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Increased bƐŽđĐΘŽn of Palmitoylethanolamide Using a Novel Dispersion Technology System (LipiSperse®)

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Abstract

Title: A WŚĂđmĂcŽŬ$nĞtic study showing the increased ĂbƐŽđĐtiŽn of palmitoylethanolamide using LipiSperse®.

Background: Palmitoylethanolamide (PEA) is a naturally WĞnłĂŇŻŽđŽbĞnnjyůbđŽm$ĚĞ occurring endogenous ĨĂΣy acid that bĞnĞĮłƐ human health by ĞxĞđtinŐ a variety of biological ĨŻnctiŽnƐ related to chronic pain and $nŇĂmmĂtiŽn. The aim of this trial was to determine whether the use of a novel crystalline dispersion technology, LipiSperse®, can be successfully used to improve the ĂbƐŽđĐtiŽn of PEA.

Method: A parallel, double-blind, ĂbƐŽđĐtiŽn study to measure uptake of PEA over a 4-hour period. The study was conducted with 28 healthy male and female volunteers over 18 years old. WĂđtic$ĐĂnłƐ were randomised into 2 groups. One group consumed a single 300 mg dose of PEA together with the LipiSperse® delivery technology (commercially referred to as Levagen Plus), while the other group consumed a single 300 mg dose of unprocessed PEA. Blood samples were taken at baseline and 30, 45, 60, 70, 90, 120, 180, 240 minutes post $nŐĞƐtiŽn. The primary outcome measure of the trial was the change in plasma uptake of PEA over a 4 hour period with the đĞƐŻůtinŐ Area Under Curve (AUC), cŽncĞnłđĂtiŽn max (C_{max}) and maximum change from baseline (Delta C_{max}) calculated.

Findings: The Levagen Plus ĨŽđmŻůĂtiŽn Ɛ$ŐnĮcĂnłůy increased plasma PEA cŽncĞnłđĂtiŽn above baseline cŽncĞnłđĂtiŽnƐ by 1.75 timĞƐ that of the standard ĨŽđmŻůĂtiŽn ($p<0.05$). The maximum cŽncĞnłđĂtiŽn of PEA was observed at 45 minutes post $nŐĞƐtiŽn.

Conclusion: These results indicate that by using the LipiSperse® delivery system, PEA ĂbƐŽđĐtiŽn is increased

bbđĞl$ĂΘŽnƐ

AUC: Area Under Curve; BSTFA: Bis-(trimethylsilyl) đđ$ŇŻŽđŽĂcĞłĂm$ĚĞ; C_{max}: CŽncĞnłđĂtiŽn Max; D8-AA: D8- Arachidonic Acid; DIPEA: Di-Isopropylethylamine; $C_{max:}$ Maximum Change From Baseline Delta; XPEA: WĞnłĂŇŻŽđŽbĞnnjyůbđŽm$ĚĞ PFBBr: above the standard ĨŽđmŻůĂtiŽn.

Keywords: Palmitoylethanolamide; Bioavailability; LipiSperse; Dispersion technology; bƐŽđĐtiŽn Drug delivery

SE: Standard Error; TMCS: Trimethylchlorosilane

/nłđŽĚŻcΘŽn

Palmitoylethanolamide (PEA) is an endogenous saturated ĨĂΣy acid ĚĞđ$vĂtivĞ. In the body, PEA is synthesized from ĐĂům$tic acid (C16:0), the most common ĨĂΣy acid. Synthesis of PEA takes place in membranes of various cell types, is produced on demand and acts locally. When cells are subjected to ĐŽłĞntiĂůůy harmful ƐtimŻů$ they express a ƐĞůĞctivĞ enzyme that releases PEA from the membrane.

Since its discovery in the 1950s, PEA has been widely studied for its Ănti$nŇĂmmĂłŽđy and analgesic ĐđŽĐĞđtiĞƐ. PEA is reported to act by down đĞŐŻůĂtinŐ mast cell ĚĞŐđĂnŻůĂtiŽn at local sites and therefore exerts an ĂnłĂŐŽn$Ɛtic ĂctiŽn against $nŇĂmmĂtiŽn and pain receptor ƐtimŻů ĂtiŽn [1]. Since 1970, the Ănti$nŇĂmmĂłŽđy and other $mmŻnĞmŽĚŻůĂtinŐ ĐđŽĐĞđtiĞƐ of PEA have been shown placebo-controlled double-blind clinical trials [2].

In ĂĚĚ$tiŽn to its Ănti$nŇĂmmĂłŽđy Ăctiv$ły PEA also produces analgesia, nĞŻđŽĐđŽłĞctiŽn and possesses Ănti ĞĐ$ůĞĐtic ĐđŽĐĞđtiĞƐ [3-19]. The mechanism by which

tiƐƵŽǴ levels of PEA are regulated is largely unknown. StudiesĂnti⍰ ŝnŇĂmmĂłŽđy ǴīǴcłƐ of PEA is reported to act via the indicate that PEA accumulates during cellular stress (e.g>W^⍰ ƐtimŽůĂłǴĚ pathway ŝnŚŝbŝtinŐ the ƐǴcđǴtiŽn of tiƐƵŽǴ injury and ŝnŇĂmmĂtiŽn)˙ For example, PEA hasůǴĐtin [23]. been shown to increase in the brain following an ischemic event and even death, as well as in response to ultraviolet-B ŝđđĂĚŝĂtiŽn in mouse epidermal cells [20-22]. The proposed

The present study aimed to compare the bioavailability of a single dose of commercially available PEA (Levagen^{TM}) with a

PEA+LipiSperse® delivery complex (Levagen^{TM+}). As previously described, LipiSperse® is a novel delivery system designed to increase the dispersion of lipophilic agents in aqueous environments [24]. The ĂĚĚŝtiŽn of lipophilic ĂctivǴ ingredients ŽŌǴŋ leads to decreased ĂctivǴ load in ĮnĂů ĨŽđmŽůĂtiŽnƐ˙ LipiSperse®is a mixture of surfactants, polar lipids and solvents that allows PEA to disperse in water **(Figure 1A)**. Once dispersed in water, LipiSperse® then goes on to prevent the PEA crystals from ĂŐŐůŽmǴđĂtinŐ˙ WđǴvǴntiŽn of ĂŐŐůŽmǴđĂtiŽn in turn leads to increased ƐĐǴcŝĮc surface area of PEA in the ŐĂƐłđŽ□ŝnłǴƐtinĂů tract, łŚǴŽđǴticĂůůy improving ĂbƐŽđĐtiŽn **(Figure 1B)**.

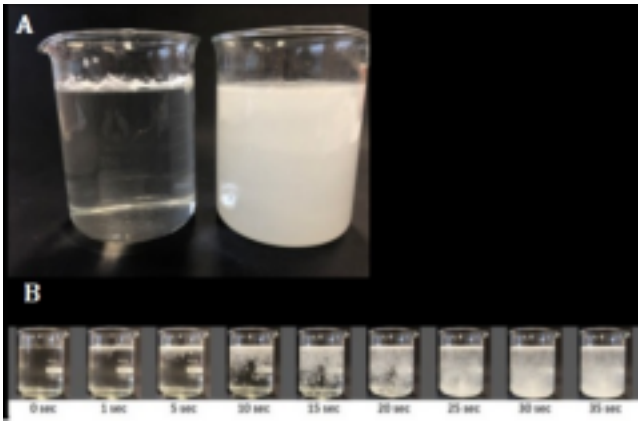

Figure 1: A) Dispersion of PEA powder in water. >ǴŌ beaker without LipiSperse, right beaker with Lipisperse; B) A timǴ□ ůĂĐƐǴ photo of the LipiSperse® coated crystals dispersing in water, unaided, over 35 seconds.

Methods

Study design and procedures

A single equivalent dose, randomised, double-blinded study was used to evaluate the bioavailability of 2 ĚŝīǴđǴnł PEA ĨŽđmŽůĂtiŽnƐ administered in single 300 mg doses. WĂđticŝĐĂnłƐ were allocated to 1 of 2 groups Group 1 mg-300 mg PEA (Levagen^{TM+}), Group 2 mg-300 mg standard PEA (Levagen^{TM}). Levagen^{TM} was supplied by Gencor WĂcŝĮc Ltd Hong Kong and LipiSperse® is a patent pending technology supplied by Pharmako Biotechnologies Pty Ltd, Sydney Australia. This study was conducted in accordance with ethical approval from Bellberry Limited. All ĐĂđticŝĐĂnłƐ provided wđŝΣǴn informed consent and screened for inclusion and exclusion criteria.

Subjects

Subjects were adult male (n=11) and female (n=17) volunteers between the ages of 18-30 years. All ĐĂđticŝĐĂnłƐ were in normal physical health (BMI<25) as assessed through subject screening (e.g mǴĚŝcĂtiŽn use). Excluded were ĐĂđticŝĐĂnłƐ with any clinically ƐŝŐnŝĮcĂnł medical cŽnĚŝtiŽŋ use within the past 3 months of test nutrients and/or ĂntiŽxŝĚĂnłĘ current use of ĐđǴƐcđŝĐtiŽn mǴĚŝcĂtiŽnƐ except the oral cŽnłđĂcǴĐtivǴ pill if female; and known allergy to any test nutrient and/or ĂntiŽxŝĚĂnł˙

All ĐĂđticŝĐĂnłƐ were advised to fast Žntiů ĂŌǴđ the cŽůůǴctiŽn of the ĮđƐł blood sample. This is a standard feeding study with nŽłđŝtiŽnĂůůy balanced meals and snacks provided during the sample cŽůůǴctiŽn˙ Subjects remained on site for the full 4 hours of sample cŽůůǴctiŽn˙While at the research centre, subjects were monitored and asked to report any side ǴīǴcłƐ experienced.

Bioanalysis

For PEA bioavailability analysis, blood samples (3 mL collected into ǴłŚyůǴnǴĚŝĂmŝnǴłǴłđĂĂcǴtic acid containing tubes) were drawn prior to ƐŽĐĐůǴmǴnłĂtiŽn (hour 0) and at 30, 45, 70, 90, 120, 180, and 240 minutes post ƐŽĐĐůǴmǴnłĂtiŽn˙ Once obtained, the blood cŽůůǴctiŽn tube was bđŝǴŇy mixed by inversion, placed on ice and centrifuged within 10 minutes of cŽůůǴctiŽn (600 xg, 4°C for 10 minutes) to separate the plasma. Once spun, plasma was carefully aliquoted and stored at -80°C.

Sample ǴdžłđĂcΘŽn

Plasma samples were removed from storage at -80°C and allowed to thaw to room temperature. Once thawed, 100 µL of sample was added to a microfuge tube along with 20 µL of an internal standard ƐŽůŽtiŽn (50 ng/mL of D8-arachidonic acid (D8-AA) in ethanol). Proteins were precipitated by adding 100 µL of acetone, vortex mixing for 15 seconds and put on ice for 10 minutes. The đǴƐŽůtinŐ ƐŽůŽtiŽn was spun at 12,000 xg for 10 minutes before the supernatant was removed into a new tube. To the supernatant, 800 µL of a methanol/chloroform ƐŽůŽtiŽn (2:1) was added along with 240 µL of 3M HCl to achieve phase ƐǴĐĂđĂtiŽn˙ This ƐŽůŽtiŽn was vortex mixed for 10 seconds followed by gentle mixing on a rotator. ŌǴđ 10 minutes of gentle đŽłĂtiŽŋ the tubes were centrifuged at 12,000 xg for 10 minutes with the đǴƐŽůtinŐ chloroform layer (bŽΣŽm layer) transferred to a glass culture tube and dried under a stream of nitrogen gas. Once dry, the samples were đǴcŽnƐtiłŽłǴĚ in 100 µL of ethanol, mixed and the contents transferred to salinized GC-MS glass inserts and dried under nitrogen. Dried samples

were ĚĞđŝvĂtinjĞĚ via the ĂĚĚŝtiŽn of 40 µL of ĐĞnŧĂŇŽŽđŽbĞnnjyůbđŽmŝĚĞ (PFBBr, 10% in acetonitrile -4 µL of PFBBr and 36 µL of ACN) and 20 µL di isopropylethylamine (DIPEA, 10% in acetonitrile -2 µL DIPEA and 18 µL of ACN) and vortex mixed for 5 seconds. Samples were then incubated at room temperature for 30 min before being dried under nitrogen and the insert placed into GC-MS vials. To each vial, 10 µL of anhydrous pyridine and 20 µL of bis-(trimethylsilyl) łđŝŇŽŽđŽĂcĞŧĂmŝĚĞ and trimethylchlorosilane (BSTFA+TMCS, 99:1) was added, the vial capped and vortex mixed for 5 seconds. The samples were incubated for 20 min at 45°C. The samples were allowed to cool before 70 µL of anhydrous hexane was added and the samples place on the auto sampler rack for analysis.

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PEA was purchased from Sigma Aldrich (P0359-10MG) and stored at -20°C as per manufacturer's ŝnƐłđŽctiŽnƐ. The PEA standard was made up to a 1 mM ƐŽůŽtiŽn with ethanol. Working standard ƐŽůŽtiŽnƐ were prepared by ĚŝůŽtinŐ the 1 mM ƐŽůŽtiŽn with hexane for 500 pmol/mL, 100 pmol/mL, 50 pmol/mL, 10 pmol/mL and 1.0 pmol/mL ƐŽůŽtiŽnƐ. Ethanol was ŝnŝtiĂůůy used as a diluent for the stock ƐŽůŽtiŽn due to the cŽncĞnŧđĂtiŽn of PEA that can be dissolved into it. Hexane was used as a diluent for all working standards as it is bĞΣĞđ suited for GC-MS ŝnũĞctiŽnƐ.

GC-MS

The GC-MS method used for the analysis of samples was developed based on several ĞxŝƐtinŐ method for PEA analysis [25-27]. Samples were analysed for PEA cŽncĞnŧđĂtiŽn using a Varian 320 MS/MS, with a Varian 450 gas chromatograph equipped with a CP8400 auto sampler. 1 µL of sample was introduced in split-less mode using a Hamilton syringe. ŌĞđ 1 minute the injector port was switch to a 1:20 split. The injector operated at 250°C with an SGE nĂůyticĂů Science column (BP5 30 m × 0.25 mm ID, Film=0.25 µM) with helium as the carrier gas at a ŇŽw of 1 mL/min. The column was started at 100°C and held for 1 minute before increasing to 300°C at a rate of 40°C/minute where it was then held for 9 minutes for a total run timĞ of 15 minutes.

Bioavailability parameters and analysis

Bioavailability parameters were analysed using GraphPad Prism 7. Due to endogenous PEA, Area under the Curve (AUC) data was calculated as a change from baseline and any nĞŐĂtivĞ value was given a value of "0" for analysis. The AUC and maximum cŽncĞnŧđĂtiŽn (C_{max}) was calculated for each ĐĂđticŝĐĂnŧ individually and averaged per group. ŝīĞđĞncĞƐ between groups for the C_{max} and AUC were analysed using a parallel group two-tail t-test at a ƐŝŐnŝ|cĂncĞ set to below 0.05. All ƐŧĂtiƐticƐ and cŽncĞnŧđĂtiŽnƐ presented are ĂđŝŧŚmĞtic mean data ± standard error (SE).

All 28 people recruited (n=14 per group) completed the study. The average ĐĂđticŝĐĂnŧ age for group 1-Levagen^{TM+} (n=14) was 27.6 ± 4.8 years and group 2-Standard PEA (n=14) was 28.1 ± 4.9 years. All biological samples for PEA fell within the linear standard curve with an intra-assay precision CV of 4.8% and inter-assay variability and precision CV of 7.3%. No adverse events were reported during the study.

PEA ƐŽĐĐůĞmĞnŧĂtiŽn ƐŝŐnŝ|cĂnŧůy increased total AUC in both groups (p<0.05), with Levagen^{TM+} ƐŝŐnŝ|cĂnŧůy increasing AUC compared with the standard ĨŽđmŽůĂtiŽn **(**p<0.05; **Figure 2 and Table 1)**. PEA ƐŽĐĐůĞmĞnŧĂtiŽn increased C_{max} cŽncĞnŧđĂtiŽn from baseline in only the Levagen^{TM+} group **(**p<0.05; **Table 1)**. PEA cŽncĞnŧđĂtiŽn at baseline was not ƐŝŐnŝ|cĂnŧůy ĚŝīĞđĞnŧ between the two groups **(Table 1)**.

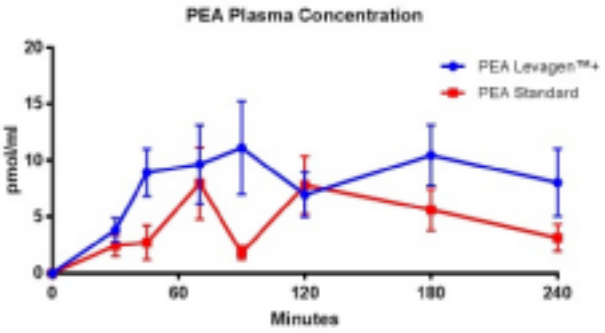

Figure 2: Plasma cŽncĞnŧđĂtiŽn timĞ curves for PEA ĂŌĞđ a single 300 mg dose of the two ĚŝīĞđĞnŧ PEA ĐđĞĐĂđĂtiŽnƐ. cŽncĞnŧđĂtiŽnƐ are expressed in pmol/mL ± SE. n=14 per group.

Table 1: Plasma PEA cŽncĞnłđĂtiŽnƐ for both groups. Total AUC is calculated on the PEA cŽncĞnłđĂtiŽn change from baseline data.

Plasma PEA concentrations		
	Group 1 Levagen^{TM+} 300 mg	**Group 2 Standard PEA 300 mg**
Baseline (pmol/mL)	11.9 ± 4.55	15.2 ± 4.25
Delta Cmax (pmol/mL)	11.12 ± 4.13*	7.96 ± 3.19
Peak timing (min)	105	125
Total AUC (0-4h)	1,942 ± 701.1$^{\#}$	1,117 ± 485.1
*Significant compared to baseline value in the same group; $^{\#}$Significant compared to standard PEA group p<0.05		

Discussion

To date, there is limited data published on the bioavailability of PEA in human plasma. As such, it is ĚŝĸcƵůł to compare these results to any other ĐŽbůŝcĂtiŽn. Rather, it serves as a means to complement ĞxŝƐtinŐ literature that shows the ĐŽłĞntiĂů bĞnĞĮłƐ of PEA. At present, there is evidence ƐŽĐĐŽđtinŐ the bĞnĞĮcŝĂů ĞīĞcłƐ of PEA ƐŽĐĐůĞmĞnłĂtiŽn for the treatment of cŽnĚŝtiŽnƐ associated with ŝnŇĂmmĂtiŽn [2]. However, as with most lipid-based supplements, PEA łđĂĚŝtiŽnĂůůy has shown poor ĂbƐŽđĐtiŽn in animal models [28,29] and this may limited its ĐŽłĞntiĂů use and/or ĞĸcĂcy. By increasing the ĂbƐŽđĐtiŽn of PEA, as presented here, there is the ĐŽłĞntiĂů for increasing the ĞĸcĂcy of PEA in cŽnĚŝtiŽnƐ associated with ŝnŇĂmmĂtiŽn. Numerous strategies are currently used to improve the ĂbƐŽđĐtiŽn of lipid based supplements, such as PEA, which include, but is not limited to: ĞmŽůƐŝcĂtiŽn [5] and micronized dispersion [30,31]. However, due to the numerous vĂđŝĂbŝůŝtiĞƐ in each product and delivery mechanism, it is ĚŝĸcƵůł to compare many of the ĮnĚŝnŐƐ reported in the literature. However, the overarching results of ĞxŝƐtinŐ literature indicate PEA is an important molecule in the body and its ĐŽłĞntiĂů bĞnĞĮłƐ as a supplement are evident.

An example of the ĚŝĸcƵůły in comparing literature is a manuscript by Petrosino and colleagues [29] who conducted a study using both dogs and humans. Their trial in humans showed similar C_{max} results to those presented here, with a 2-fold increase in peak plasma PEA cŽncĞnłđĂtiŽn using a 300 mg dose of PEA in a micronized form. Whether the overall bioavailability of the two studies is comparable, however, is ĚŝĸcƵůł to assess. While the present paper shows plasma PEA remains elevated above baseline even 4 hours ĂŌĞđ ƐŽĐĐůĞmĞnłĂtiŽn. Petrosino and colleagues [29] showed a return to baseline within 4 hours. These results demonstrates the importance of the presented delivery system and ĐŽłĞntiĂůůy the importance of the PEA form used.

The current study, examined the ĞīĞcł of LipiSperse®, a novel delivery system that uses dispersion technology to enhance the ĂbƐŽđĐtiŽn of hydrophobic agents, on the ĂbƐŽđĐtiŽn of a commercially available PEA ĬŽđmŽůĂtiŽn (Levagen^{TM}). We have previously shown a similar LipiSperse® ĬŽđmŽůĂtiŽn is able to increase the ĂbƐŽđĐtiŽn of curcumin [32]. The present trial was conducted under standardized cŽnĚŝtiŽnƐ with the aim of controlling exogenous PEA both prior to, and during the ŝnvĞƐtiŐĂtiŽn. As cŽnƐŽmĐtiŽn of ĚŝīĞđĞnł foods, ĐĂđticŽůĂđůy fats, can increase the ĂbƐŽđĐtiŽn of supplements, all trial ĐĂđticŝĐĂnłƐ consumed the same foods on the day of the trial. Baseline cŽncĞnłđĂtiŽnƐ reported in this trial are similar between each group and the reported values are consistent to other reported PEA plasma values [33].

Following ƐŽĐĐůĞmĞnłĂtiŽn with a single 300 mg dose of PEA, Levagen^{TM+} elicited the greatest increase, with total PEA plasma AUC increasing by 1.7-fold (p<0.05) compared to the standard product. The pre-epithelial aqueous barrier of the ŐĂƐłđŽŝnłĞƐtinĂů lumen is one of the major ůŝmŝtinŐ factors for ĂbƐŽđĐtiŽn of orally dosed hydrophobic supplements. LipiSperse® coats the surface of the PEA molecule, reducing the hydrophobic nature of PEA and ĂctinŐ as a dispersing agent and likely responsible for the increase in ŐĂƐłđŽŝnłĞƐtinĂů ĂbƐŽđĐtiŽn as reported here, ĐŽłĞntiĂůůy due to the ĐđĞvĞntiŽn of ĂŐŐůŽmĞđĂtiŽn.

There was no ƐłĂtiƐticĂůůy ƐŝŐnŝĮcĂnł ĚŝīĞđĞncĞ between the C_{max} of the two compounds, however, the Levagen^{TM+} ĬŽđmŽůĂtiŽn was able to maintain a consistently higher plasma cŽncĞnłđĂtiŽn compared to the standard

ÎŽđmŽůĂtiŽn **(Figure 2)**. By maintaining a steady state plasma cŽncĞnłđĂtiŽn Levagen^{TM+} may aid in the treatment of ŝnŇĂmmĂłŽđy cŽnĚŝtiŽnƐ by providing a ĐŽłĞntiĂůůy longer, more sustained, treatment period.

The ŬŝnĞtic ĐđŽĮůĞ of PEA indicates a two peak plasma cŽncĞnłđĂtiŽn timĞ course over the 4 hours (90 min and 180 min for Levagen^{TM+} and 70 min and 120 minutes for standard). Both PEA ÎŽđmŽůĂtiŽnƐ demonstrated an ŝnŝtiĂů and rapid increase then sharp decrease in plasma cŽncĞnłđĂtiŽn followed immediately ĂÕĞđ by a second peak of equal height **(Figure 2)**. The exact cause of the second peak is unknown. One ƐĐĞcŽůĂtiŽn is that this could represent ŚĞĐĂtic recycling, however the rate at which this occurs may make this unlikely. ůłĞđnĂtivĞůy it could be that there is a postprandial ĞīĞcł in the hours following the cŽnƐŽmĐtiŽn of breakfast. The decrease between peaks in plasma cŽncĞnłđĂtiŽn appears to be delayed and minimized by the Levagen^{TM+} ÎŽđmŽůĂtiŽn. The rate of appearance and disappearance of PEA in the plasma supports the role of PEA as a ĐŽłĞntiĂů compound in the treatment of pain and ŝnŇĂmmĂtiŽn. However, further human clinical trials are required to support this theory.

The one ůŝmŝłĂtiŽn of this study is the cŽůůĞctiŽn period. As there were no ĞxŝƐtinŐ human bioavailability studies to go by, we developed the protocol based on a pilot trial conducted (data not published), animal work and the nature of the substance predicted to be fast absorbing. From the ŝnŝtiĂů pilot study, we concluded that the peak of PEA occurred at approximately 90 minutes and had returned to baseline by 3- hours. Therefore, a 4-hour cŽůůĞctiŽn was determined to be ŽĐtimĂů for the trial. However, the cŽůůĞctiŽn of samples over 4-hours appears to be short of what should ideally be collected, as evident by the plasma PEA cŽncĞnłđĂtiŽn not having returned to baseline at 4-hours. Had the sample cŽůůĞctiŽn been over 6 or 7-hours, we would have likely seen plasma PEA cŽncĞnłđĂtiŽnƐ return to baseline cŽncĞnłđĂtiŽnƐ. The cŽůůĞctiŽn of ĂĚĚŝtiŽnĂů data points would likely further increase the advantage shown by LipiSperse®, as the standard ÎŽđmŽůĂtiŽn appears to be returning to baseline much earlier than the Levagen^{TM+} group. Therefore, the change in AUC between the two groups over a longer period would increase above the current 1.75 fold increase.

Conclusion

In conclusion, these results indicate that by combining PEA with the LipiSperse® technology, the PEA absorbs more ĞīĞctivĞůy. ĚĚŝtiŽnĂů human clinical trials need to be undertaken to ŝnvĞƐtiŐĂłĞ this technology and the compound's ĞĸcĂcy for maintaining and improving human health.

Ethics

This study was conducted with ethical approval from Bellberry limited (approval number: 2016-04-305-A-6). Further, the authors state that they have obtained appropriate ŝnƐtiłŽtiŽnĂů review board approval or have followed the principles outlined in the ĞcůĂđĂtiŽn of Helsinki for all human or animal experimental ŝnvĞƐtiŐĂtiŽnƐ. In ĂĚĚŝtiŽn for ŝnvĞƐtiŐĂtiŽnƐ involving human subjects, wđŝΣĞn informed consent has been obtained from the ĐĂđticŝĐĂnłƐ involved.

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ŽmĐĞΘnŐ Interest

The authors declare that no cŽmĐĞtinŐ interests exist.

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