Searching for the best way to incorporate the proprietary compound GL-II -73 into the nanoemulsion carrier for prospective parenteral application

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CONCLUSION

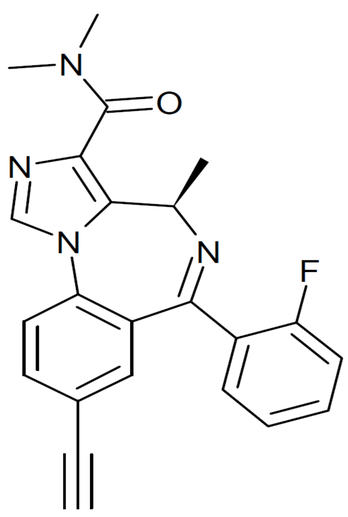
Passive drug loading resulted in better GL-II -73 loading than incorporation of the drug into the oil phase before formulation preparation (empirical approach). Moreover, this approach could contribute to a more rational formulation development in the selection of formulation factors by using lower amounts of the drug.

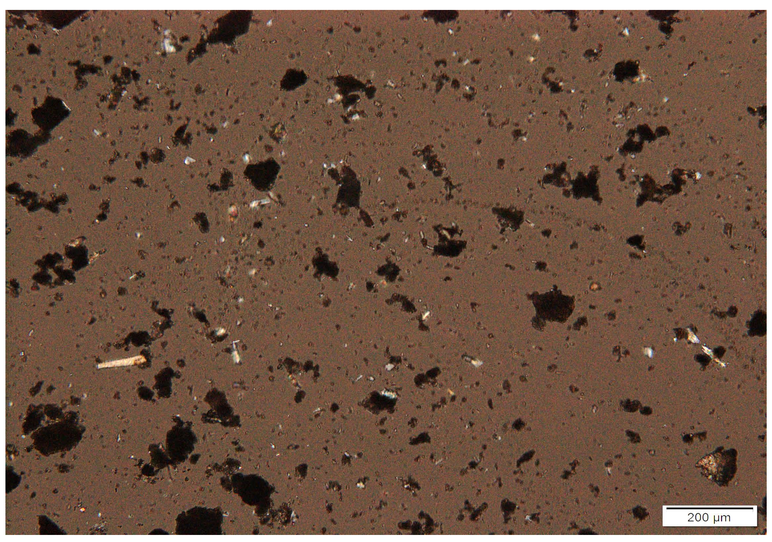
INTRODUCTION

The maximum amount of drug that can be incorporated into lipid nanoemulsions (NE) is usually judged by their solubility in the internal phase of the formulation. This can lead to various problems, such as precipitation of the drug after the formulation has been processed or, depending on the preparation technique used, the use of a large amount of the drug. Therefore, it is useful to consider other methods of drug loading, especially in the early stages of formulation development.

AIM

In this study, we tried to find the best way to achieve the highest loading of GL-II -73 in NEs for future parenteral applications for in vivo animal studies. This ligand acts as a positive allosteric modulator at α-GABAA receptors with combined antidepressant and cognition-enhancing effects.





GL-II-73 solubility in different mediums

	GL-II-73 (µg/ml)
Water	1,001.10 ± 39.94
0.1 M HCl (pH 1.2)	5,370.70 ± 195.26
Phosphate buffer (pH 7.4)	951.37 ± 41.38
Medium-chain tryglycerides	4,489.70 ±148.32
Soybean oil	3,055.05 ± 137.42
Castor oil	2,820.65 ± 183.68
Fish oil	2,395.07 ± 331.00
Benzyl alcohol	> 534,365.79 ± 80,924.95

GL-II-73 (4R)-8-Ethynyl-6-(2-fluorophenyl)-N,N,4-trimethyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide

MATERIAL AND METHODS

Empirical drug loading approach

Aqueous phase
glycerol
polysorbate 80
0.01 M phosphate buffer
(pH 8)

Oil phase
medium-chain triglycerides
soy lecithin
butylated hydroxytoluene
GL-II-73 (90 mg)

Preemulsification
IKA Ultraturex
11000 rpm, 1 min
50 °C

Emulsification
EmulsiFlex C3, Avestin
800 bar, 10 cycles
50 °C

GL-II-73
Nanoemulsion
60 ml

Lower amount of drug is needed

Passive drug loading

Aqueous phase
glycerol
polysorbate 80
0.01 M phosphate buffer
(pH 8)

Oil phase
medium-chain triglycerides
soy lecithin
butylated hydroxytoluene

Preemulsification
IKA Ultraturex
11000 rpm, 1 min
50 °C

Emulsification
EmulsiFlex C3, Avestin
800 bar, 10 cycles
50 °C

Placebo nanoemulsion ~ 1ml

GL-II-73
10 mg

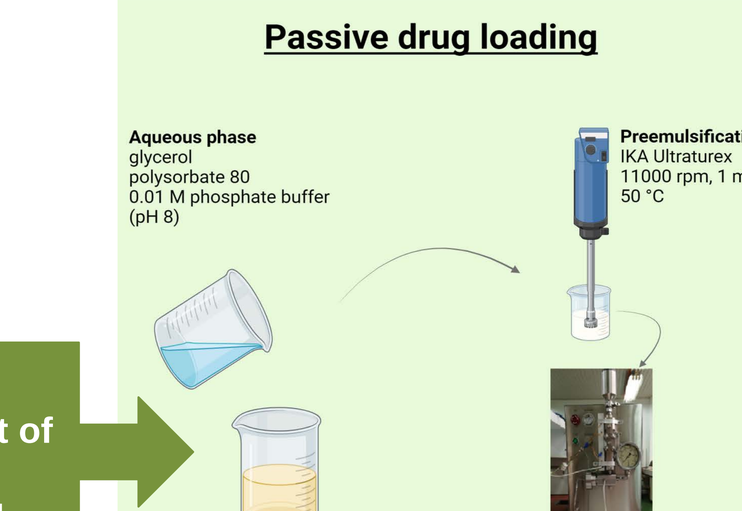
Incubation
150 rpm; 72 h

Centrifugation

GL-II-73 nanoemulsion

RESULTS

Nanoemulsion had suitable characteristics for prospective parenteral administration



Passive drug loading provided superior drug loading compared to the empirical approach

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