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Supercritical Fluid Technology: A Promising Approach for Preparation of nano-scale Drug Delivery Systems

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Abstract: *Various technological approaches are widely used to prepare drug nanocarriers in order to protect the active substances from the unfavourable impact of the environment (hydrolysis, enzymatic degradation, etc.) and to improve the dissolution and bioavailability. Conventional methods like grinding, spray drying, polymerization, coacervation, lyophilisation etc., are extensively used but they have some drawbacks. Ensuring a control on the particle size, particle size distribution and drug loading during the processing is the main challenge. These particle characteristics have enormous impact on the dissolution and bioavailability of the drug used. Moreover, these traditional technologies are very expensive in terms of materials, time and energy. Conversely, supercritical fluid technologies could save time and energy and provide mild conditions for the preparation of nanocarrier drug delivery systems, notably, using supercritical carbon dioxide. This mini-review aims to highlight the advantages of the supercritical fluid technologies and to emphasize the benefits of their usage compared to conventional technologies without having the claims to refer to all known methods applied already in the practice.*

Keywords *– drug delivery systems, nanotechnologies, supercritical fluids*

I. INTRODUCTION

Many of the drugs used for the treatment of various diseases suffer from poor physico-chemical and pharmacokinetic properties, which predetermine the inability to deliver the drug at an adequate amount on the target place. One of the most promising strategies to overcome the limitation of classical drugs is their nanocarrier formulation. These nano-scale carriers can provide passive or active targeting, increased bioavailability, and increased chemical stability of the drug, sustained drug delivery, modified biodistribution and lower organ toxicity, increased solubility of the lipophilic drugs and co-delivery of drug combinations [1]. Drug nanocarriers as nanocrystals and nanosuspensions, microemulsions, liposomes and different non-ionic surfactant vesicular systems (niosomes, proniosomes, *etc*.), solid lipid nanoparticles (SLNs) and polymeric nanoparticles (NPs) (micelles, dendrimers, *etc*.), metal NPs, quantum dots, fullerenes and non-organic NPs are an object of interest and study by many scientists. Various technological approaches for their preparation are found in the literature [1]. Nanocarriers can be prepared using top down techniques of comminution of larger particles (grinding, crashing, milling), or via bottom up techniques where the formation of NPs starts from a molecular solution. Coacervation and nanoprecipitation techniques, ionotropic gelation methods, techniques such as emulsification-solvent evaporation, solvent displacement, as well as different polymerization methods are just some examples for the bottom up techniques for preparation of polymeric NPs. These conventional methods possess drawbacks such as thermal and chemical degradation of the drug used; excessive use of solvent and high residual solvent concentration; time- and energy- consumption; and primarily, difficult controlling the particle size, particle size distribution and drug loading during the process of preparation.

The application of supercritical fluid (ScF) technologies is a promising alternative for the NP formation because they can overcome these drawbacks. Briefly, a ScF is any substance above its critical temperature and pressure. At this condition the fluid has unique properties: liquid-like density, gas-like viscosity and larger diffusivities than those of typical liquid (intermediate to that of a liquid and a gas), resulting in higher mass-transfer rate. Furthermore, by changing the experimental conditions (temperature and pressure), its solvent power and selectivity can be adjusted [2]. Although a number of substances are useful as ScFs (*e.g*. water), carbon dioxide (CO_2) is the most widely used ScF. This is because CO_2 avoids water discharge; it is chemically inert, non-toxic, non-flammable and readily available at high purity and at low cost. Moreover, it has low critical parameters (304.19 K and 73.8 bar) allowing the fluid to be used at mild conditions without leaving harmful organic residues. Due to its properties and the ability to be recycled, supercritical CO_2 ($ScCO_2$) is described as a "green" solvent.

Various precipitation processes based on the use of ScFs have been proposed for the production of solid composites of drug delivery systems. In these methods the ScFs performs different functions as solvent, anti-solvent, co-solvent or solute, propellant, *etc*. Some of them, after modification, can be applied for obtaining solid-liquid composites. For the preparation of

micelles or liposomes, the methods of Supercritical Extraction from Emulsions (SFEE) as well as the so-called "Improved Supercritical Reverse-Phase Evaporation Method" are a possible alternative. Very promising are the methods as Supercritical Anti Solvent process (SAS) or the Aerosol Solvent Extraction System (ASES). Dry precursors of liposomes, which can be reconstituted by hydration, have been obtained by the last two methods [3].

II. SUPERCRITICAL FLUID TECHNOLOGIES

2.1. Rapid Expansion of Supercritical Solutions (RESS)

For application of RESS technology, high solubility of the drug in $ScCO_2$ is required, because this method uses $ScCO_2$ as a solvent. In the conventional process, a supercritical solution is rapidly expanded through a nozzle to precipitate the solute as nano- or micro-particles. Key factors to control particle size and the particles grow inside the expansion chamber to their final size are a shorter residence time and less time available for particle growth as well as a higher dilution of the particles in the expansion chamber [2]. Pure powder griseofulvin, free of any stabilizing agents, has been obtained using menthol as co-solvent which increases drug solubility in $ScCO_2$ about 28-fold. With the use of a simple capillary nozzle, griseofulvin NPs, in the range of 50−250 nm, have been obtained. This is a 10-fold reduction from the conventional RESS process [4]. In another study, carbamazepin-loaded SLNs have been prepared by RESS [5] using stearic acid as a lipid component. Co-precipitation of the drug and the lipid using RESS produced SLNs with drug loading capacity of 2.2 %. RESS yielded ultrafine spherical particles (100 nm) of carbamazepin-loaded SLNs. The RESS process could also produce ultrafine spherical particles of ibuprofen-loaded SLNs with high drug loading capacity, using the stearic acid as a lipid matrix [6]. The ibuprofen dissolution profile showed that the formulated SLNs have effectively increased the drug solubility.

2.2. Supercritical Anti-Solvent precipitation and related processes (SAS, GAS, ASES, SEDS)

In this process, a ScF is used as anti-solvent, causing the precipitation of the substance which is dissolved in a certain liquid solvent (*e.g.* ethanol) and solute is recrystallized from the solution. This method has been called gas anti-solvent (GAS) or supercritical anti-solvent (SAS) recrystallization. Using this method, very important characteristics of the drug, like crystallinity and polymorphism may be affected and controlled. In this regard, Allesi *et al*. have used SAS process to obtain quercetin (very poorly soluble in water) NPs with better dissolution compared to raw quercetin [7]. Three different polar solvents: acetone, ethanol and dimethylsulfoxide have been used. The authors have confirmed strong reduction in crystallite size for quercetin-ethanol NPs compared to the raw drug ((22.5 ± 1.5) nm and (40.9 ± 7.0) nm, respectively). Better dissolution behaviour has also been found for the quercetin-ethanol NPs obtained by SAS process.

Aerosol Solvent Extraction System (ASES) process involves jet break-up of the drug/polymer solution as fine droplets into compressed CO_2 through an atomization nozzle. In order to improve the solubility and dissolution rate of the drug used, the particle size, morphology and crystallinity of solid dispersion could be controlled by changing temperature and pressure during ASES process. For example, adefovir dipivoxil particles have been recrystallized by using the ASES process [8]. $ScCO_2$ has been adopted as an anti-solvent. To explore the influence of the solvents on the particle production, ethanol, methanol, and isopropyl alcohol have been used as a dissolving solvent for adefovir dipivoxil. As a result, particle size decreased when the system temperature decreased and the system pressure increased. Higher concentration of adefovir dipivoxil in the solution and increasing the solution injection rate also increased particle size. Moreover, the order of recrystallized particle size and the width of particle size distribution has been methanol < ethanol < isopropyl alcohol.

Solution enhanced dispersion by ScFs (SEDS) has been developed in Bradford University in order to achieve smaller droplet size and intense mixing of ScF and solution for increased transfer rate [9]. Enhanced oral bioavailability of silymarin using liposomes containing a bile salt has been achieved by application of SEDS technology to obtain silymarin-loaded liposomes [10]. The liposomes obtained by the SEDS method have exhibited the highest encapsulation efficiency and drug loading, smallest particle size, and best stability compared to liposomes produced by the thin-film dispersion and reversed-phase evaporation methods. Compared to the silymarin powder, silymarin-loaded liposomes prepared by SEDS have showed increased *in vitro* drug release. The *in vivo* AUC_{0-t} of silymarin-loaded liposomes prepared by SEDS has been 4.8-fold higher than that of the silymarin powder.

These processes are suitable for solids which are not able to dissolve into ScFs, so RESS is not applicable.

2.3. Particles from Gas-Saturated Solutions/Suspensions (PGSS)

This process is based on the high solubility of $ScCO_2$ in many molten fats, lipids and polymers or liquid-suspended substances at moderate pressures, leading to so-called gas-saturated solutions/suspensions. The PGSS process can be used to encapsulate liquids if the liquid is mixed together with the coating material and CO_2 into the static mixer. Thereby, an emulsion of the liquid drug into the gas-saturated coating material is formed in the static mixer and the coating material becomes solid during the expansion, encapsulating the liquid. This process allows NP formulation from varies of substances that are not soluble in $ScCO_2$ and can also be used with suspensions of drug used in the polymer leading to obtain nano- or microparticles. For example, progesterone-loaded Gelucire 44/14 dispersion systems have been prepared using the PGSS method and $ScCO_2$. [11]. The authors have concluded that a higher pressure and temperature, a larger sample loading, a longer processing time, a longer sonication, a lower drug-to-excipient ratio and a larger orifice size during expansion are the optimal conditions for the preparation of progesterone-loaded Gelucire 44/14 dispersion systems. Gelucire 44/14 dispersion systems processed using $ScCO_2$ may be considered as a promising carrier for transdermal delivery of progesterone.

2.4. Supercritical Extraction from Emulsions (SFEE)

The SFEE uses $ScCO_2$, which is very good miscible with most organic solvents, to remove them from the emulsion, causing a precipitation of the active substances dissolved in an organic phase. $ScCO_2$ presents a behaviour as an anti-solvent and an extraction fluid at the same time in the process. This SFEE process allows a very good control of the particle size reduction by dispersing the drug inside micelles of the surfactant used to form emulsions. A stable aqueous dispersion of poorly water-soluble active compounds can also be obtained. Moreover, hydrophilic drugs can be incorporated in the polymeric matrix via SFEE process. For example, PLGA polymeric matrix-type NPs incorporating pFlt23K and pEGFP plasmid DNA have been successfully fabricated using SFEE [12]. This allowed plasmid incorporation efficiencies to reach > 98%, incorporate up to 19.7% w/w plasmid DNA in PLGA, reduce residual organic solvent levels beneath detection, and release plasmid effectively from the NPs.

III. CONCLUSION

Various processes using ScF technology provide a choice of a suitable method for the preparation of drug-loaded nanocarriers. It is obvious that this is determined by the physico-chemical properties of the drug and the characteristics, required for the final product - drug-loaded NPs. The use of $ScCO_2$ in all processes provides a better chemical stability of the drug, avoiding harmful solvents. Particle size, particle size distribution, their morphology, drug loading and crystallinity of the drug could be controlled by changing temperature and pressure during the process. The optimization of these parameters leads to higher solubility which means higher dissolution rate and better bioavailability. All ScF technologies provide high yield without residual solvents reducing the toxic effects of the individual materials used to make the NPs. Last but not least, these methods are fast, cheap and environmentally friendly. These findings give grounds the ScF technologies to be the first choice for preparation of nano-scale drug delivery systems. Depending on the fluid and the equipment used, ScF processes can remove technological barriers, optimize the manufacturing processes and provide a sustainable alternative to conventional production methods.

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