J. of Supercritical Fluids 101 (2015) 193–214

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

journal homepage: www.elsevier.com/locate/supflu

Review

# Supercritical fluids applications in nanomedicine

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ARTICLE INFO

*Article history:*
Received 19 December 2014
Received in revised form 26 January 2015
Accepted 26 January 2015
Available online 19 March 2015

*Keywords:*
Supercritical fluids
Nanomedicine
Nanoparticles
Nanocarriers
Nanostructured
Nanoporous materials

ABSTRACT

Nanomedicine consists of the application of nanotechnologies in the medical field. In many nanomedical applications, supercritical fluids based processes represent the best potential choice, since they allow controlled fabrication of biological active nanoparticles, nanostructured microparticles, nanoporous/nanostructured materials. These products can be used to develop cell diagnostic kits, intracellular devices, engineered drug delivery systems, implantable materials and devices.

This review is a critical analysis of the results reported in the literature on this fascinating and explosively growing field.



**Contents**



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http://dx.doi.org/10.1016/j.supflu.2015.01.030

## 1. Introduction

Nanomedicine is the medical application of nanotechnologies. It is widely diffusing since nanoparticles, nanostructured composite particles, nanoporous and nanostructured materials can be used in a large variety of medical applications, ranging from cell diagnostic tools, intracellular devices, drug delivery, nanotherapeutics, implantable materials and devices [1]. Looking at some of these applications, drug delivery systems operate not only producing controlled or prolonged delivery, but, also targeted, pulsed or, generally speaking, engineered delivery. Also nanoporous and nanostructured implantable or biodegradable structures (scaffolds) can be produced. In several cases, the research is still at the very beginning; in some others, the first nanomedical products are already on the market. In all cases, the field is very challenging since the manipulation of matter at nanoscale involves complex technologies and new processing solutions are continuously proposed.

Processes based on supercritical fluids (SCFs) and their mixtures can play a relevant role in nanomedicine, since their specific properties like: very fast mass transfer, near zero surface tension and effective solvents elimination, allow innovative processing applications that can overcome the limitations characterizing classical liquid based processes. Summarizing this concept, the hybrid liquid-like gas-like properties and the possibility to manipulate several process parameters, as for example, pressure, temperature, surface tension, can be the keys to produce several medical products at nanoscale. For these reasons, many proposals to applicate SCFs processing to nanomedicine appeared in the literature.

The aim of this review is to critically analyze SCFs based processes proposed for medical applications to produce:

- Nanoparticles
- Nanostructured and nanoporous microparticles
- Nanoporous materials

indicating their advantages, drawbacks and their possible applications and the future perspectives of the field.

## 2. Materials and methods

We performed a systematic review of the scientific literature, consisting of a comprehensive search on PubMed, Google Scholar, ISI Thompson, Scopus databases, using various combinations of the keywords “nanomedicine”, “supercritical fluids”, “nanoparticles”, “nanocarriers”, “nanodevices”, “tissue engineering”, “scaffolds”, “drug carriers”, “membranes”, “nanoporous” and “nanostructured” over the years 2000–2015. However, some older, but, relevant papers, have also been added to the list, when necessary. We also set the definition of nanoparticles ($np_s$) and or nanopores to a maximum of 250 nm, since we decided that this dimension can represent a good compromise between fundamental researches (in physics, chemistry, catalysis, etc.) that frequently set nano-objects at a maximum dimension of 100 nm and several pharmaceutical and medical applications, where the concept of nanometric is applied in a more extended manner. Articles were initially screened for relevance by title and abstract and obtaining the full-text article, if the abstract did not allow the investigators to define inclusion and exclusion criteria. The three investigators, separately reviewed the abstract of each publication and, then, performed a close reading of all articles and extracted data to minimize extraction bias and errors. A cross reference research of the selected papers was also performed, to find other relevant articles useful for the review.

Several SCFs based processes applied to nanomedicine applications will be described; in particular: Supercritical AntiSolvent precipitation (SAS), Rapid Expansion of Supercritical Solutions (RESS), Supercritical Emulsion Extraction (SEE), Supercritical Assisted Atomization (SAA), Supercritical Assisted Injection in Liquid Antisolvent (SAILA), Depressurization of an Expanded Solution into an Aqueous Medium (DESAM), Supercritical Assisted Liposome formation (SuperLip), Supercritical assisted phase separation, Supercritical gel drying, Electrospinning in SC-$CO_2$. A description of these processes and their general principles is reported in supplementary information file.

## 3. Nanoparticles

Nanoparticulate systems can be classified in:

- nanoparticles and nanocarriers
- lipid nanovesicles

### 3.1. Nanoparticles and nanocarriers

$Np_s$ are promising materials used to overcome bioavailability problems of many active pharmaceutical principles, by enlargement of the exposed surfaces and, therefore, to increase the dissolution rate of poor water-soluble compounds [2]. Indeed, it is known that the dissolution rate is directly proportional to the surface area of the drug.

Nanocarriers can be used to deliver biologically active molecules at a desired rate and for a desired time, maintaining the drug concentration level in the body within the therapeutic window. This approach is particularly useful when very active drugs with narrow therapeutic windows are used [3]. Nanoencapsulation can enhance the transfer across the main hurdle: the brain blood barrier (BBB). Nanoscale particles can travel through the blood stream without sedimentation or blockage of the microvasculature, can circulate through the body and penetrate tissues like tumors. In addition, $np_s$ can be taken up by the cells by endocytosis. Another advantageous feature of these particles is that they could be easily sterilized by filtration, since the size of bacteria and viruses is larger.

A major challenge in nanomaterials science is the accurate control of the size and shape, which, in turn, is directly linked to the nanomaterials processing method [4]. Traditional milling technology is still used; but, using this technique, it is difficult to reduce the particles size below 5 μm. Some wet milling and homogeneization technologies are used to submicronize materials; but, the physicochemical stability of the materials processed in this way can be compromised by high temperature and contamination by the