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REVIEW ARTICLE

A Review on Supercritical Fluid Technology

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ABSTRACT
Supercritical fluids (SCFs) are unconventional solvents exhibiting tunable physicochemical properties that make them highly interesting to perform both physical processing and chemical reactions. Most of the processes based on SCFs take advantage of the near-critical region where substances exhibit gas-like transport properties (viscosity, diffusivity), but they can assume densities from gas-like to liquid-like values depending on the pressure. Most of the investigations are performed using supercritical carbon dioxide (SC-CO2) that cumu-lates tunability of thermodynamic and transport properties with favourable technoeconomical features such as wide availability and low cost, biocompatibility, and mild critical parameters. The conventional techniques used in the production of these drug carrier formulations have several drawbacks, including thermal and chemical stability of the APIs, excessive use of organic solvents, high residual solvent levels, difficult particle size control and distributions, drug loading-related challenges, and time and energy consumption.
Keywords: Supercritical fluids, thermodynamic, viscosity, diffusivity, chemical reactions.

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1. Introduction

The active pharmaceutical ingredients (APIs) suffer from poor physico-chemical, pharmacokinetic, and pharmacodynamic properties which limit their therapeutic effect. The API's poor solubility and stability mandates frequent administration, which is highly undesired. To overcome such limitations, micro- and nano-carrier formulations have been developed as drug delivery systems. Such formulations encapsulate the API, ideally at high drug loads, transport it to the site of action, and release it in a controlled manner; hence improving the efficacy and safety. The encapsulated API is therefore protected from external conditions such as light, oxygen, temperature, pH, enzymes, and others. There are several limitations for the conventional techniques that are currently used to manufacture drug delivery systems[1-6]. Conventional methods such as jet milling and hammer milling are regularly used to reduce particle size. These methods do not provide reproducible particle size control and also create particles with high surface energy, which in turn can lead to

physical and/or chemical instability. APIs are combined with polymers to make amorphous solid dispersions (ASD) to improve their bioavailability. Spray drying and hot melt extrusion are commonly used conventional techniques to make ASDs. Spray drying, while highly successful, suffers from the excessive use of organic solvents, the potential for high residual solvent in the end product, and the inability to effectively control the form of the API. Hot melt extrusion cannot be used to process thermally labile APIs. In the case of sustained release applications, the API is typically embedded in either a biodegradable or non-biodegradable polymer matrix to control the release profile of the API. Many of the conventional techniques used for making these implants, like hot melt extrusion, spray drying, and solvent casting, typically cannot be applied to sensitive APIs, like proteins, peptides, and enzymes. Thus, conventional techniques used in the production of these carriers have several drawbacks, including thermal and chemical stability of the APIs, excessive use of organic solvents, high residual solvent levels, difficulty in controlling particle size and distributions, drug loading-related challenges, and time and energy consumption[7-10].

One of the leading alternatives is supercritical fluid (SCF) technology. Any substance can exist in its supercritical form if it is kept above its critical temperature and critical pressure. The use of SCF technology has gained a lot of attention in recent decades due to the non-toxic, inert, economical, and environmentally friendly properties. The physical properties of SCF, such as viscosity, density, and diffusivity, can be easily controlled by adjusting the temperature and pressure conditions. Increasing the pressure yields an increase in the SCF's density without significantly increasing the viscosity. An SCF can therefore be considered as a hybrid fluid sharing the best features of gases (low viscosity and high diffusivity) and liquids (high density and solvating power). A number of substances, including H_2O, N_2, Xe, SF_6, N_2O, C_2H_4, CHF_3, ethylene, propylene, propane, ammonia, *n*-pentane, ethanol, and CO_2, have been tried as SCFs, with CO_2 being the best behaving SCF. CO_2 is the most widely used SCF in the pharmaceutical industry and is classified as a safe solvent by the FDA. CO_2 is an inert, colorless, odorless, non-toxic, non-flammable, cost effective, and recyclable gas[11-15]. This process involves formation of a homogenized oil-in-water emulsion comprised of lipid (in this case tripalmitin, tristearin, or Gelucire 50/13) and drug (indomethacin or ketoprofen) dissolved in chloroform with a surfactant (soy lecithin) dispersed in an aqueous phase of sodium glycocholate, which is then introduced into an extraction column with counter-current flow of SCF CO_2. Within the extraction column, SCF CO_2 is simultaneously extracting solvent from the oil phase of the emulsion and expanding the organic phase of the emulsion, ultimately resulting in precipitation of the lipid–drug mixture in an aqueous nanodispersion. Noted advantages of this process over non-SCF-based solvent extraction methods are higher solvent extraction efficiency, more uniform particle size distribution, depression of the lipid melting point, and plasticization of the amorphous lipid structure[16-18].

Residual solvent levels in the low parts per million range were achieved, SLNs displayed high levels of crystallinity, and dissolution rates were 5-to-10-fold faster than micronized powders. This paper neatly addressed the benefits of SCF-mediated SLN production and the critical-to-quality parameters that should be investigated in designing such a process. PGSS has garnered significant attention in the production of SLNs, owing to its simple process, solvent-free nature, and direct production of dry SLN powders. In the PGSS process, lipid and drug are melted and then saturated with SCF CO_2, leading to the formation of a gas-saturated solution. This solution is then passed through a nozzle, resulting in rapid depressurization and precipitation of the lipid–drug matrix, and dry particles are collected in the depressurization chamber. PGSS has been found to be an attractive choice for sensitive molecules, including peptides and proteins, since it can be operated solvent-free and requires relatively mild conditions in the initial melt step due to the plasticizing effect of melting lipid and drug under an SCF.

In order to overcome this limitation and produce sub-micron solid lipid nanoparticles, the gas-assisted melting atomization (GAMA) process was developed. In this technique, lipid and protein are mixed in the melt under SCF CO_2. The contents of this chamber are then atomized into a precipitation vessel with a coaxial air stream, where rapid depressurization of the mixture results in super saturation and precipitation of the lipid–drug mixture. The GAMA process has been used to produce protein-loaded SLNs due to its relatively mild operating conditions. Salmaso et al. encapsulated insulin and recombinant human growth hormone in tristearin/phosphatidylcholine/PEG mixtures, resulting in spherical particles in the 80–400 nm size range, and both proteins were released under physiological conditions in their active form for up to 100 h. In another alternative process termed RESS, an SCF is used as a solvent to dissolve the lipid and drug. This solution is then depressurized through a nozzle into a low-pressure expansion chamber, causing the SCF solution to become supersaturated and, consequently, precipitation of the lipid–drug matrix[19-25]. This process was employed for the production of ibuprofen-loaded stearic acid SLNs and carbamazepine-loaded stearic acid SLNs. A limitation of the RESS process is the use of SCF as the solvent for dissolution of the lipid and drug. Owing to the nature of the lipids used in SLN production and the molecular dispersion of drug within the lipid matrix, lipid crystallization to the $ß_i$ and ß-form during solidification results in a matrix with little space for incorporation of drug molecules. To overcome this limitation, a modification of the SLN platform was developed in which the nanostructure of the solid lipid matrix was engineered to permit more space for drug molecules to be incorporated. Termed nanostructured lipid carriers (NLC), these nanoparticles retain the solid lipid matrix defining the SLN platform, but aim to create an imperfect lipid matrix, leaving more sites available for drug incorporation. In 2015, Goncalves et al. compared formulations of ketoprofen produced by a PGSS process, in which glyceryl monooleate, a liquid glycerolipid, was

incorporated into the formulations of three different solid glycerolipids. Although the particles generated were in the micron range, some general principles of SLN versus NLC carriers can be interpreted. Their findings demonstrate that addition of a liquid glycerolipid increased the stability of the particles compared to a pure solid formulation, with no significant change to the enthalpy of fusion after 6 months of storage for the binary systems. Encapsulation efficiency of ketoprofen was directly correlated to the mass ratio of the liquid glycerolipid, and a maximum encapsulation efficiency of 97% was achieved.

2. Conclusion

This review concludes that the oral delivery, SCF-based methods have been touted as a way to reproducibly control particle size and morphology, and have been compared with conventional methods such as jet and bead milling[26-30]. While SCF is indeed better than conventional technologies, more studies are needed to establish their superiority over emerging bottom-up methods such as microfluidics and flash nanoprecipitation. Secondly, from a practical perspective, there is a very high bar for introduction of new technologies in the pharmaceutical industry due to regulatory considerations. At present the use of SCF-based technology to reduce particle size and improve flow for oral delivery provides only incremental rather than transformative benefit to make the case for a shift in manufacturing technologies. SCF may clearly provide the advantage over conventional milling technologies in terms of improved aerosolization, ability to combine multiple drugs, and potential ease of formulation due to reduced surface energy of the particles.

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3. References

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