NANO-CANNABIS PRODUCTS: EMULSIONS, CONJUGATES, AND PARTICLES. *ARE THEY ALL CREATED EQUAL?*

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Abstract

Due to the lipophilic nature of cannabinoids, they present significant challenges both for bioavailability and formulation. A viable solution is the creation of hydrophilic nano-dispersed systems ("water soluble cannabinoid"). The cannabis industry has a true need for products with superior pharmacokinetic (PK) properties combined with simple administration, straightforward integration, and good taste. Oral delivery is particularly challenging for nano-drug delivery systems (DDS). Orally-administered DDS first face the hostile environment of the stomach, rich with enzymes and low pH, usually requiring a protective coating to withstand what naturally breaks down xenobiotics. If the DDS successfully navigates the stomach, it then must overcome the absorption challenge, which depends on physicochemical parameters such as diameter, surface potential and recognition by endogenous transport mechanisms. Multiple types of nano-DDS are available; however, only a select few have made their way into pharmaceutical or consumer products.

Nano-DDS can generally be divided into three categories: i) nanoemulsions; ii) nanoconjugates; and iii) nanoparticles. All have associated advantages and disadvantages. While some cannabis products currently use nanoemulsions, they require inclusion of multiple additional excipients to support the nanostructure. Nanoconjugates are prohibited under current cannabis regulation due to the molecular change in the chemical structure of the active ingredients. Nanoparticles are common in the food industry and only recently emerged as suitable nano-DDS for cannabis. Nanoparticles combine both the desired PK profile and excipient-free manufacturing. Ultimately, there is significant need for a cannabinoid nano-DDS platform with virtually no restrictions on formulation or route of administration.

Nanotechnology

Nanoemulsions, nanoconjugates, and nanoparticles are all different classes of **nanotechnology**, a rapidly growing field with many applications, including in foods, cosmetics, pharmaceuticals, etc.

- They share the similarity of size – all being in the nm size range (1 nm = 10^{-9} m).
- Nano sized particles behave much differently than their larger scale counterparts.
- They have been designed to improve the properties of drugs that are hydrophobic and have less than ideal drug characteristics.
- Significant differences which impact their behavior in biological systems, compatibility in product formulations, and drug efficacy.

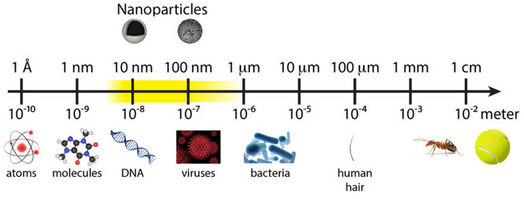

Figure 1: Illustration of nanoscale[3].

Nanoemulsions

- Non-equilibrium emulsion systems with extremely small particle size, typically between 50-500 nm
- They generally consist of i) oil ii) emulsifier or surfactant, and iii) an aqueous phase. Several combinations of oils/surfactants.
- Currently find widespread use in cannabis consumer products.

Nanoconjugates

- Consist of nanoparticle, usually the API or cannabinoid in this case, with hydrophilic macromolecules (synthetic or organic) covalently attached to its surface.
- The efficiency of nanoconjugates is determined by particle size, surface charge, confirmation and biocompatibility[1]
- Considered "new chemical entities" and separate from the API - restricted use.

Nanoparticles

- Any particle (unbound or bound, aggregate, or agglomerate) with one or more dimensions between 1 - 100 nm[2]
- Characterized based on size, shape, and material properties.
- Classification systems are often based on their ultimate application.

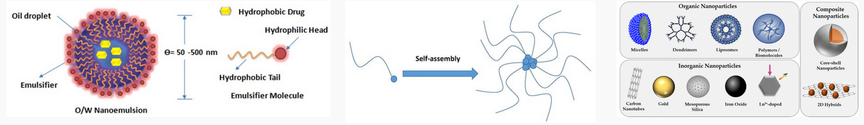

Figure 2: An illustration of different types of nanoparticles. From left to right– nanoemulsion[3], nanoconjugate[4], and nanoparticles[5].

Other Considerations of Nanotechnology

- Drug loading, typically <10%
- Ingredients
- Long-term safety and stability
- PK data
- Characterization data
- Encapsulation efficiency
- Drug release profiles
- Synthesis methods
- Flavor profiles

Protein Based Nano-DDS

- In tertiary structures of proteins there are disulfide bridges, ionic and hydrogen bonds, and **hydrophobic interactions**.
- Protein-based particles have previously been investigated as drug delivery systems, as they are decomposable, metabolizable and easy to functionalize[6].
- Provide protection from premature degradation in the stomach.
- Input agnostic (isolates, distillates, full spectrum extracts, etc).
- No synthesis or synthetic compounds involved.
- Drug loading between 30-50%.
- Neutral flavor profile
- Excellent PK profile
- 200 – 400 nm

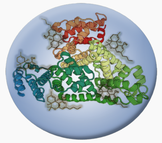

Figure 3: Illustration of cannabinoids within the chemical structure of a protein.

PK Data

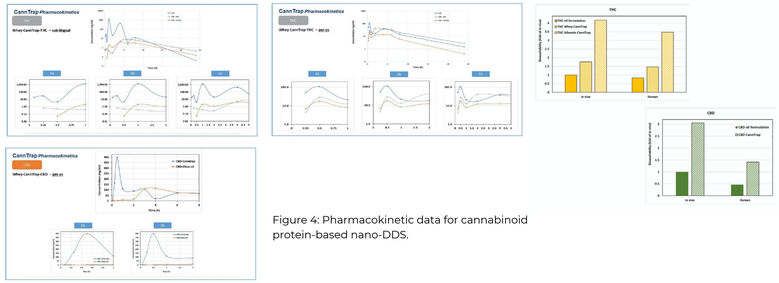

Figure 4: Pharmacokinetic data for cannabinoid protein-based nano-DDS.

Conclusions

- Nanotechnology is an exciting and rapidly developing technology with broad application.
- It has the potential to overcome the limitations of cannabinoids.
- It should be noted that the FDA does not include nano-sized particles (<100 nm) under GRAS. They also express concerns that nanoparticles could potentially impact the safety of food substances[7].
- The EU's European Food Safety Authority, also expresses concerns, stating that there is "insufficient information" to confirm its (i.e. nanoparticles) safety for human consumption[8].
- More work needs to be done to obtain a full understanding of cannabis-based nanotechnologies, including but not limited to:
  - complete characterization (size distribution, chemical composition, etc.), -validation of their PK/PD profiles in both pre-clinical models and clinical studies,
  - stability, both as they are and as part of consumer formulations,
  - long-term human health and safety studies.
  - **Protein-based cannabis nano-DDS provide an excellent PK profile, are highly water-soluble, and show broad formulation compatibility. Additionally, they have higher drug loading capacity and excellent safety profiles.**

References

1. Abioye, A.O., et al. "Polymer-drug nanoconjugate – an innovative nanomedicine: challenges and recent advancements in rational formulation design for effective delivery of poorly soluble drugs", https://dora.dmu.ac.uk/bitstream/handle/2086/11995/Abioye-2016.pdf?sequence=1.
2. King, S., et al. "Nanoparticles," Encyclopedia Britannica, 2019.
3. Manickam, S. "What is a pharmaceutical nanoemulsion?" University of Nottingham, 2013. https://blogs.nottingham.ac.uk/malaysiaknowledgetransfer/2013/06/25/what-is-pharmaceutical-nanoemulsion/.
4. Tran, T.T.D., et al. "Nanoconjugation and encapsulation strategies for improving drug delivery and therapeutic efficacy of poorly water-soluble drugs," Pharmaceutics, 11(7): 325, 2019.
5. Gessner, I. "Nanoparticles modified with cell-penetrating peptides: conjugation mechanisms, physicochemical properties, and application in cancer diagnosis and therapy," Int. J. Mol. Sci., 21(7): 2536, 2020.
6. Patra, J.K., et al. "Nano based drug delivery systems: recent developments and future prospects," J. Nanobiotechnology, 16(71): 2018.
7. https://www.fda.gov/media/115075/download.
8. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015R2283&from=IT