An insight into cannabidiol-*in vitro* release profile from lipid nanocapsules

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Introduction

As the intravenous admnistration of lipohpilic drugs is often impaired by the need for organic solvent to be administered, recently developed lipid nanocapsules (LNC) consisting of an oily core surrounded by a surfactant shell may well provide a novel platform to enable intravenous administration of lipophilic drug substances devoid of organic solvents given their small size (ranged from 18 to 80 nm) and their lipophilic nature. Since intravenous administration allows release times to be prolonged much longer than oral administration, the aim of the present study is to evaluate the aptness of these novel nanocarriers to extend drug release over time, taking cannabidiol (CBD), the main non-psychotropic cannabinoid, as a model of lipophilic drug substance to encapsulate.

Materials and Methods

❖ Materials

- **Lipid nanocapsules (LNCs).**
Labrafac WL 1349 (caprylic-capric acid triglycerides) was provided by Gattefossé S.A. (Saint-Priest, France). Solutol HS15 (mixture of free polyethylene glycol 660 and polyethylene glycol 660 hydroxystearate) and Lipoïd S75 (soybean lecithin at 70% of phosphatidylcholine) were gifts from BASF and Gmbh (Ludwigshafen, Germany), respectively. NaCl was supplied by Panreac. De-ionized water was obtained from a MilliQ® Purification System (Millipore, Paris, France). **Cannabidiol (CBD)** was provided by THC Pharma GmbH (Frankfurt am Main, Germany).

-***In vitro* release assay.**
SpectraPor® dialysis membranes, molecular weight cut-off 50 kDa were purchased from Spectrum Labs Inc. (California, United States of America

❖ Methods

-LNCs preparation. 50 nm-sized CBD-loaded LNCs were developed according to an expanded phase inversion method.

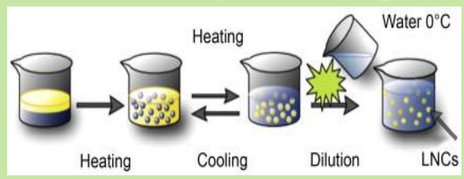


Fig. 1. Phase-inversion based method scheme

-*In vitro* release assay. A dialysis method was performed, since no centrifugation procedure has proven successful in separating nanoparticles from an aqueous medium. The release profile was assayed for 50-nm CBD-loaded LNCs over fifteen days.

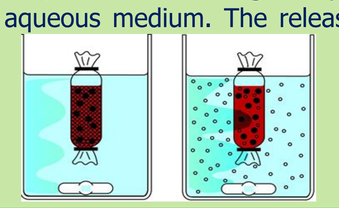


Fig. 2. Dialysis assay scheme

Results

❖ Stability while heating

Thermostability of the drug substance under the heating conditions required by the expanded phase inversion method was determined. 78% of the initial amount of cannabidiol (CBD) was kept unaltered after the three temperature cycles (60-90ºC) applied during the preparation procedure.

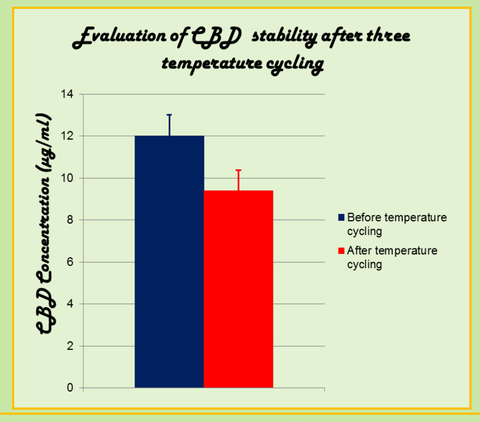


Fig. 3. Cannabidiol stability while heating

❖ Encapsulation efficiency

Only traces of cannabidiol (CBD) were detected in free solution. As a result, it was concluded that all remaining CBD would be encapsulated into the oily core of the lipid nanocapsules (LNC). Therefore, the encapsulation efficiency of the cannabidiol-loaded nanocarriers was supposed to be close to 100%.

❖ *In vitro* release assay

Phosphate buffer solution pH 7,4 added with polysorbate 80 was chosen as release medium in order to mimic physiological conditions with the highest accuracy and to ensure sink conditions by enhancing CBD solubility in water. The assay was performed under magnetic stirring (250 rpm) at 35ºC.

Firstly, CBD stability under the assay conditions was evaluated to correct CBD concentrations values at the various time points. CBD proved to experiment a temperature-dependent degradation, according to results shown in Figure 4.

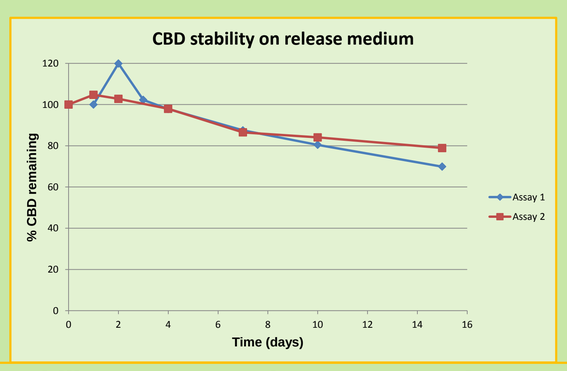
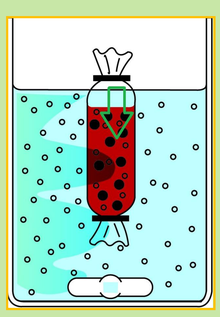


Fig. 4. CBD stability at 35ºC under magnetic stirring over fifteen days.

The amount of CBD remaining into LNCs was evaluated over fifteen days. The content of dialysis bags were freeze-dried and the LNCs were lysated for quantification of CBD remaining encapsulated. The extrapolated amount of CBD at time zero does indeed further fit the previously reported encapsulation efficiency.



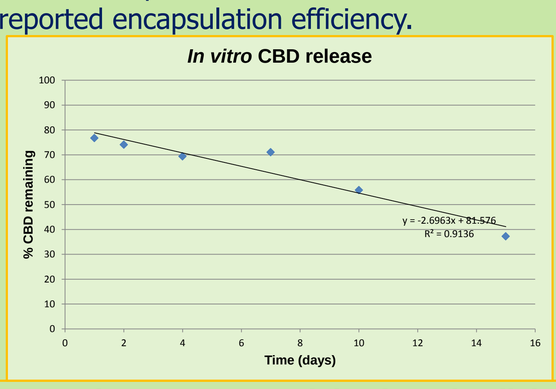
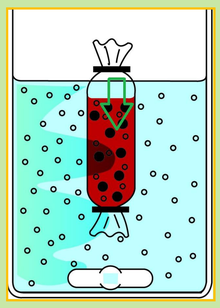


Fig. 5. *In vitro* CBD release: CBD remaining into the dialysis bag (1).

The inclusion of time zero and considering 100% as the amount of CBD present at the beginning of the assay, further improved the correlation coefficient, as shown in Figure 6.



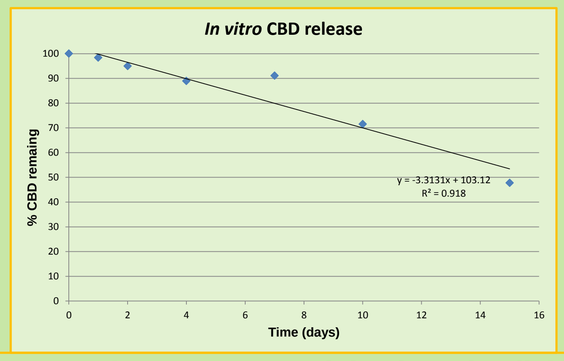
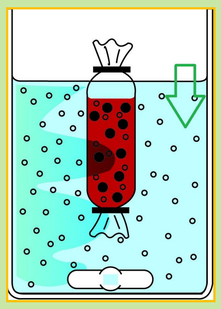


Fig. 6. *In vitro* CBD release: CBD remaining into the dialysis bag (2).

Additionally, samples were taken from release medium to draw a parallel release profile. Such release profile was compared with the theoretical profile inferred from measures performed into dialysis bags. To this end, previous results on CBD temperature-dependent degradation were taken into account. Overall, very similar profiles were achieved with both procedures.



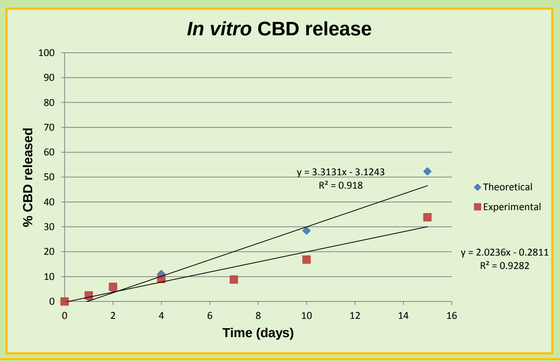


Fig. 7. *In vitro* CBD release: CBD in release medium.

Conclusions

1. Loss of CBD below 25% after three temperature cycling was observed in the extended phase inversion procedure used to prepare LNCs . Extremely high encapsulation rates were obtained in all cases, with only traces of CBD being non-encapsulated into the oily core of LNCs.

2. CBD encapsulated into LNCs exhibited a sustained-release pattern devoid of any burst effects with around 30% of the dose released after fifteen days under the assayed conditions. Since LNCs efficiently extend CBD release at least over fifteen days with high encapsulation efficiency, they represent promising platforms to enable intravenous administration of lipophilic cannabidiol.

References

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