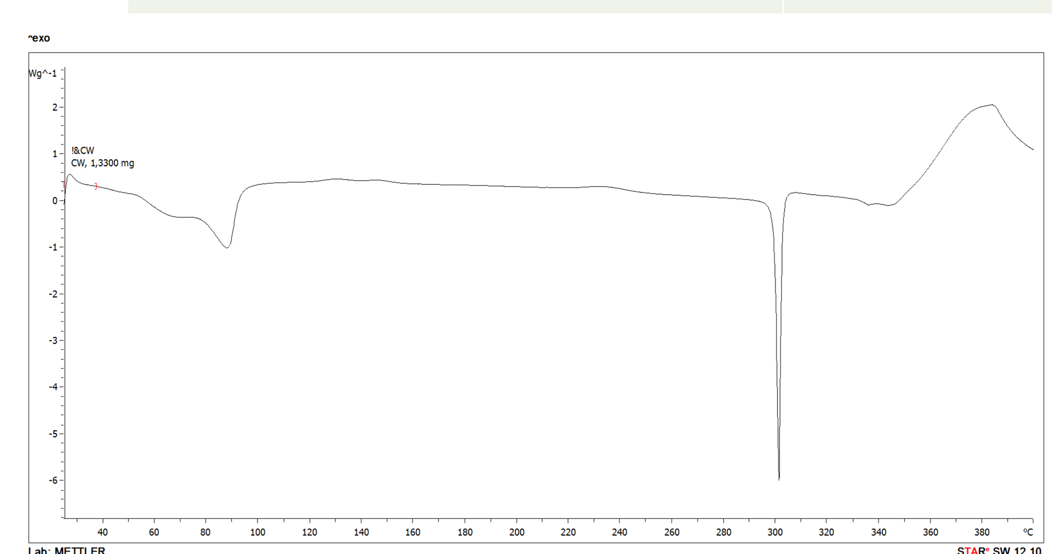


Figure 4. **DSC thermogram of CW-02-79**

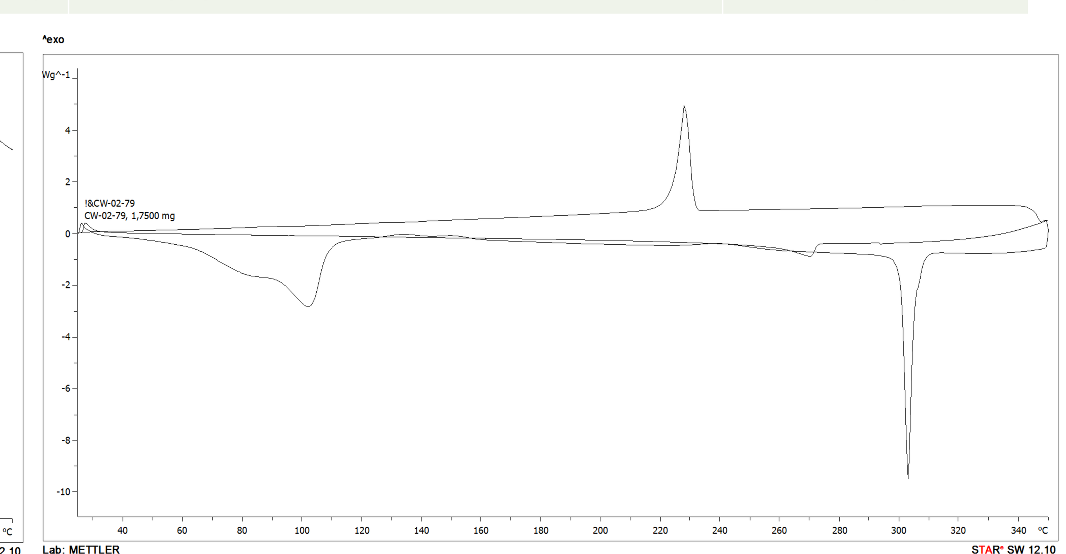


Figure 5. **DSC thermogram of CW-02-79 obtained with melt quenching approach**

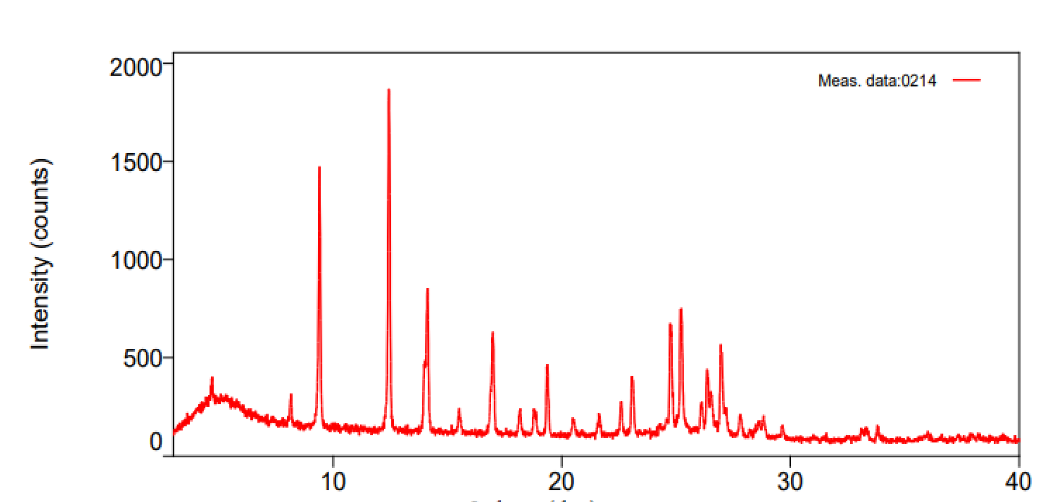


Figure 6. **XRPD pattern of unprocessed CW-02-79**

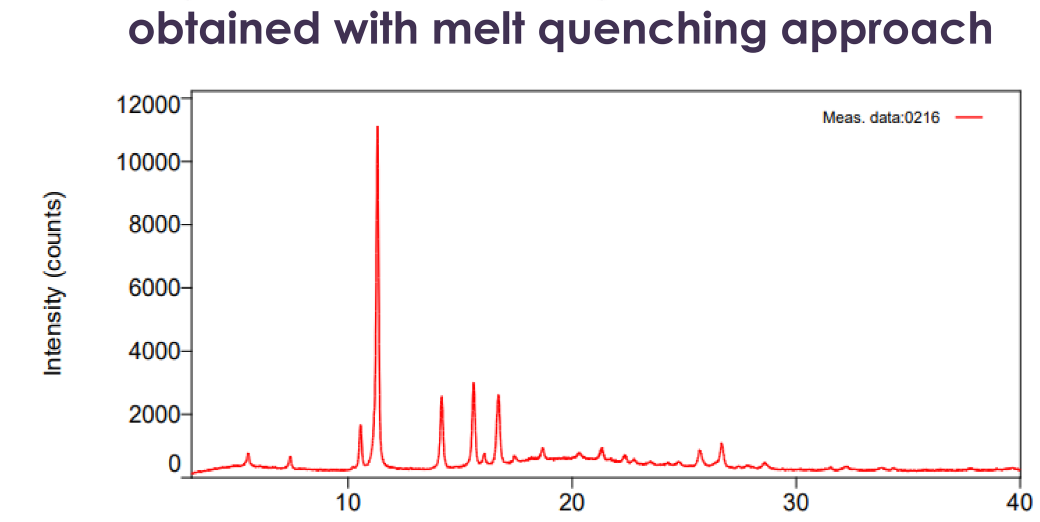


Figure 7. **XRPD pattern of nanoemulsion CW-NE20%**

Results

The obtained results showed that it was possible to formulate CW-02-79 loaded nanoemulsions with 20% oil phase (medium chain triglycerides:castor oil in 1:1 ratio), stabilized with biocompatible emulsifiers (lecithin/polysorbate 80) and containing nanosized droplets (< 200 nm) with narrow size distribution (polydispersity index < 0.2), zeta potential (> |-30| mV), pH (~ 5.7), and osmolality (295 mOsm/kg). The sterilization process had no significant effect on the physiochemical properties of the nanoemulsions, making them suitable for parenteral administration.

Table 2. **The physicochemical parameters of the tested CW-02-79-loaded nanoemulsions before and after sterilization**

Parameters	CW-NE20%	CW-NE20% Thermal sterilization	CW-NE20% Aseptic filtration
Z-ave ± SD (nm)	139.7±0.7	138.1±5.8	137.8±3.1
PDI ± SD	0.097±0.032	0.123±0.011	0.135±0.005
ZP ± SD (mV)	-50.9±0.9	-40.8±0.3	-34.0±0.7
pH	5.71±0.02	5.45±0.03	5.39±0.01
Electrical conductivity (µS/cm)	114.1±0.2	123.3±1.3	125.4±1.1

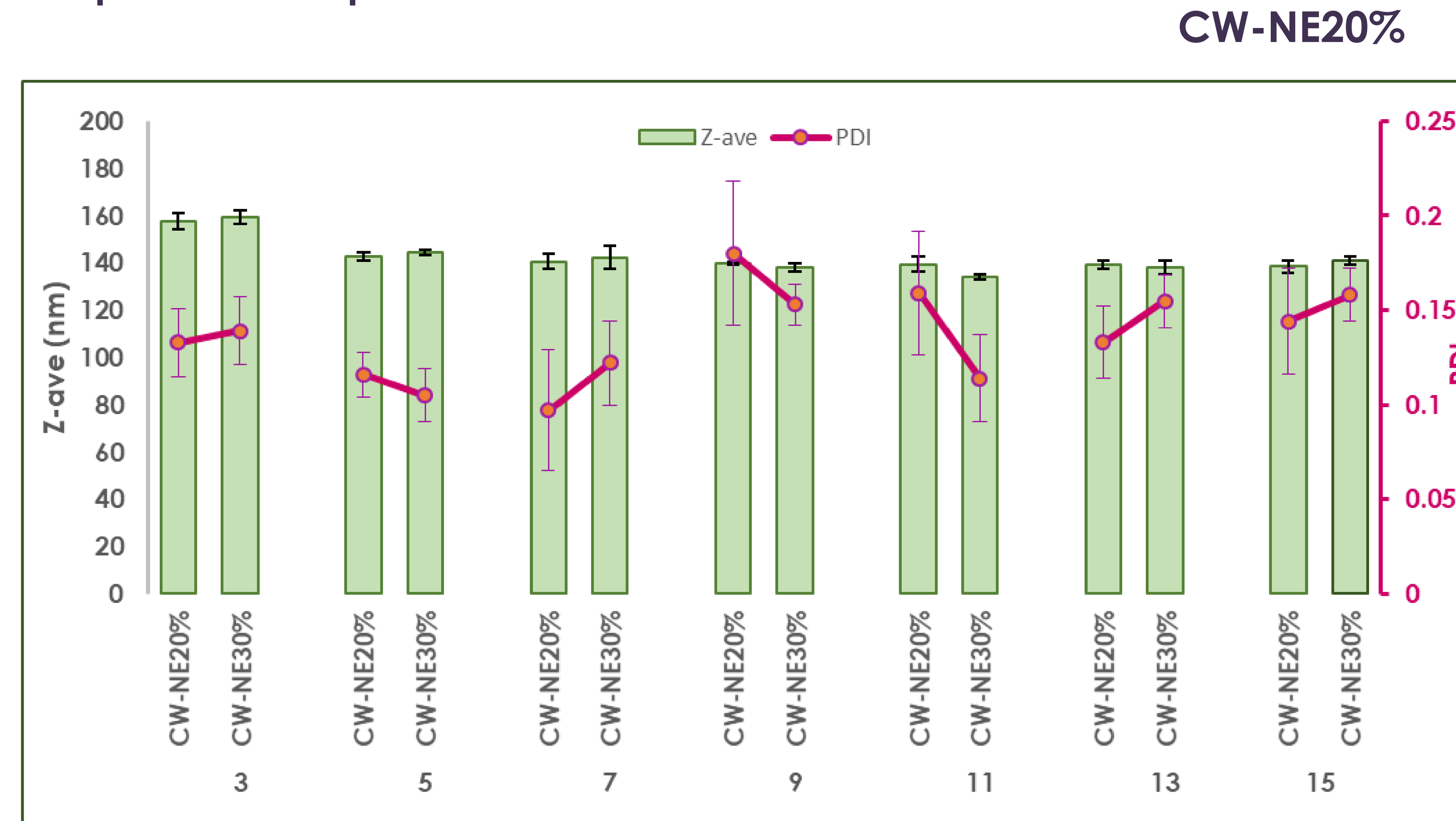


Figure 8. **The impact of the number of homogenization cycles on droplet size (Z-ave) and polydispersity index (PDI)**

ACKNOWLEDGEMENT

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