

Supercritical Fluid Technology and its Pharmaceutical Applications: A Revisit with Two Decades of Progress

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ABSTRACT

Over the past two decades, supercritical fluid technology has emerged as one of the most important technologies applied in many fields such as cosmetic, food and pharmaceutical. Supercritical fluid extraction process offers numerous advantages such as easy, effective, inexpensive, high quality of solute extraction and environmentally friendly. This mini-review describes the fundamentals of supercritical fluid technology, the function of supercritical fluid as solvent and anti-solvent, mechanism of supercritical fluid, advantages and disadvantages and revisit the application of supercritical fluid technology in pharmaceutical sciences. In-depth discussion with recent examples of extraction of natural products, particle design in drug delivery, preparation on pharmaceutical powder, drug solubilization, inclusion complex, polymer impregnation, liposomal formulations, purification and polymorphism as well as drug extraction analysis are also presented. Key aspects and processing considerations of supercritical fluid technologies are reviewed to assist scientists to generate other related experimental works.

Key words: Bioavailability enhancement, Biomedical applications, Drug delivery, Polymeric carriers, Supercritical fluids.

INTRODUCTION

The pharmaceutical research expands rapidly in pace with the fast growth of research and technology worldwide. Most of the pharmaceutical development involves time consuming, high temperature process and consume of large volume non-economical and non-environmentally friendly organic solvents. Rapid methods of drug development and purification and a predictable scale-up that influence the success of the product by improving cost, quality and safety and reducing environmental hazards are highly desirable.¹ Supercritical fluid technology has a long history of application in the field of food and textile industry. Recently it is

gaining momentum in the pharmaceutical research field.²

Supercritical fluid technology is a concept to utilize the distinct properties of solvent in their supercritical state. The compound will change from one state to another under different set of pressure and temperature condition. There are three basic states namely the solid, liquid and gaseous state. A phase diagram, in thermodynamics is defined as a graphical representation of the physical states of a substance under different conditions of temperature and pressure.³ Critical temperature (T_c) is defined as the highest temperature at which a gas can be converted into a liquid by an increase in

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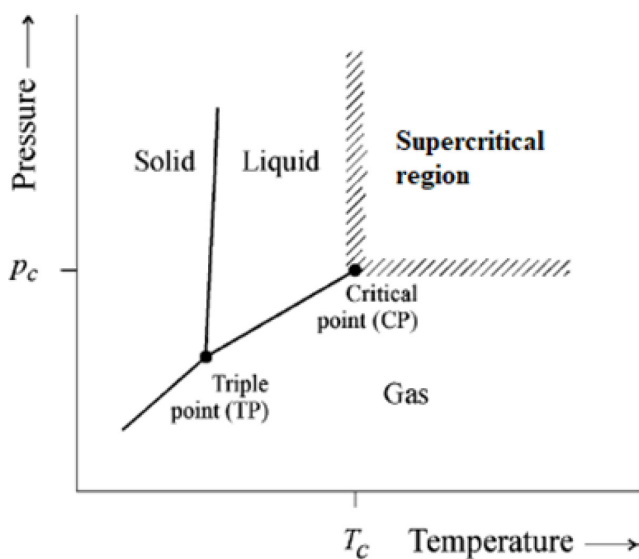


Figure 1: Phase diagram for a single substance. P_c, critical pressure; T_c, critical temperature. (Figure is adopted from G Brunner)⁴

pressure. Critical pressure (P_c) is defined as the highest pressure when a liquid is converted into its gaseous phase by an increase in the liquid temperature.¹ A critical point is denoted by the end point of a phase equilibrium curve. A compound is defined in its supercritical state when the temperature and pressure of the environment exceed the critical point in a phase diagram.⁴ A supercritical fluid is a phenomenon whose temperature and pressure values eventuate above its critical point synchronously.¹ The supercritical region is illustrated as the hatched line region in the phase diagram in Figure 1. A compound is neither a solid, liquid nor gas in the supercritical region. The physical characteristic of a compound lies between the state of a liquid and gas when it is under supercritical region.

Fundamentals of supercritical fluid

Supercritical fluid has a distinct physical feature. Supercritical fluid is dense yet compressible. It can behave either like a liquid or a gas but it is actually neither. The viscosity and diffusivity of a supercritical fluid has a value near to a gas but densities closer to a liquid. As a result, a supercritical fluid has a high solvent strength for extraction of solute from solid compound yet diffuse faster in a solid matrix than a liquid,⁵ These properties contribute to the high solvation power of a supercritical fluid to dissolve solid. The solubility of solid in supercritical fluid can be 3-10 folds magnitude higher than in the liquid form. The solubility of a solid in supercritical fluid is highly dependent on the density. Whereas the density of a supercritical fluid will change

drastically when there is a slight change in temperature and pressure when the condition is near to the critical point.⁶ By adjusting the temperature and pressure, the solubility can be manipulated.⁷ Generally, by increasing the pressure, the solubility of solute increases in supercritical fluid. Increasing the temperature might have an effect of increasing, decreasing or no change on the solubility of the solute in supercritical fluid depending on the range of pressure.⁸

Mechanism of supercritical fluid

The working principles of supercritical fluid basically can be categorized into two major categories. (1) Supercritical fluid can be used as a good solvent. (2) On the other hand, supercritical fluid can be used as an anti-solvent. In this case, supercritical fluid is used to precipitate a solute from an organic solvent that the solute dissolve.¹ The anti-solvent mechanism is used mostly to process poorly soluble compounds in supercritical fluid. This technique is used more for the preparation of drug delivery system.¹

Supercritical fluid as solvent

Rapid Expansion of Supercritical Solution (RESS)

RESS is a conventional method of utilizing supercritical fluid for extraction and drug encapsulation. The saturated supercritical fluid with solid substrate is rapidly depressurized (leaving the supercritical region into ambient condition) will cause rapid expansion of the supercritical fluid and hence rapid reduction of the solvation power through a heated capillary or laser-drilled nozzle into a low-pressure chamber. Due to the diminishing in solvation power, the solvent immediately becomes super-saturated and hence super fluid nucleation and particle generation.⁹ Parameters that can be manipulated are solute solubility in supercritical fluid (commonly used SC-carbon dioxide), temperature, pressure, capillary design angle and impact of the capillary jet against the surface. This method produces dry particle which does not require further processing step.¹⁰

Rapid Expansion of Supercritical Solution into a Liquid Solvent (RESOLV)

RESOLV is a modified method of conventional RESS to minimize aggregation of particles during particle formation. The mechanism is same as RESS beside at the end of the process, the particles are sprayed into a collection chamber containing a liquid solvent at room temperature.^{11,12}

Supercritical fluid AS AN ANTI-SOLVENT

Gas Anti-Solvent Recrystallization (GAS)

Supercritical fluid functions as an anti-solvent in this method. The solute is first dissolved in a suitable organic solvent. Supercritical fluid is diffused into the organic solvent leading to the evaporation of the organic solvent. As a result, the solvation power of the organic solvent is reduced and it is no longer a good solvent for the solute. The overall process favors the onset of nucleation, bringing on precipitation of the solute.¹³ In order to maximize this technique, ideally the solute should have limited solubility in the supercritical fluid and the supercritical fluid should be miscible with the organic solvent.¹⁴

Aerosolised Solvent Extraction System (ASES)

In an ASES system, a solvent and an anti-solvent (supercritical fluid) are sprayed to achieve uniform small size particle. It is believed that by introducing the anti-solvent supercritical fluid into the liquid droplet, the anti-solvent causing volume expansion, simultaneous reduction in solvation power and sharp supersaturation within the liquid droplet which produce uniformly distributed small size particle. The supercritical fluid is first sprayed into a high-pressure vessel for conditioning. Once the desired pressure is achieved and stabilized, the solute and the solvent is sprayed using a higher pressure pump into the high pressure vessel through an orifice with definite size. The particles are then collected at the filter surface fixed at the bottom of the vessel.¹²

Supercritical Anti-Solvent Recrystallization (SAS) and Precipitation with Compressed Anti-Solvent (PCA)

In this method, an organic solvent containing drug and polymer is sprayed into a compressed gas or supercritical fluid. By controlling the critical parameters such as pressure and temperature, the particles are precipitated and collected on a filter attached at the bottom of a precipitation vessel. PCA method utilizes either a liquid or supercritical anti-solvent, whereas the SAS makes use of supercritical fluids as an anti-solvent.¹⁵

ADVANTAGES OF SUPERCRITICAL FLUID TECHNOLOGY

Ease of removal of solvent from extracted compound

The process to remove the solvent from the extracted compound is simple after the extraction process by

simple expansion.¹⁶ Most of the solvent used in supercritical fluid does not produce any harm to the environment. Solvent such as Carbon dioxide offers various advantage such as inexpensive, easily available, can be reusable and suitable to extract a thermal labile and non-polar bioactive compound. The selectivity can be manipulated according to the temperature and/or pressure which can results in high quality and purity of the solute extracted. If required, a small quantity of co-solvent can be added to expand the selectivity on the polar compound.¹⁷

High solvation power

The supercritical fluid has liquid-like density but gas-like diffusivity. Hence, supercritical fluid has superior mass transfer characteristic that contributes to high solvation power of solute. The high diffusivity characteristic enables the supercritical fluid to penetrate the porous matrix of solid particles, hence increasing the effective surface area for extraction. In comparison to typical liquid solvent extraction, supercritical fluid produce a faster extraction and separation phase and extraction yield is free from any residue.¹⁸

DISADVANTAGES OF SUPERCRITICAL FLUID TECHNOLOGY

Although Supercritical fluid technology offers a variety of advantages and conveniences to the users, however, it is also reported that there are drawbacks of Supercritical fluid technology which limit its use.

Lack of standard extraction procedure

Although using Supercritical fluid extraction is time and organic solvent saving, but there is a lack of universal method that works for different types of matrices and analytes. The Supercritical fluid extraction technique requires an experienced analyst to develop the method and run the sample. It requires the analyst to understand the mechanism and working mechanism and it's not a day-to-day routine analysis.¹⁹

Difficulties in extracting polar compound

Carbon dioxide could be an excellent solvent for non-polar analytes. However, it's polarity might not be suitable to extract polar compounds due to the insufficient solubility of polar analytes in Sc- carbon dioxide. In addition, Supercritical fluid extraction might not be suitable to extract compounds dissolve in water medium or blood plasma. Introduction of a co-solvent as modifier is required for the extraction of polar compound.

These co-solvents include methanol, hexane, aniline, toluene and diethylamine.²⁰

Inefficiency in cleaning up

The matrix of previous sample is always found in the instrument if proper clean up steps are not followed. Proper clean-up methods need to be applied after the extraction step.¹⁹

APPLICATION OF SUPERCRITICAL FLUID TECHNOLOGY IN PHARMACEUTICAL SCIENCES

Over the past two decades, supercritical fluid technology has undergone rapid transformation. Some new appli-

cations are used in the field of extraction of natural products, particle design in drug delivery, preparation on pharmaceutical powder, drug solubilization, inclusion complex, polymer impregnation, liposomal formulations, purification and polymorphism as well as drug extraction analysis. In this section, key aspects and processing considerations of supercritical fluid technologies are reviewed to assist scientists to generate other related experimental works. The examples of supercritical fluid technology in the literature are presented in Table 1.

Supercritical fluid extraction

Supercritical fluid extraction is one of the most common application of supercritical fluid technology. The

Table 1: Supercritical fluid technology application and its technique used.

Application	Drug	Technique used	Reference
Microparticles	Naproxen	SAS	[21]
Microparticles	Protein and catalase	Antisolvent	[22]
Microparticles	Cefadroxil	Supercritical assisted atomisation (SAA)	[23]
Microparticles	Griseofulvin	RESS processing	[24]
Microparticles (0.1 – 5 µm)	Lysozyme	SAA	[25]
Microparticles (0.5 – 3 µm)	Griseofluvin	SAA	[26]
Microparticles (1-2 µm)	Budesonide-poly lactice	Precipitation with a compressed anti-solvent (PCA) method	[27]
Microparticles (15 - 30µm)	Nifedipin	SAA	[28]
Microparticles (HPMC based)	Ampicillin trihydrate	SAA	[14]
Nanoparticles	Ibuprofen	RESOLV	[29]
Nanoparticles (152– 863 nm)	Atorvastatin calcium	SAS	[30]
Nanoparticles (200 –1000 nm)	gentamicin, naltrexone and rifampicin	PCA	[31]
Complexation	piroxicam and 2-hydroxypropyl-β-cyclodextrin	supercritical cyclodextrin complexation	[32]
Complexation	ketoprofen (KP) and a cyclodextrin (CD)	supercritical cyclodextrin complexation	[33]
Polymer impregnation (CDDS)	naphthalene per gram of PMMA	supercritical carbon dioxide	[34]
Polymer impregnation (CDDS)	Flurbiprofen and timolol maleate with chitosan	supercritical carbon dioxide	[35]
Polymer impregnation	PVP K-15 and piroxicam	supercritical carbon dioxide	[36]
Polymer impregnation	<i>N</i> -carboxybutylchitosan (CBC) and agarose (AGA) loaded with quercetin (anti-inflammatory) and thymol	SSI process	[37]
Liposomes (Nanosize particles)	Amphotericin B	supercritical fluids	[38]
Liposomes (Microsize particles)	miconazole	aerosol solvent extraction system (ASES) process	[39]
Extract	<i>Extract Bioactive Compounds from Natural Sources</i>	Ultrasonic-assisted Supercritical fluid extraction methods	[40]
Drug delivery	<i>Food bioactives</i>	Pressurized Gas-eXpanded (PGX) liquid technology	[41]
Food products	low-cholesterol dairy cream powder	supercritical fluid extraction	[42]
Dry powder	Plasmid DNA-loaded particles	solution enhanced dispersion	[43]
Controlled release matrixes	Paclitaxel	Modified SAS system using ultrasonic	[44]
Solid dispersion	Oxeglitazar	SAS technique	[45]

Table 2: Critical values of various supercritical fluid.

Supercritical fluid	Critical Temperature (TC) °C	Critical Pressure (PC) MPa	Comments
Water	374	22	High critical temperature required
Xenon	16.6	5.9	Inert but costly production
Sulpha hexafluoride	45.5	3.8	Costly production
Nitrous oxide	36.5	4.1	Safety concern
Ethylene	9.1	5.1	Flammable
Trifluoromethane	25.9	4.7	Safety concern
Carbon dioxide	31.2	7.4	Safe, non-flammable, non-toxic and cost effective
Propene	36.5	4.6	Flammable and hazardous
Methane	19.0	4.6	Highly explosive and can cause death by asphyxiation

technique has been applied to large range of solid compounds in pharmaceutical and food field. Several organic solvents show high solvation power under supercritical state. Almost all gases can be converted into supercritical fluid beyond critical point, but some require relatively very high temperature and pressure to achieve that.⁴⁶ There are some solvents have relatively low critical values but high cost of production such as Xenon and hexafluoride whereas some have safety concern such as nitrous oxide or ethane.⁴⁶ Table 2 summarizes critical values of various supercritical fluid.¹ Supercritical carbon dioxide (Sc-carbon dioxide) is the most common solvent used in Supercritical fluid extraction. Almost 98% application reported were using Sc- carbon dioxide.⁴⁷ Sc- carbon dioxide is widely used because it is safe, non-toxic, non-flammable, recyclable, abundantly available, inexpensive, easy to remove from the product and its critical temperature and pressure are relatively low ($T_c=31.1^\circ\text{C}$, $p_c=72$ bar).^{48,49} Therefore, Sc- carbon dioxide is suitable for the extraction of thermolabile compounds which are very common in the food, pharmaceutical and nutraceutical industries. When Sc-carbon dioxide extraction is operated at non-elevated temperature using a non-oxidant medium, the thermal sensitive or easily oxidized compound can be

extracted safely compared to conventional method which requires heating.⁵ This is especially important where the color, composition, odor, taste and texture are a major concern in the field. Furthermore, this method is considered as environmentally friendly because only a small amount of organic solvent is required in the process compared to conventional extraction methods.

However, due to the non-polar nature of carbon dioxide, the affinity of extraction might be limited to non-polar small bioactive molecule compounds. The solubility decreases with increasing polarity of the molecule. The solubility of polar compounds in Sc-carbon dioxide can be improved by adding in a small amount of co-solvent, also known as the modifier such as 1-10% of methanol and ethanol.⁵⁰ Another way of extracting polar compound using Sc- carbon dioxide is through modification of the polarity of the compound by chemical modification. As a result, chemical in situ derivatization is required to improve the selectivity of the extraction towards a specific group of compounds.⁵¹ Sc-carbon dioxide has stronger affinity towards smaller molecular weight compound than large molecular weight compound. The solubility decreases with increasing molecular weight. Free fatty acid and their glycerides and pigments have limited solubility in Sc-carbon dioxide in general. Proteins, polysaccharides, sugars and mineral salts are insoluble. However, the solubility can be modified by increasing the pressure, using a suitable modifier or chemical modification of the compound.⁵²

Plant material extraction

Industry involved in extraction process capitalizing on supercritical fluid as it offers various unique features that can be exploited. When comparing with conventional solvent extraction process, supercritical fluid is a rapid process with higher selectivity which require less parameters to monitor and solvent used are environmentally friendly that results in higher quality of extraction yield. The process of plant material is very complex with several parameters such as nature of the plant, process parameters, physicochemical properties of the solvent and phenomena associated with mass transfer need to be considered.¹⁷ Supercritical fluid have been extensively used in the extraction of plant materials. Fatty acid, essential oil, flavonoids, saponins, phenolic group and carotenoid has been extracted from various plant by adjusting the extraction.⁵³

H Abbasi *et al.*⁵⁴ extracted phenolic compounds from *Punica granatum* using various extraction conditions. When comparing the result of solvent extraction method

using non-supercritical condition and supercritical carbon dioxide as solvent, it shows extraction was more selective and produce a significance difference in the total amount phenolic compounds extracted when using the later method. The extraction condition included the temperature range from 40-60°C and pressure range of 200, 275 and 35 MPa yielded the phenolic compound of 7.8-72.1 mg/g.⁵⁴ K Chhouk *et al.*⁵⁵ combined hydrothermal process in a study of bioactive compound extraction from *Garcinia mangostana* pericarp using supercritical extraction. The extraction process was performed with temperature range 120-160°C and pressure range of 5-15 MPa. The optimum total phenolic compound of 22.0 mg/g with antioxidant activity of 73.2 µg/ml and alpha-mangostin of 0.203% w/w extract.⁵⁵ J Viganó *et al.*⁵⁶ successfully extracted different compounds in sequential supercritical conditions: tocots in 60°C in 70 MPa during the first step, followed by fatty acid without tocol and low carotenoid content at 50°C and 17 MPa and lastly concentrated carotenoids with 60°C and 26 MPa. By using the sequential steps, it enhances the tocots and carotenoids extraction concentration by 1.5 and 5.8 times, respectively, when compared with single stage condition.⁵⁶ LA Conde-Hernández *et al.*⁵⁷ successfully extracted essential oils with two temperature: 40°C and 50°C and pressure of 10.34 MPa and 17.24 MPa. Higher rosemary oil content and antioxidant activity was reported when sample treated with 40°C and 17.24 MPa.⁵⁷

P Benelli *et al.*⁵⁸ studied the extraction methods of orange pomace using supercritical technology with pressure range between 100-300 bar and temperature of 40°C and 50°C with the addition of ethanol as co-solvent enhance the yields, antioxidant activity and the total phenolic content.⁵⁸ In another study, addition of ethanol as co-solvent reportedly increase the extraction yield of phenolic compound in bamboo leaves and flavonoids in ginkgo ginkgolides.⁵⁹ Similarly, extraction *Puffia glomerata* roots using ethanol and Supercritical carbon dioxide produce greater amount of saponins yield in condition of 50°C and 30 MPa.⁶⁰ In a study by J Liu *et al.*⁶¹ the author compared effect of the process parameters to extract flavonoids in *Maydis stigma*. It was found out that aqueous ethanol as co-solvent can enhance the extraction yield and maximum flavonoid extract concentration was observed when pressure of 40 MPa was used.⁶¹

Particle design in drug delivery application

Conventional particle size reduction method involves high milling energy or high temperature process which might subject the particles to morphological and crys-

tallographic modification. The physicochemical properties and stability of the downsized particles are in doubt. Furthermore, the particle size distribution obtained using conventional method is not uniform.⁶² The limitations of the conventional methods can be overcome by using Supercritical fluid technology to achieve micron or sub-micron size particle. The SAS process was reported to be used to produce micro particles of various compounds such as lysozyme, trypsin, insulin and hydrocortisone.⁶³

preparation of pharmaceutical powder

The Supercritical fluid technology technology can be used to convert preparation into pharmaceutical powder including proteins, peptides and nucleic acid samples. The method has advantages over the conventional methods because Supercritical fluid technology can preserve the biological activities of molecules and control over the morphology of the powder. Studies showed that aqueous protein solutions are converted into powder using Supercritical fluid technology.⁴³ The supercritical fluid expanded and nucleated with the liquid solvent, thereby facilitating the formation of submicron protein particles.²²

Drug solubilization application

Drug solubility is an important factor that will determine the bioavailability of the drug *in-vivo*. With the advent of Omics, the use of high throughput screening and bioengineering, novel drug molecules are plagued by poor aqueous solubility which eventually limit their oral bioavailability. Supercritical fluid technology is reported to improve the solubility of various drug compounds. GP Sanganwar and RB Gupta⁶⁴ reported a method of increasing fenofibrate by adsorbing the drugs on silica through Supercritical fluid technology. Fenofibrate is first dissolved in Sc-carbon dioxide. By depressuring the Sc-carbon dioxide, fenofibrate molecules are adsorbed on the silica. The result shows that silica adsorbed drug compound has better dissolution rate than micronized drug compound. It can be explained by an increase in effective surface area decrease in crystallinity of the drug compound after adsorption onto silica. In this process, organic solvent is not used, hence there's no concern of organic solvent residual. As a result, it is generally believed that Supercritical fluid technology can be used to replace conventional organic solvent method to adsorb drug compounds onto a complex / polymer which eventually produce finer molecules with increase effective surface area and wettability.¹

Inclusion complexes

Cyclodextrin (CD) is reported in the literature as a frequently used complex to improve the solubility of poorly aqueous soluble drugs. The approach is through complexation of poorly soluble drug into a solid carrier (eg. cyclodextrin) to improve the solubility of the drug. However, conventional processing methods such as solvent evaporation, solid dispersion, kneading normally requires the use of organic solvent to dissolve the drugs before complexation. Sc-carbon dioxide can be used to dissolve the poorly aqueous drug, complexing the drug into CD and followed by depressurization to remove the carbon dioxide. It is reported that complexation of carbamazepine with PVP K30 using Sc-carbon dioxide has achieved an improvement in intrinsic solubility up to 4-fold than the original carbamazepine powder.⁶⁵

Polymer impregnation

The process involves the mixing of a polymeric substance with a carrier liquid and an additive for impregnation into the polymer in a closed pressure vessel system. The common polymers used for this purpose are lactic acid, glycolic acid, polyolefin, polyamide, polyurethane, silicone and protein derivatives. Combination of polymers can also be used.³⁴ The impregnation additive should be practically insoluble in the supercritical fluid. Under the supercritical condition, the polymer swells which allows the impregnation additive to be entrapped in the polymeric structure. After the pressure is released and it returns back to ambient condition, the carrier liquid diffuses out from the swollen polymeric structure, but the impregnation additive is entrapped within the polymeric structure.⁶⁶

Liposomal formulations

Conventional methods to prepare liposomes require large amount of organic solvent with low encapsulation efficiency. Supercritical fluid such as Sc-carbon dioxide can be used as a co-solvent to reduce the amount of organic solvent used. K Otake *et al.*⁶⁷ has developed liposomes using a reverse phase evaporation method. The emulsification process was achieved through introduction of water into a homogeneous mixture of Sc-carbon dioxide /1- α -dipalmitoylphosphatidylcholine/ethanol with sufficient stirring and subsequent pressure reduction. The one step preparation method produced large unilamellar liposomes with high entrapment efficiency.

Purification and polymorphism

Impurities are often a side product during the synthesis of active pharmaceutical ingredient (API). These impurities must be removed from the API to avoid interference with the chemical stability and biological activity of the API. Supercritical fluid technology is found as a useful method to remove the impurities. Anti-solvent recrystallization (GAS) is reported as a successful technique to separate and isolate for this purpose. Furthermore, this technique can also be applied for polymorph isolation and chiral control. These include the purification of anthracene, bilirubin, β -carotene, cholesterol, citric acid and proteins and for fractional crystallization of mixtures of anthracene and anthraquinone and lecithin from egg yolk, hydroxybenzoic acid isomers, natural products, phenanthrene and naphthalene and racemic mixtures.⁶⁸

Drug extraction and analysis

Drug extraction from plasma is conducted conventionally using liquid-liquid extraction, solid state extraction and deproteinization.⁶⁹ Beside extraction active compounds and essential oils from natural products, Supercritical fluid technology can be applied to extract drug from biological fluid sample for analysis as well. Sc-carbon dioxide is reported to be used to extract ibuprofen, indomethacin and flufenamic acid from plasma sample and analysed using high performance liquid chromatography method.⁷⁰ Apart from this, benzodiazepines are also reported to be separated from the dosage form matrix using supercritical fluid technology.⁷¹

CONCLUSION

It is evident that supercritical fluid technologies is gaining momentum in the past two decades. Supercritical fluid still versatile in pharmaceutical because this technology is useful to control particle size, morphology, shape and particle form. Most recent supercritical fluid applications utilised controlled release matrixes, complexation, polymer impregnation, nano-micron particles, to enhance solubility of poorly water-soluble drugs. Therefore, supercritical fluid technologies are very much relevant to the pharmaceutical industries with its wide application and it is foreseen that the technologies will be expanded in the next decade.

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CONFLICT OF INTEREST

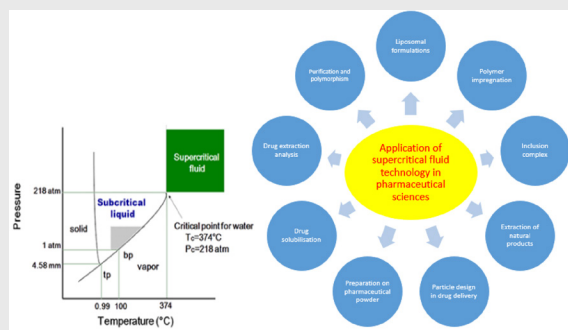
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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PICTORIAL ABSTRACT



SUMMARY

Over the past two decades, supercritical fluid technology has emerged as one of the most important technologies applied in many fields such as cosmetic, food, and pharmaceutical. Supercritical fluid extraction process offers numerous advantages such as easy, effective, inexpensive, high quality of solute extraction, and environmentally friendly. This mini-review describes the fundamentals of supercritical fluid technology, the function of supercritical fluid as solvent and anti-solvent, mechanism of supercritical fluid, advantages and disadvantages, and revisit the application of supercritical fluid technology in pharmaceutical sciences. In-depth discussion with recent examples of extraction of natural products, particle design in drug delivery, preparation on pharmaceutical powder, drug solubilization, inclusion complex, polymer impregnation, liposomal formulations, purification and polymorphism as well as drug extraction analysis are also presented. Key aspects and processing considerations of supercritical fluid technologies are reviewed to assist scientists to generate other related experimental works.

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