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PAIRING 3D-PRINTING WITH SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM: A CONCISE REVIEW

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ABSTRACT

"This study explores the synergy between Self Nano-Emulsifying Drug Delivery Systems (SNEDDS) and 3D printing technology for the development of advanced pharmaceutical formulations. SNEDDS, known for enhancing drug solubility and bioavailability, are integrated into 3D printing processes to create novel drug delivery systems. The research investigates the feasibility of incorporating SNEDDS into 3D-printable formulations, exploring their impact on drug release profiles, and assessing the potential for personalized medicine. The combination of SNEDDS and 3D printing opens new avenues for the precise manufacturing of pharmaceuticals with improved therapeutic outcomes."

Keywords: 3D Printing, Self-Nanoemulsifying drug delivery system, Bioavailability, Fused deposition modelling, Bioprinting

INTRODUCTION:

A self-nano-emulsifying drug delivery system (SNEDDS) is a formulation technique used to enhance the solubility and bioavailability of poorly water-soluble drugs. It typically involves the formulation of an oil phase, surfactants, and a co-surfactant to form a nano-emulsion upon contact with an aqueous phase **[1, 2]**. The resulting nano-emulsion has a small droplet size, which improves drug absorption and allows for efficient drug delivery. The emulsion formed by the SNEDDS undergoes rapid and spontaneous self-emulsification due to the energy provided by gentle agitation (e.g., gastric motility) **[3]**. This results in the formation of small droplets with a nanoscale size range (typically less than 200 nm) and high surface area. The small droplet size of the nano-emulsion significantly increases the interfacial area between the oil phase (containing the drug) and the surrounding aqueous medium **[4, 5]**. This improves the interfacial tension and enhances the drug dissolution rate, increasing drug solubility and potentially improving drug absorption **[6]**.

The main components of a SNEDDS typically include **[7, 8]**:

1. **Liquid phase**: This consist of oils or lipid excipients, such as triglycerides, medium-chain fatty acids, or surfactants. These lipids help solubilize the drug and aid in formulating the nano-emulsion.
2. **Surfactants:** Surfactants are amphiphilic compounds that lower the interfacial tension between oil and water, enabling the formation and stabilization of the nano-emulsion. They also assist in enhancing drug solubility and absorption.
3. **Co-surfactants**: Co-surfactants are often added to improve the stability and self-emulsification properties of the formulation. Commonly used co-surfactants include polyethylene glycols (PEGs) or glycerol.

SNEDDS offer several advantages over conventional drug delivery systems:

1. **Improved drug solubility**: SNEDDS enhance the solubility of poorly water-soluble drugs by dispersing them in the lipid phase, which improves their bioavailability.
2. **Enhanced absorption**: The nano-emulsion droplets formed by SNEDDS have a large interfacial area and small particle size, which increases drug absorption by promoting diffusion across biological membranes **[9]**.
3. **Improved stability**: SNEDDS is designed to form stable nano-emulsions upon dilution in the gastrointestinal fluid. This stability ensures drug delivery and prevents drug precipitation [10].
4. **Versatile formulation**: SNEDDS can be tailored to suit various administration routes, including oral, topical, and parenteral, depending on the specific drug and application **[11, 12]**.

3D printing, on the other hand, is an additive manufacturing technology that enables the fabrication of three-dimensional objects layer by layer. It has gained significant attention in the field of pharmaceutics, as it offers the potential for personalized medicine, complex dosage forms, and drug delivery systems **[13]**. The incorporation of nanocarriers into Self-Nano-Emulsifying Drug Delivery Systems (SNEDDS) using 3D printing is an innovative approach in pharmaceutical research and development. This combination aims to enhance drug delivery efficiency by utilizing nanotechnology and 3D printing advantages. Combining the concepts of SNEDDS and 3D printing, researchers have explored the development of SNEDDS for use in 3D printing **[14, 15]**.

Types of 3D printing:

3D printing technology in the pharmaceutical industry was still an emerging field with significant potential. There were several types of 3D printing techniques being explored for pharmaceutical formulations. These techniques offer the possibility of personalized medicine, precise dosing, and the ability to create complex drug delivery systems. Here are some of the commonly investigated 3D printing methods used in pharmaceutical formulations:

3D Printing	Approaches	References
Fused Deposition Modeling (FDM)	**FDM is one of the most widely used 3D printing techniques. FDM creates solid dosage forms in pharmaceuticals by extruding a thermoplastic filament containing the active pharmaceutical ingredient (API) and other excipients.**	**[16]**
Powder Bed Fusion (PBF)	**PBF techniques, such as Selective Laser Sintering (SLS) and Selective Laser Melting (SLM), involve selectively fusing powdered materials together using a laser to create drug-containing structures or implants.**	**[17]**
Stereolithography (SLA)	**SLA uses a UV laser to polymerize liquid resin layer by layer, creating precise and complex 3D structures for pharmaceutical applications.**	**[18]**
Hot-Melt Extrusion (HME)	**HME is a traditional pharmaceutical manufacturing process that can be integrated with 3D printing to create personalized dosage forms with controlled drug release profiles.**	**[19]**
Bioprinting	**Bioprinting is used to create 3D structures using biological materials, such as cells, tissues, and hydrogels, with potential applications in regenerative medicine and drug testing.**	**[20]**

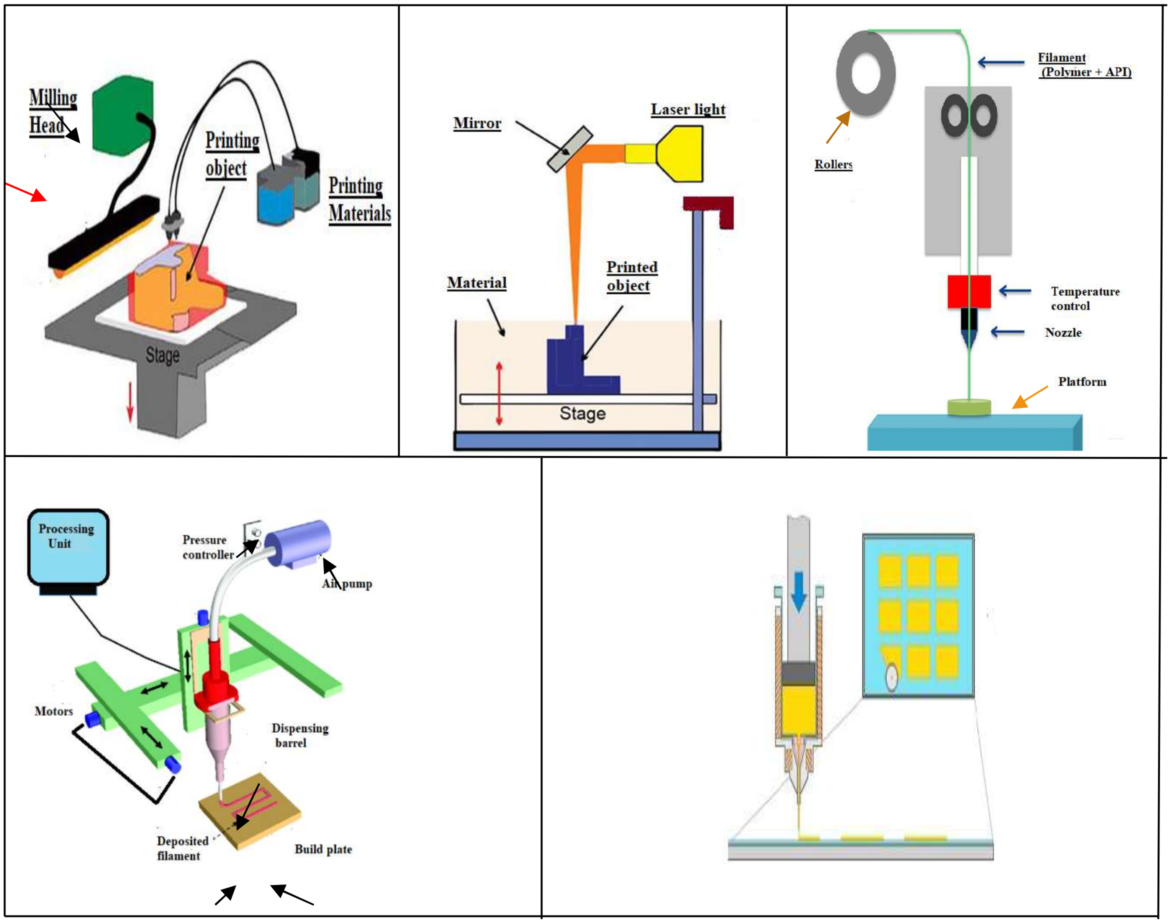

Figure 1. a) Fused Deposition Modelling b) Powder Bed Fusion c) Stereolithography d) Hot-Melt Extrusion e) Bioprinting

Benefits of 3D Printing:

- **Personalization:** 3D printing allows the fabrication of drug delivery systems tailored to individual patients' needs, which can improve treatment outcomes and reduce adverse effects.
- **Complex geometries**: 3D printing enables the creation of intricate drug delivery structures that may not be achievable through traditional manufacturing methods, allowing for better control over drug release rates and targeting **[21]**.
- **Multi-drug delivery**: It's possible to create drug delivery systems that release multiple drugs in a controlled manner, which is beneficial for combination therapies or treatments of complex diseases **[22]**.

Challenges of 3D printing in drug delivery:

- **Material selection**: Identifying suitable materials that are biocompatible, stable, and meet the drug's specific requirements can be challenging.
- **Regulatory considerations**: The regulatory approval process for 3D-printed drug delivery systems can be complex due to the need to demonstrate safety, efficacy, and consistency.
- **Manufacturing quality control**: Ensuring uniformity and reproducibility in 3D-printed drug delivery systems is critical for consistent dosing and reliable performance **[23, 24]**.

Integration of SNEDDS with 3D Printing

1. **Selection of appropriate oil phase**: The choice of oil phase depends on the drug's physicochemical properties and compatibility with the 3D printing process. Commonly used oils include medium-chain triglycerides (MCT), soybean oil, and castor oil.
2. **Selection of surfactants and co-surfactants**: Surfactants and co-surfactants are chosen based on their ability to form stable nano-emulsions and compatibility with 3D printing. Examples of commonly used surfactants and co-surfactants include Tween 80, Labrasol, and Transcutol. Most commonly for fabricating SNEDDS 3D printing surfactant-complexed chitosan is used **[25]**.
3. **Preparation of the self-nano emulsifying formulation**: The oil phase, surfactants, and co-surfactants are combined and mixed thoroughly to form a homogenous self-nano emulsifying formulation.
4. **Incorporation into 3D printing materials**: The self-nano emulsifying formulation can be incorporated into 3D printing materials, such as hydrogels or filaments, depending on the specific 3D printing technology used. The formulation should be compatible with the printing process and maintain its stability during printing. 3D printing of personalized dosage forms: The self-nano emulsifying formulation is then 3D printed into the desired dosage form, such as tablets, capsules, or implants. The printing parameters, such as temperature, speed, and layer thickness, should be optimized to ensure accurate and precise fabrication **[26, 27]**.

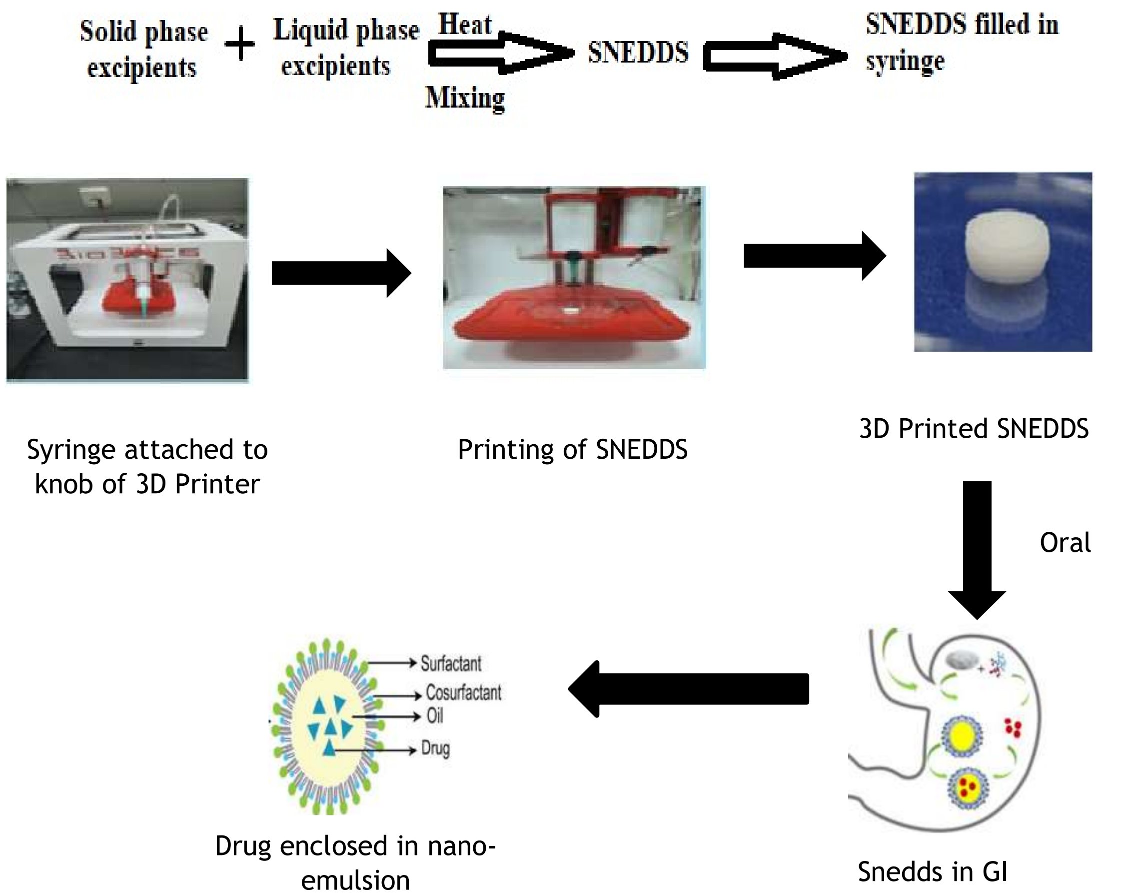

Figure 2: Overview of SNEDDS based 3D Printing

Design, consideration, and formulation of SNEDDS-based 3D printing

1. **Selection of Drug and Excipients:**

Suitable drugs with poor aqueous solubility that would benefit from SNEDDS-based delivery should be selected. Appropriate excipients such as surfactants, co-surfactants, and oils can form stable nano-emulsions and enhance drug solubility.

2. **Compatibility and Stability:**

To assure chemical stability and prevent any interaction or degradation, the compatibility of drugs and excipients must be evaluated. The stability of the formulation is maintained during printing and subsequent storage by factors like pH, temperature, and storage conditions **[28]**.

3. **3D Printing Technique:**

3D printing techniques include inkjet, laser sintering, SLS, etc. When printing, several factors need to be taken into account, including printing resolution, material compatibility, and printing technique **[29]**.

4. **Formulation Optimization:**

The formulation of the SNEDDS must be optimized to achieve the desired drug solubility and release characteristics. For this screening, experiments were conducted to identify the optimal ratio of surfactants, co-surfactants, and oils. Using the design of experiments (DoE) approaches to systematically study and optimize formulation variables **[30]**.

REGULATORY CHALLENGES AND GUIDELINES FOR 3D PRINTING DRUG DELIVERY:

1. **Regulatory Classification**: 3D-printed drug delivery systems are often classified as combination products since they combine medical device components (the 3D-printed structure) and pharmaceutical components (the drug). Determining the appropriate regulatory pathway can be complex, as it may involve compliance with both medical device and drug regulations **[31]**.
2. **Material Characterization:** The materials used in 3D printing drug delivery systems must meet strict regulatory requirements for biocompatibility, safety, and stability. Extensive material characterization and testing are necessary to demonstrate the suitability of the 3D-printed materials for their intended use.
3. **Manufacturing Process Control**: Ensuring consistency, reproducibility, and quality control in the 3D printing process is critical for regulatory approval. Manufacturers must implement robust manufacturing processes and demonstrate the ability to produce drug delivery systems that meet specifications consistently **[32, 33]**.
4. **Biocompatibility:** 3D-printed drug delivery systems should not cause adverse reactions or harm when they come into contact with the human body. Biocompatibility studies are required to assess potential risks associated with the materials used in the 3D printing process **[34]**.
5. **Quality Control and Testing:** Stringent quality control measures are essential to ensure the safety and efficacy of 3D-printed drug delivery systems. Analytical testing, performance testing, and validation studies are necessary components of the regulatory submission **[35]**.
6. **Preclinical and Clinical Studies:** Depending on the complexity of the 3D-printed drug delivery system and the specific drug involved, preclinical and clinical studies may be required to demonstrate safety and efficacy. These studies should follow regulatory guidelines for pharmaceutical products **[36]**.
7. **Post-Market Surveillance:** After regulatory approval, manufacturers must establish post-market surveillance plans to monitor the performance and safety of the 3D-printed drug delivery system in real-world settings **[37]**.

Future Scope of SNEDDS with 3D Printing:

1. **Personalized Medicine**: The combination of SNEDDS and 3D printing can pave the way for personalized medicine. Tailoring drug formulations based on individual patient characteristics, such as age, weight, and specific health conditions, could enhance treatment efficacy and minimize adverse effects **[38]**.
2. **Complex Drug Delivery Systems**: 3D printing allows for the fabrication of intricate structures. Future research could explore the creation of complex drug delivery systems that release multiple drugs at different rates, enabling more sophisticated treatment strategies for conditions requiring a combination of therapies **[39]**.
3. **Modified Release Profiles**: Fine-tuning the printing parameters and SNEDDS formulations could enable the precise control of drug release profiles. This could lead to the development of medications with optimized release kinetics, improving patient adherence and therapeutic outcomes.
4. **Pediatric Formulations**: Tailoring drug formulations to suit the needs of pediatric patients is a critical area of research. The combination of SNEDDS and 3D printing may offer a way to create age-appropriate dosage forms and formulations that are easier for children to consume **[40]**.
5. **Patient-Specific Dosage Forms**: The ability to create customized dosage forms through 3D printing, incorporating SNEDDS, could be especially beneficial for patients with unique requirements or those who struggle with conventional forms of medication.
6. **Regulatory Considerations**: Future research will likely involve addressing regulatory considerations associated with 3D-printed pharmaceuticals. Establishing standards and guidelines for quality control, safety, and efficacy will be crucial for the widespread adoption of these technologies **[41]**.
7. **Biosensors and Monitoring**: Integrating sensors into 3D-printed drug delivery devices could enable real-time monitoring of drug release and patient response. This could provide valuable data for optimizing treatment regimens and improving healthcare outcomes.

CONCLUSION:

The recent work on fabricating 3D printing into SNEDDS represents a cutting-edge approach with the potential to revolutionize drug delivery in terms of customization, efficiency, and versatility. Continued research and collaboration between pharmaceutical, engineering, and medical disciplines will be crucial to harness the full benefits of this innovative technology.

As with any emerging technology, the future scope of SNEDDS integrated into 3D printing will depend on ongoing research, technological advancements, and successful collaboration between researchers, clinicians, and regulatory bodies. Addressing challenges related to scalability, standardization, and regulatory compliance will be key to realizing the full potential of this innovative approach in pharmaceutical manufacturing and drug delivery.

The integration of SNEDDS with 3D printing technology was explored as a promising approach to enhance drug delivery systems. SNEDDS are known for their ability to improve the solubility and bioavailability of poorly water-soluble drugs. When combined with 3D printing, this could potentially offer customized dosage forms, improved drug release profiles, and better patient compliance.

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