

6-2008-2126 | Pro-Nano Lipospheres as an Oral Delivery Platform for Lipophilic Drugs
[Domb Abraham](#), HUJI, School of Medicine - IMRIC, School of Pharmacy- Institute for Drug Research

Background

Micro-emulsions are formed more or less spontaneously when their components are brought into contact. They have been the only successful delivery systems for certain types of pharmaceutical compounds, particularly compounds such as Cyclosporins. Usually, they are stable over periods in excess of 24 hours and can be used as "micro-emulsion pre-concentrates", spontaneously forming micro-emulsions in an aqueous medium.

After successfully developing the process for the oral delivery of cyclosporine, it is now being extended to other water-insoluble (Lipophilic) drugs.

Our Innovation

The PNL formulation composed of GRAS materials enabling co-administration of lipophilic drugs and bio-enhancers for improved bioavailability:

The PNL vehicle serves as a platform for the successful oral delivery of lipophilic drugs separately or together with natural absorption enhancers such as Piperine (black pepper component).

Our work centered in application of the PNL for $\Delta 9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) which are the primarily investigated compounds of the cannabis plant. These molecules have great therapeutic potential but their oral administration is hindered by poor solubility and extensive metabolism.

Advantages

- GRAS (Generally Regarded as Safe) based materials
- Dissolves lipophilic drugs and absorption enhancers found in foods such as piperine, resveratrol etc.
- The drug is co-administrated with absorption enhancer, allowing it to perform its inhibitory effects on first pass metabolism
- The formulation self emulsifies in the GI milieu forming an O/W nano emulsion with particle size of 50nm and less
- The formulation overcomes absorption obstacles of lipophilic drugs
- Increase in oral bioavailability leads a lower inter and intra subject variability

Technology

The poorly absorbed drug is dissolved in the oily formulation with the absorption enhancer. Upon contact with water, the formulation forms nano particles. These nano particles trap the lipophilic components in their lipid core. This allows the lipophilic drug and absorption enhancer to be solubilized in the aqueous environment of the GI.

Highlights

Pre-clinical studies in male Wistar rats showed a 6 fold increase in the relative oral bioavailability of THC given in PNL (Figure 1) and an additional 1.5 fold increase with piperine-PNL. Similarly, there was a 3 fold increase in the relative oral bioavailability of CBD-PNL and an additional 2 fold increase with piperine-PNL (Figure 2).

A two-way crossover, single administration clinical study with 9 healthy volunteers was conducted. The volunteers received a THC-CBD piperine-PNL capsule and the oromucosal spray Sativex® with a washout period in between formulations. Single oral administration of the cannabinoids in piperine-PNL formulation resulted in a 3-fold increase in C_{max} and a 1.5-fold increase in AUC for THC compared to Sativex®. A 4-fold increase in C_{max} and a 2.2-fold increase in AUC for CBD compared to Sativex® were observed (Figure 3 and 4)

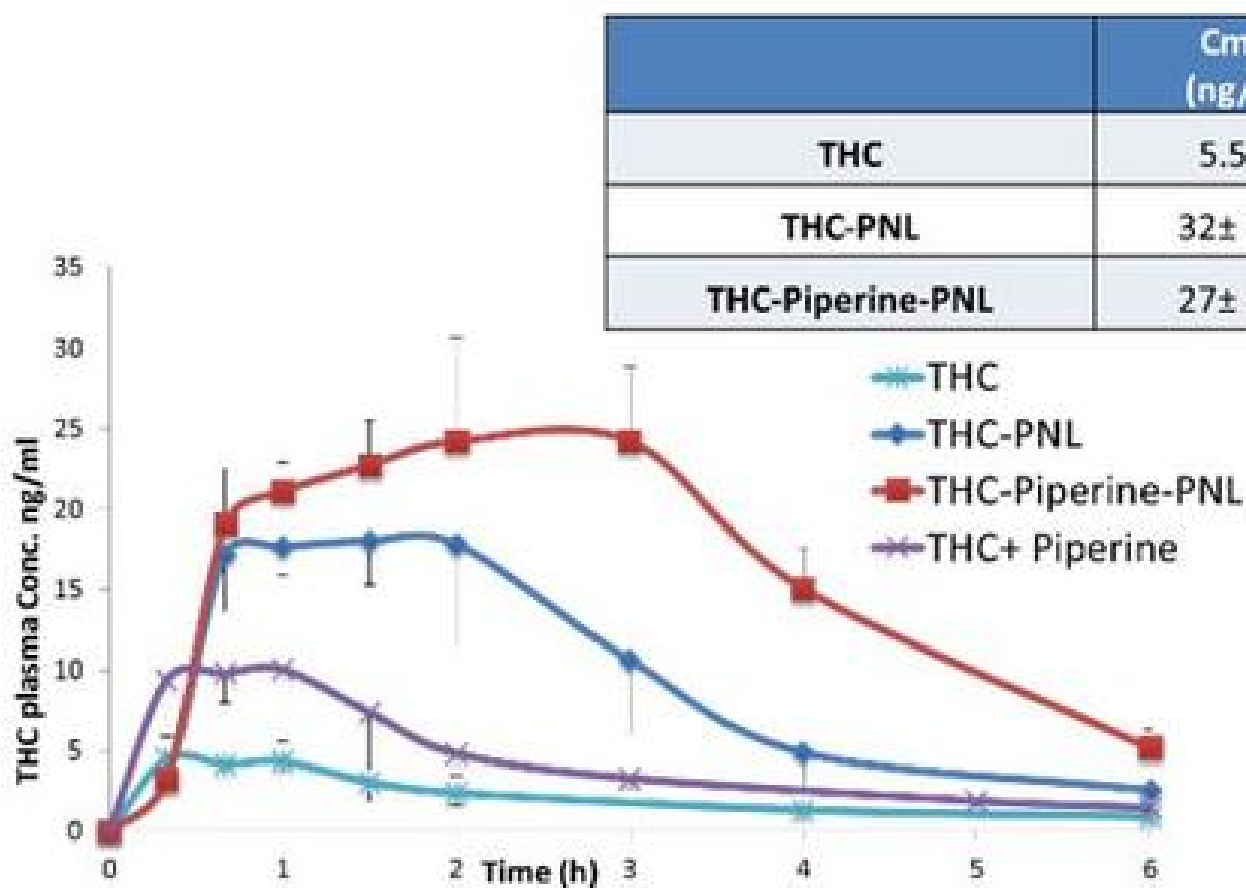


Figure 1: Pro-NanoLipospheres (PNL) and piperine-PNL enhance THC bioavailability. Plasma THC concentration-time plot (mean ± S.E.M.) following PO administration of dispersed THC PNL (20mg/kg) and THC-piperine-PNL (THC 20mg/kg, piperine 10mg/kg) (n=6 for each group).

	Cmax (ng/ml)
CBD	39±8
CBD-PNL	137±43(*)
CBD-Piperine-PNL	170±13(*†)

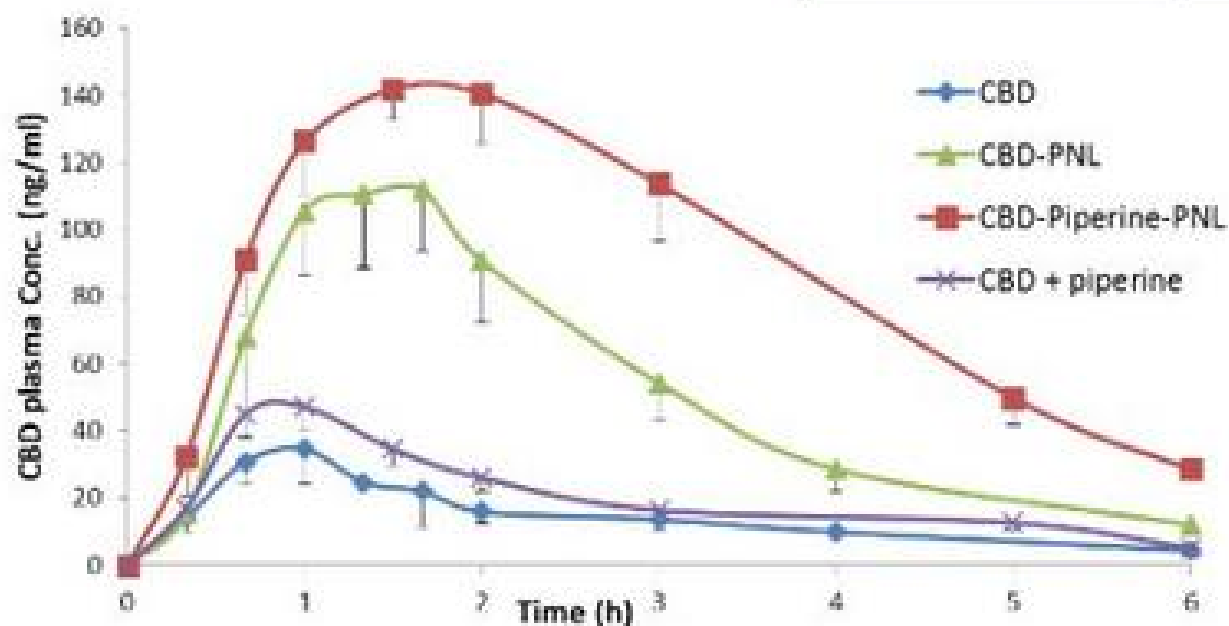


Figure 2: Pro-NanoLipospheres (PNL) and piperine-PNL enhance CBD bioavailability. Plasma CBD concentration-time plot (mean \pm S.E.M.) following PO administration of dispersed CBD PNL (15mg/kg) and CBD-piperine-PNL (CBD 15mg/kg, piperine 10mg/kg) (n=6 for each group).

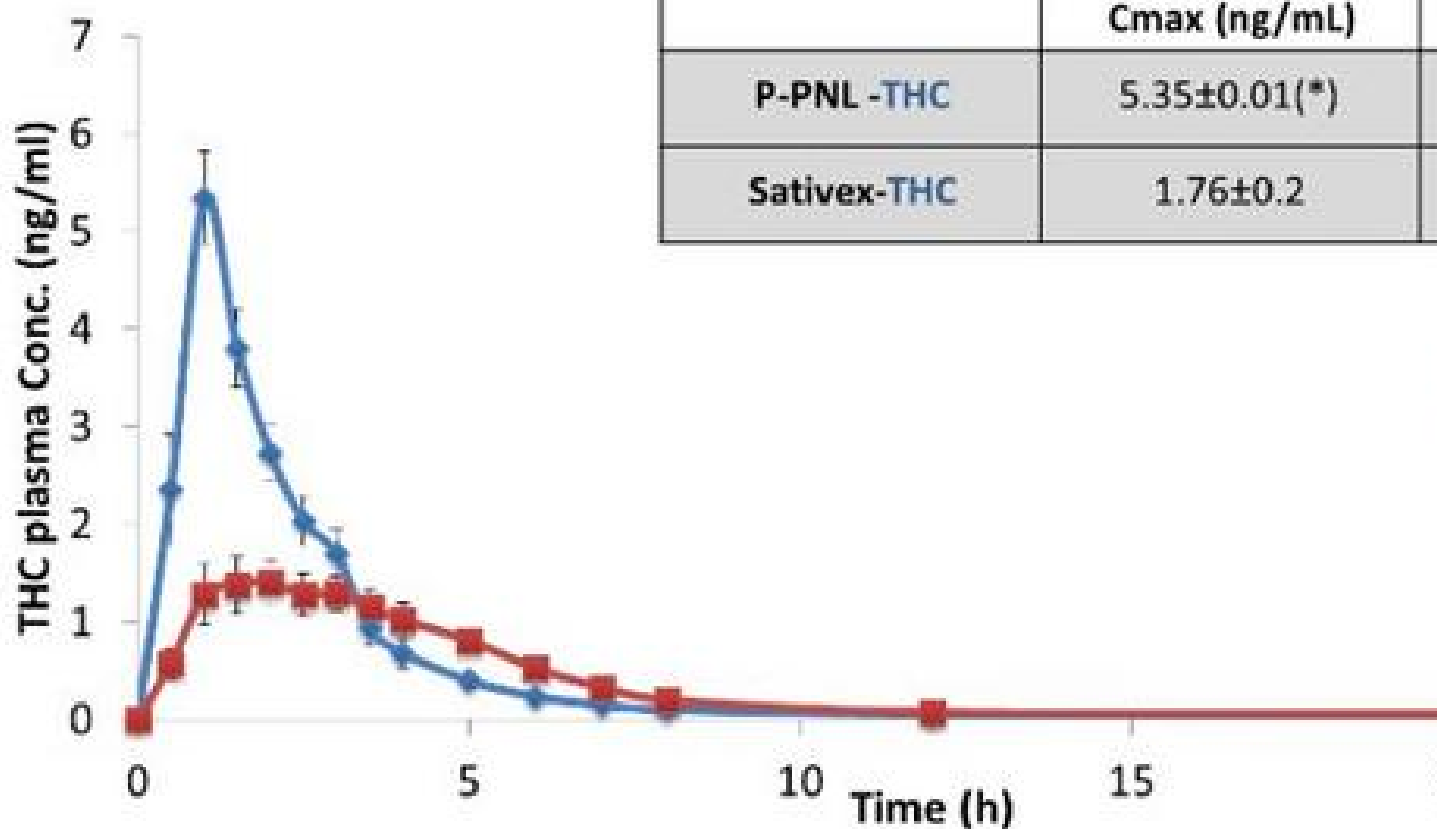


Figure 3: Plasma THC concentration vs. time plot (mean \pm SEM) following oral administration of THC-CBD-piperine-PNL and buccal administration of Sativex® at a dose of 10.8 mg (n = 9 for each group)

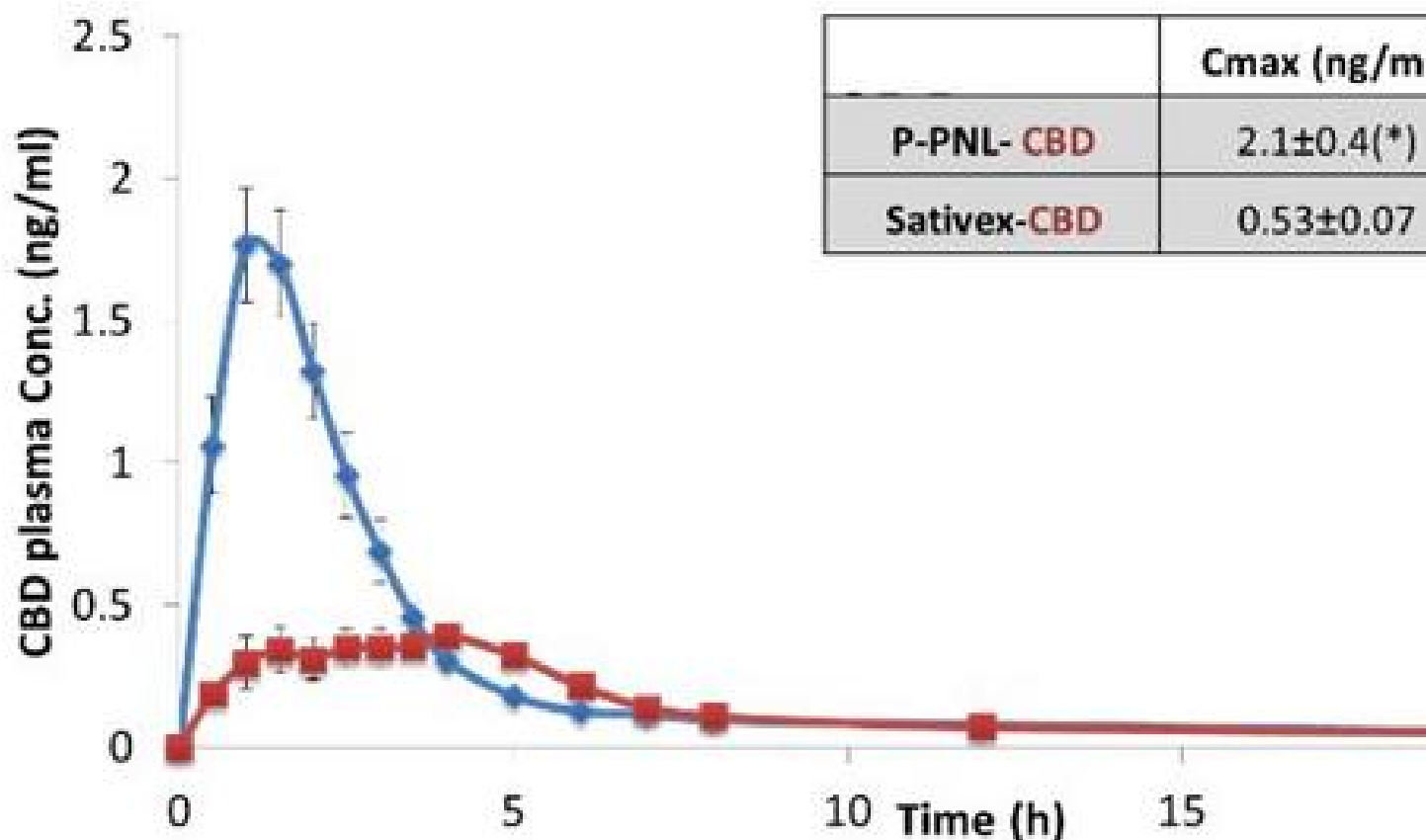


Figure 4: Plasma CBD concentration vs. time plot (mean \pm SEM) following oral administration of THC-CBD-piperine-PNL and buccal

The Opportunity

Many of today's leading compounds and drugs in pipeline fail to reach clinical stages due to poor oral bioavailability. This formulation presents an ideal, simple solution for the optimal oral delivery of these compounds and a direct to clinic development.

Patent Status

Granted Europe 2804587

Contact for more information:



Mel Larrosa

VP Business Development Healthcare

+972-2-6586692

Yisum Research Development Company of the Hebrew University of Jerusalem

Hi-Tech Park, Edmond J. Safra Campus, Givat-Ram, Jerusalem

P.O. Box 39135, Jerusalem 91390 Israel

Telephone: 972-2-658-6688, Fax: 972-2-658-6689