Integration of 3D Printing Technologies with Deuterated Polyunsaturated Fatty Acids (D-PUFAs)

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Abstract: Deuterated polyunsaturated fatty acids (D-PUFAs) represent a novel class of bioactive lipids characterized by enhanced oxidative stability and promising therapeutic potential. Although direct research on integrating D-PUFAs with 3D printing technologies remains limited, this paper discusses the emerging opportunities for their use with these stable lipids. By drawing on similar studies with conventional PUFAs and other bioactive compounds, this paper highlights their chemical properties, availability, and potential compatibility with different biomaterials and substrates suitable for 3D printing applications. 3D bioprinting has enabled development of tailored carriers, scaffolds, and functional systems that can help improve product stability, enable more controlled release, and potentially enhance overall performance. This conceptual overview presents current developments, knowledge gaps, possible material combinations and processing strategies to incorporate D-PUFAs into 3D printed constructs, focusing on cosmetics applications. Finally, future research directions are discussed, emphasizing material requirements, processing conditions, and characterization techniques essential for real-case implementation.

Keywords: D-PUFAs, 3D printing, Oxidative Stability, Drug Delivery, Cosmetic applications

1. Introduction

The integration of 3D printing technologies with drug delivery systems represents a promising direction [1]. Deuterated polyunsaturated fatty acids (D-PUFAs) have deuterium at bis-allylic sites, boosting oxidative stability while maintaining function, making them suitable for oxidative environments due to high resistance to lipid peroxidation [2]. Lipid-based compounds have been successfully embedded into 3D printed systems [1], suggesting that the chemically robust D-PUFAs could be integrated using similar strategies. This short review paper examines the potential for incorporating D-PUFAs into the bioprinting constructs.

2. Methodology

Polyunsaturated fatty acids (PUFAs) are vital constituents of lipid membranes, contributing to their essential fluidity. Fatty acids are classified as polyunsaturated when they contain two or more double bonds and can exist as free acids (R = H), esters (R = Et), or in the form of mono-, di-, and tri-glycerides [2]. Deuterated polyunsaturated fatty acids (D-PUFAs) are synthesized via a single-step reaction that utilizes a ruthenium-based catalyst along with deuterium oxide (D_2O) as the deuterium source [2]. The general structure of both natural and deuterated PUFAs is shown in **Figure 1**.Various *in vitro* and *in vivo* studies, including a human trial, have demonstrated the exceptional oxidative stability of D-PUFAs, particularly in relation to lipid peroxidation [3].

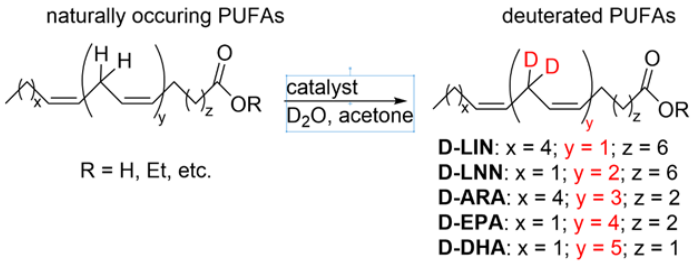

Figure 1. General structure of natural and deuterated polyunsaturated fatty acids

In contrast to standard polyunsaturated fatty acids, D-PUFAs exhibit greater resistance to oxidative degradation due to the replacement of bis-allylic hydrogen atoms with deuterium, which forms stronger carbon–deuterium (C–D) bonds. These bonds require more energy to break than carbon–hydrogen (C–H) bonds, thereby slowing the rate of lipid peroxidation in D-PUFAs through the kinetic isotope effect, and enhances their longevity and structural integrity in biological environments [3]. This effect is evidenced by kinetic isotope effect values of 23 for D-LIN and 32 for D-LNN, indicating significantly reduced oxidative degradation rates [3]. Preliminary studies suggest D-PUFAs, due to their oxidative stability and membrane affinity, could protect skin lipids from light-induced damage, making them promising ingredients for cosmetic formulations targeting oxidative stress.

3. Results and Discussion

The therapeutic potential of deuterated polyunsaturated fatty acids (D-PUFAs) is increasingly supported by clinical evidence. Notably, D2-LA demonstrated similar absorption and transport dynamics to natural linoleic acid and achieved steady-state plasma concentrations within four weeks of administration, indicating strong bioavailability. These pharmacokinetic characteristics highlight their suitability for clinical applications. To ensure stability and optimal delivery, various carriers such as liposomes, solid lipid nanoparticles, and gelatin-based hydrogels have been effectively tested in preclinical studies. The list of the main types of currently available D-PUFAs is given in **Table 1.** emphasizing their therapeutic potential. The most suitable carriers for drug delivery systems are hydrogels, liposomes, including various nanoparticles, considering 3D bioprinting.

Table 1. The main types of D-PUFAs

Name	Full Name	Parent PUFA	Key properties	Therapeutic potentials
D2-linoleic acid (D2-LA)	11,11-D_2-linoleic acid	Linoleic acid (LA, 18:2 n-6)	One of the most studied D-PUFAs; resists peroxidation	Neuroprotection, metabolic disease: (insulin resistance and obesity models)
D4-linoleic acid (D4-LA)	11,11,14,14-D_4-linoleic acid	Linoleic acid	Greater oxidative resistance than D2	Anti-Inflammatory effects
D6-arachidonic acid (D6-AA)	Multiple deuterium substitutions	Arachidonic acid (AA, 20:4 n-6)	Targets neuroinflammation, brain health	Neurodegeneration; Pain modulation
D2-docosahexaenoic acid (D2-DHA)	20,20-D_2-DHA	DHA (22:6 n-3)	Protects neuronal membranes from lipid peroxidation	Cognitive & retinal protection; Oxidative stress resistance
D6-docosahexaenoic acid (D6-DHA)	Multi-D substituted DHA	DHA	More protective but more complex to synthesize	Superior neuroprotection; Supports mitochondria
D2-eicosapentaenoic acid (D2-EPA)	19,19-D_2-EPA	EPA (20:5 n-3)	Anti-inflammatory & antioxidative	Cardiovascular & mood support
D8-eicosapentaenoic acid (D8-EPA)	7,7,10,10,13,13,16,16-D_8- EPA	EPA (20:5 n-3)	Highest antioxidative stability	Cancer, inflammation & aging-related protection

Recent studies have highlighted the potential of deuterated PUFAs (D-PUFAs) in skincare applications, primarly due to their strong antioxidative properties. By reducing lipid peroxidation and protecting skin cells from UV-induced damage, D-PUFAs present a promising approach for use in advanced formulations like personalized 3D-printed dermal patches.

3D bioprinting is an advanced method that employs bioink, a combination of cells and biomaterials, to create functional tissue structures with precise geometry and controlled cell arrangement. This method enhances cell migration, differentiation, and proliferation compared to traditional 2D systems. Inkjet, extrusion, and laser bioprinting are techniques that create 3D biological structures by depositing bioinks via droplets, continuous flow, or laser pulses, without direct contact, enabling precise tissue formation while preserving cell viability. 3D bioprinting enables the creation of tissue models that mimic natural structures and shows promise in regenerating complex tissues and cosmetic applications, though challenges with dimensional stability and shape fidelity remain [4]. Future research on combining D-PUFAs with 3D bioprinting will focus on developing stable, high-strength hydrogels and bioinks with lipid additives, evaluating their printability, rheology, and biocompatibility, and exploring their effects on regeneration, angiogenesis, and cell viability through lipid metabolism and signaling.

5. Conclusion

Integrating deuterated polyunsaturated fatty acids (D-PUFAs) with 3D printing offers a promising multidisciplinary approach, combining lipid biochemistry and additive manufacturing. D-PUFAs provide superior oxidative stability and maintain biological function, making them ideal for long-term applications. Their proven compatibility with hydrogels supports potential use in engineered drug delivery systems, and although the direct integration with 3D printing is still theoretical, related strategies and adaptable printing technologies suggest strong feasibility.

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References

[1] K. Vithani, A. Goyanes, V. Jannin, A.W. Basit, S. Gaisford, B.J. Boyd, An overview of 3D printing technologies for soft materials and potential opportunities for lipid-based drug delivery systems, Pharmaceutical Research 36 (2019) 4.

[2] A. Smarun, M. Petkovic, M. Shchepinov, D. Vidovic, Site-specific deuteration of polyunsaturated alkenes, The Journal of Organic Chemistry 82 (2017) 13115–13120.

[3] C.R. Lamberson, L. Xu, H. Muchalski, J.R. Montenegro-Burke, V.V. Shmanai, A.V. Bekish, J.A. McLean, C.F. Clarke, M.S. Shchepinov, N.A. Porter, Unusual kinetic isotope effects of deuterium reinforced polyunsaturated fatty acids in tocopherol-mediated free radical chain oxidations, Journal of the American Chemical Society 136 (2014) 838–841.

[4] A. Schwab, R. Levato, M. D'Este, S. Piluso, D. Eglin, J. Malda, Printability and Shape Fidelity of Bioinks in 3D Bioprinting, Chem. Rev. 120 (2020) 11028–11055. https://doi.org/10.1021/acs.chemrev.0c00084.