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Supercritical fluid technology: A promising approach to enhance the drug solubility

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Introduction:

In recent technologies, innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities (Mooter et al., 2006). However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility (Lipinski et al., 1997; Lipinski, 2000). The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability and the rate-limiting step to absorption of drugs from the gastrointestinal tract. Consequently poor solubility results in low bioavailability, increase in the dosage, large inters and intra-subject variation and large variation in blood drug concentrations under fed versus fasted conditions. The enhancement of oral bioavailability of such poorly water-soluble drugs remains one of the most challenging aspects of drug development (Hecq et al., 2005).

Techniques for solubility enhancement are salt formation, solubilization by co solvents, use of pro- drug, particle size reduction (Wadke DA e al., 1989; Nijlen et al., 2003), solvent evaporation, pro drug (Patro et al., 2005), lyophilization (Fathy et al., 2000), melt agglomeration process (Vilhelmsen et al., 2005), extruding method (Wang et al., 2005), spray drying technology (Ueno et al., 1998), use of surfactant (Bakatselou et al., 1991), super critical fluid technology, etc. But at the same time there are some limitation which is described in the table 1.

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Introduction on Supercritical fluid technology:

In the 1980s, the use of supercritical fluids began to be touted as the solution to a wide variety of problems. Prior to 1985, there were fewer than 5 articles per year in the literature discussing solubilities of substances in supercritical carbon dioxide; in the past 10 years, that number exceeded 65 per year (Drug Delivery Applications of Supercritical Fluid Technology, 2002).

The number of applications and technologies involving supercritical fluids has also grown explosively. A simple search of the Web site <www.bn.com> recently showed 92 books about supercritical fluids alone. A search conducted using SciFinder Scholar returned 11 907 items dealing with supercritical fluids, 4255 dealing with supercritical fluid extraction (SFE) processes, and 1252 articles in the same time span dealing with supercritical solubilities, all in just the past 10 years alone. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid.

In the pharmaceutical field, the SCF technology was industrially applied in the early 1980s; in the same period, interest in using SCFs for precipitation and crystallization processes was developing for pharmaceutical materials. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research (Markku Rantakyla et al., 2004)

A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc).

Table 1: Limitation of some of the methods to increase the solubility of poorly soluble drugs.

Method	Limitations
1. Micronization	Difficult to control important character of the final particle such as size, shape, morphology, surface properties and electrostatic charges. High-energy process, which causes disruptions in the drug crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions (Takano et al., 2004).
2. Salt formation	High reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity. Even though use of co solvent to improve dissolution rate pose problems such as patient compliance and commercilation (Gibaldi et al., 2005).
3. Spray drying	Mechanical forces during comminution may degrade some pharmaceuticals, and spray drying may cause thermal stress and degradation of some products. Use of the organic solvent (Chen et al., 2004).
4. Hot-melt Extrusion`	Hot-melt extrusion technologies have been limited due to the temperature-sensitive nature of the drugs (Zajc et al., 2005).
5. Solvent Evaporation	High preparation costs and difficulties in completely removing the liquid solvent. Toxicity potential of organic solvents (Kim Eun et al., 2000).
6. Conventional methods for manufacturing of solid dispersions.	Laborious and expensive methods of preparation, Reproducibility of physicochemical characteristics, Difficulty in incorporating into formulation of dosage forms, Scale-up of manufacturing process, and Stability of the drug and vehicle (Hamsaraj Karanth et al., 2006)

SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications (R. D. Dupta et al., 2008).

As described above, carbon dioxide is one of the most commonly used SCFs because of its low critical temperature (Tc = 31.1^0C) and pressure (Pc = 73.8 bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of CO2 makes it attractive for processing heat-labile molecules (e.g., products of

biotechnology).

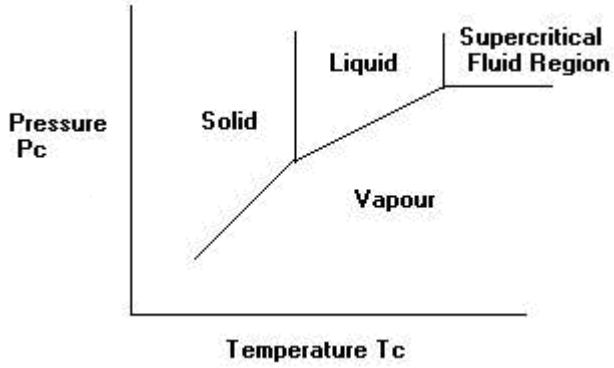

Fig: 1. Typical diagram of supercritical region

Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water (Table 2). (Van Hees T. et al., 1999)

Table 2: Critical condition for some solvent

Substance	Tc, K	Pc, atm	Density (g/ml)
Ammonia	405.6	112.5	0.24
Benzene	562.1	48.3	0.30
Carbon dioxide	304.2	72.9	0.47
Ethane	305.5	48.2	0.20
Ethanol	516.6	63.0	0.28
Methane	190.6	45.8	0.16
Propane	370.3	41.9	0.22
Chloroform	299.3	47.9	0.62
Water	647.3	218.3	0.32

Basic techniques in SCF technology:

1) Rapid Expansion of Supercritical Solutions:

A supercritical solvent saturated with a solute of interest is allowed to expand at a very rapid rate, causing the precipitation of the solute. The rapid expansion/decompression is achieved by allowing into pass through a nozzle at supersonic speeds. This rapid expansion of supercritical solutions leads to super saturation of the solute in it and subsequent precipitation of solute particles with narrow particle size distributions.

This process is also known as supercritical fluid nucleation (SFN). Figure 2 provides schematic view of the rapid expansion of supercritical solutions (RESS) process. The SF is pumped through a pre-heater into the vessel containing the solid solute at a particular temperature and pressure.

The SF dissolves and gets saturated with the solute, and the resultant solution is introduced into a precipitation chamber by expansion through capillary or laser-drilled nozzle (Moneghini et al., 2001). Typically, by altering the pressure, the precipitation unit is maintained at conditions where the solute has much lower solubility in the SF.

During expansion or decompression phase, the density and solubilising power of the SF decreases dramatically, resulting in a high degree of solute super saturation and subsequent precipitation. The morphology and size distribution of the precipitated material is a function of its pre expansion concentration and expansion conditions. The pre-expansion concentration is dependent on the choice of SF, nature of solute, addition of cosolvents and operating pressure and temperature. The higher the pre-expansion concentration, the smaller the particles and narrower the particle size range. Limitation of RESS is the inability to process those materials which are insoluble or very less soluble in the SCF. So for this material the SAS process has been successfully used.

2) Gas Antisolvent Recrystallisation:

It is a well-known phenomenon that a poor solvent of a particular solute can be added to the solution to precipitate the solute. This is called salting out and is widely used for crystallization purposes. However, disadvantages of this technique include poor control over the precipitated crystal morphology, size distribution and presence of residual solvents.

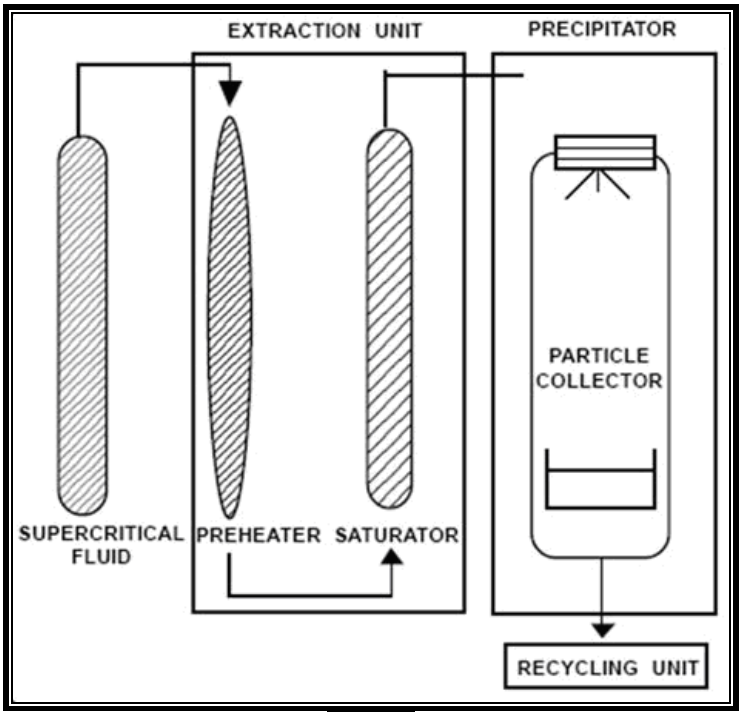

Fig 2: RESS Apparatus

Utilizing similar principle, the solubility of pharmaceutical compounds in supercritical solvents can be decreased by using SFs in gaseous form as antisolvents. It is possible to induce rapid crystallization by introducing the antisolvent gas into a solution containing dissolved solute (Winters MA. et al., 1997). One of the requirements for this approach is that the carrier solvent and the SF antisolvent must beat least partially miscible. This process works in a semi batch mode, with the supercritical solvent introduced into an already existing stationary bulk liquid phase.

Fig 3

This mode offers better control over the particle characteristics as governed by the rate of addition of the SF. However, the liquid phase cannot, in general, be completely removed, and requires additional processing steps before a dry product can be recovered.

3) Precipitation with Compressed Fluid Antisolvent:

The solute can be crystallized from a solution using Antisolvents in two ways:

• Gas antisolvent rechrystallisation (GAS) method; or

• By spraying liquid into the SF antisolvent.

In the latter, the antisolvent rapidly diffuses into the liquid solvent and the carrier liquid solvent a schematic view of the rapid expansion of supercritical solutions (RESS) process.

The SF is pumped through a pre-heater into the vessel containing the solid solute at a particular temperature and pressure. The SF dissolves and gets saturated with the solute, and the resultant solution is introduced into a precipitation chamber by expansion through acapillaror laser-drilled nozzle. Typically, by altering the pressure, the precipitation unit is maintained at conditions where the solute has much lower solubility in the SF.

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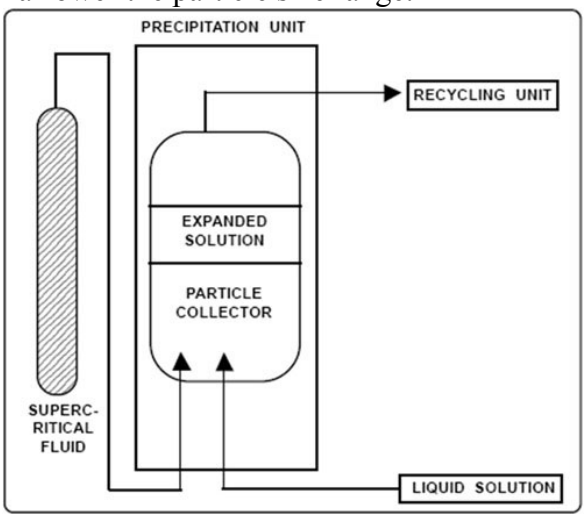

Fig: 4. Precipitation with Compressed Fluid Antisolvent

4) Impregnation or infusion of polymers with bioactive materials:

Some gases cause swelling of polymers or drug carriers at high pressures. This swelling behavior can be exploited –for various such as control delivery of drugs. Substances such as fragrances, pest control agents, and pharmacologically active materials can be impregnated with a solid polymer, which is exposed to a supercritical fluid during the impregnated process.

The polymers evaluated in this study included polypropylene, polyethylene, ethylene-vinyl acetate copolymer, and ethylene-ethyl acrylate copolymer and causes the migration of active material in to the polymer methods the diffusion of active material is increase significantly due to the swelling of polymer or drug carrier matrix when the pressure is reduced, the SCF is driven out slowly resulting in the drug loaded polymer particles it has been found that the swelling is increase with increasing temperature at a constant pressure this approach can be utilize to develop novel control release dosage form to deposit thermolabile material into the polymer (Steckel H. et al., 1997).

5) Solution enhanced Dispersion by Supercritical Fluid:

This technique was developed at the University of Bradford to overcome some of the limitations of the RESS and GAS methods. The drug solution and the SF are introduced simultaneously into the arrangement causing rapid dispersion, mixing and Extraction of the drug solution solvent by SF leading to very high super saturation ratios.

The temperature and pressure together with accurate metering of flow rates of drug solution and SF through a nozzle provide uniform condition for particle formation. This helps to control the particle size of the product and by choosing an appropriate liquid solvent it is possible to manipulate the particle morphology

 # Applications of SCFs to increase the solubility of poorly soluble drugs:

1) Micro particles and Nanoparticles:

Drug and polymeric micro particles have been prepared using SCFs as solvents and antisolvents. Krukonis et al., 1984, first used RESS to prepare 5- to 100-µm particles of an array of solutes including lovastatin, polyhydroxy-acids, and mevinolin.

RESS process employing CO_2 was used to produce poly (lactic acid) (PLA) particles of lovastatin and naproxen (Chen A. et al., 2006). A GAS process was used to produce clonidine-PLA microparticles. In this process, PLA and clonidine were dissolved in methylene chloride, and the mixture was expanded by supercritical carbon dioxide to precipitate polymeric drug particles (Bodmeier R. et al., 1995).

SCF technology is now claimed to be useful in producing particles in the range of 5 to 2,000 nm. This patent covers a process that rapidly expands a solution of the compound and phospholipid surface modifiers in a

liquefied-gas into an aqueous medium, which may contain the phospholipid.
Expanding into an aqueous medium prevents particle agglomeration and particle growth, thereby producing particles of a narrow size distribution (Palakodaty S. et al., 1999). However, if the final product is a dry powder, this process requires an additional step to remove the aqueous phase. Intimate mixture under pressure of the polymer material with a core material before or after SCF salvation of the polymer, followed by an abrupt release of pressure, leads to an efficient solidification of the polymeric material around the core material.

2) Inclusion complexes: For many nonpolar drugs, previously established inclusion complex preparation methods involved the use of organic solvents that were associated with high residual solvent concentration in the inclusion complexes.
Earlier, cyclodextrins were used for the entrapment of volatile aromatic compounds after supercritical extraction. Based on this principle, Van Hees et al 1999, employed supercritical fluids for producing piroxicam and ß-cyclodextrin inclusion complexes. Inclusion complexes were obtained by exposing the physical mixture of piroxicam-ß-cyclodextrin (1:2.5 mol: mol) to supercritical CO_2 and depressurizing this mixture within 15 seconds. Greater than 98.5% of inclusion was achieved after 6 hours of contact with supercritical CO_2 at 15 MPa and 150°C.

3) Solid Dispersions: SCF techniques can be applied to the preparation of solvent-free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Traditional methods suffer from the use of mechanical forces and excess organic solvents. A solid dispersion of carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine (Moneghini et al., 2001). In this method, a precipitation vessel was loaded with solution of carbamazepine and PEG4000 in acetone, which was expanded with supercritical CO_2 from the bottom of the vessel to obtain solvent-free particles.

4) Solubilization of pharmaceuticals: RESS technology has been used for most of pharmaceutical compounds below 60^0C and 300 bars showed a considerable higher solubility (Ker S. et al., 1999). In many a process of solubilization of polar or non-volatile compounds a limited solubility in SC CO_2 is fails to form a homogenous solution under practical conditions. To aid the solubilization in such cases the CO_2-philic solubilizers are being developed which rather the SC CO_2 insoluble substances and make them solubilize in SC CO_2.

5) Micronization of Pharmaceuticals: The RESS process has been shown to be capable of forming micron-sized particals. Krukonics et al., 1984, first extensively studied RESS in micronization of a wide variety of materials, including pharmaceuticals, biologicals, and polymers. He produced uniform submicron powder of estradiol. Loth and Hemgesberg studied the micronization of phenacetin by RESS and compared with jet-milled phenacetin. The main limitation of RESS is the inability to process those materials which are insoluble or very less soluble in the SCF.So for this materials the SAS process has been successfully used to produced micron sized particles like insuline, bovine liver catalase, lysozyme, trypsin, methylprednisolone and hydrocortisone acetate. Insuline were in two crystalline forms; spheroidal (smaller than 1 micron) and needle (5 micron). ASES process has been studied for the preparation of a range of steroids for pulmonary delivery (R.D.Gupta et al., 2008).
The supercritical antisolvent technique has found many applications in the pharmaceutical field, mainly because of the possibility of producing a powder with controlled particle size and distribution using

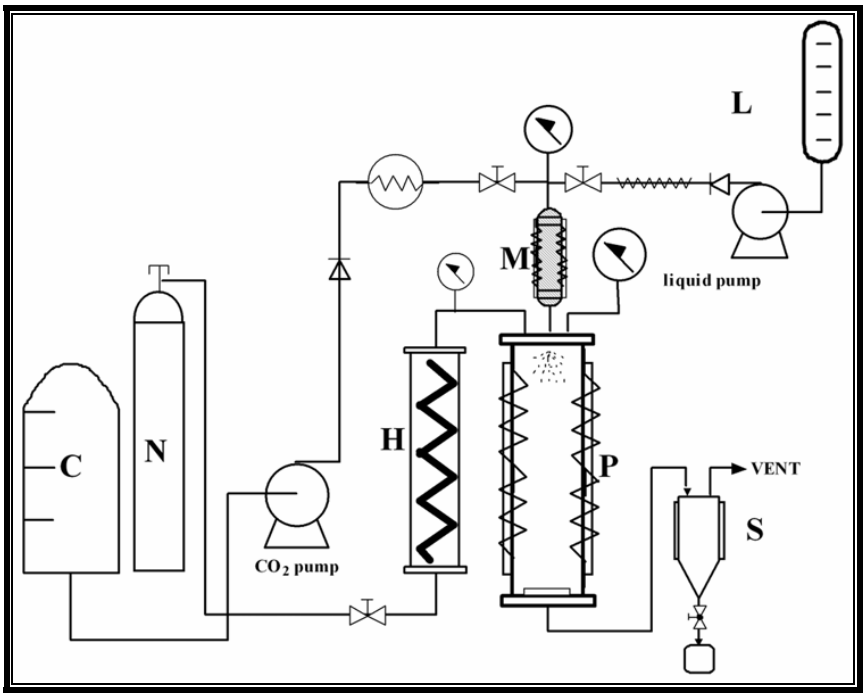

Fig 3: Schematic representation of Gas antisolvent or SAS laboratory scale apparatus: C) CO_2 cylinder; L) liquid solution; N) N_2 cylinder; H) heat exchanger; M) saturator; P) precipitator; S) condenser.

Table: 3. Pharmaceutical compounds micronized and converted in amorphous form using SCF based techniques.

Drug used	Method	Observations and Conclusion	Reference
1. 5 fluorouracil	SEDS	Increases in the solubility as spherical particles are formed.	4. Chen A. et al., 2006
2.α-chymotrypsin	PCA	Nanometric irregular particles interconnected of less than 100 nm	48. Sarkari M. et al., 2003
3. Amoxicillin	SAS	Amorphous spherical particles of 0.2-1.6 µm.	3. Kalogiannis C. et al., 2005
4. Atenolol	ASES	Spherical aggregated particles (mean 42.74 ± 20.62 µm) with enhance solubility.	22. Kikic et al., 2006
5. Budesonide	PCA	Spherical particles mean size of 1-2 µm, results in increases in solubility.	32. Martin T.M. et al.,
6.Cromolyn sodium	ASES	Amorphous particles are formed of size 0.1-20 µm	16. Jaarmo S. et al., 1997
7. Fluticasone-17-Propionate	ASES	Spherical amorphous particles, ribbons particles with different polymorphic form with less	7. Steckel H. et al., 1997

		than 5 μm size.	
8. Lysozyme	GAS	Amorphous spherical particles, more or less agglomerated 200-300 nm.	36. Muhrer G. et al., 2003
9. Rifampicin	SAS	Amorphous particles, coalescent nanometric spherical separated micrometric, with mean particle size of 0.4–1 μm-2.5–5 μm	11. Reverchon et al., 2002
10. Sulfathiazole	SEDS	Form I crystals, amorphous spherical particles >10 μm <2 μm	24 Kordikoski et al., 2001
11.Terbutaline sulphate	SEDS	Water amorphous, crystals, form A, form B, monohydrate 3-10 μm	42 Rehman et al., 2004
12.Tetracycline	SAS	Needle-like particles, irregular amorphous particles 0.6-0.8 μm150 nm.	46 Reverchon et al., 1999
13.Triamcinolone acetonide	ASES	Decrease of degree of crystallinity <5 μm	13 Steckel H et al., 1997
14.CyclosporineA	PGSS	Amorphous spherical particles; mean 4.5 μm	55. Tandya et al, 2006
15. Nifedipine	PGSS	Irregular porous particles; mean 15-30 μm	50.Sencar P., et al., 1997
16. Rapeseed	ScMM	70 empty balloons, form α, 84% crystallinity 8-90 μm	37. Munuklu P. et al., 2007
17.Amphotericin-B	CAN-BD	Irregular particles mean 1 μm	51. Sievers R. et al., 2003
18. Ampicillin	SAA	Amorphous spherical particles mean 0.8-5.6 μm	47. Reverchon et al., 2003
19. Dexamethasone	SAA	Amorphous spherical particles <3 μm	43. Reverchon et al., 2002
20. HMR1031	SAA	Amorphous spherical particles MMAD 1.6-4 μm.	6 Della Porta et al., 2005
21. Hydroxypropyl-β-cyclodextrin	SAA	Water amorphous spherical particles, 95% are in range of 0.1-5 μm.	45 Reverchon et al., 2006
22. Lysozyme	CAN-BD	Water aggregates, divided when sucrose and tween-80 used as additive, amorphous powder1–3 μm.	49 Sellers S.P. et al., 2001
23. Naproxen	CAN-BD	Irregular coalescing particles, primary particles of 0.91 μm, agglomerates 0.5-5 μm.	51 Sievers R. et al., 2003
24. Triclabenzadol	SAA	Irregular crystals <2 μm.	43 Reverchon et al.,

			2002
25. Chitosan	SAA	Spherical particles with decreased degree of crystallinity 9% 0.1-1.5 μm.	44 Reverchon et al., 2006
26.Nifedipine	RESS, SAS and PGSS	Experimental results confirm that dissolution rates do not only depend on the surface area and particle size of the processed powder, but are greatly affected by other physico-chemical characteristics such as crystal morphology and wettability that may reduce the benefit of micronization.	21 Ker, S. et al., 1999
27. Nifedipine and felodipine, fenofibrate.	SCFT	Greater dissolution rate was achieved, by preparation of drug co precipitates with PEG 4000	38 Petra Senar-Bo et al., 1997
28.Nifedipine	PGSS	Co precipitates of nifedipine with PEG 4000 prepared by PGSS process shows enhancement in dissolution rates.	
29. Artemisinin with PVPK25	Jet mill and SCFT	Solid dispersions prepared by this method show promising effect in improvement of intestinal absorption characteristics of artemisinin with PVPK25.	54 T. Van Nijlen et al., 2003
30. Rifampicin	SAS	Particles where amorphous and no degradation occurred as a consequence of supercritical processing.	11 Ernesto et al., 2002
31. Bixin	SEDS	With the increase of SC-CO_2 flow rate the smaller particles are produced while with the increase of solution flow rate leading to formation of bigger particles.	40 Quan Ling et al., 2005
32. Tartaric acid	PCA	Amorphous particles obtain.	12 H. Krober et al., 2002
33. Insulin	SAS	The processed insulin retained its potency, was slightly degraded chemically, and exhibited reversible structural	59 William K. et al., 2002

		changes.	
34. Sulphamethoxazole	SAS	Micronized Sulphamethoxazole exhibited a higher dissolution rate in a simulated intestinal fluid than that of the original compound.	61. Yun et al., 2008
35. Cefonicid	SAS	Sub-microparticles or empty shells ranging from about 0.2 μm to more than 50 μm	10. Ernesto et al., 2004
36. Cephalosporin	SAS	Amorphous spherical Nanoparticles ranging from 0.1 to 14 μm with improved kinetic property.	36. Ernesto et al., 2006
37. Fibroblast growth factor (bFGF)	GAS	Release rate was greater and at constant rate from polymer	14. Hile DD et al., 2000
38. Atorvastatin hemi-calcium	SAS	enhanced bioavailability was attributed to amorphous nature and particle size reduction with narrow particle size distribution	17 Jeong Soo Kim et al., 2008
39. XYZ	SEDS	A true solid solution was obtained with increase in the dissolution rate	18. Juppo AM. et al., 2003
40. Aromatic compounds	SCFT	Studied the effects of moisture content, pressure and temperature on the formation of inclusion complexes with cyclodextrins.	20. Kamihara H. et al., 1990
41. Nifedipine and felodipine and fenofibrate	SCFT	Increase in dissolution rate and hence their bioavailability.	21. Kerc J et al., 1999
42. Naproxen	RESS	Polymeric micro particles with higher solubility	23. Kim JH. Et al., 1996
43. Anthracene Phenanthrene	RESS	Homogeneous crystals of the solid solution	26. Liu G-T. et al., 1997.
44. Oxeglitazar	SAS	quasi amorphous solid dispersions with high density, good flowability and exhibited significantly greater dissolution rate	28. Majerik V et al., 2007
45. Ketoprofen	SCFT	Amorphous solid dispersion which results in Improved dissolution kinetics.	29. Manna L. et al., 2006.
46. Atorvastatin calcium	SAS	The dissolution rates of amorphous Atorvastatin	33. Kim Min-Soo et al., 2008

		calcium nanoparticles were highly increased in comparison with unprocessed drug due to reduction of particle size.	
47. Pheytoin	GAS	Enhanced oral bioavailability.	35. Muhrer G. et al., 2006
48. Plasmid DNA-loaded particles	SEDS	Valuable results were obtained showing the influence of pH effects to be crucial for the recovery of intact DNA	56. Tservistas et al., 2000.
49. Piroxicam	SCFT	Supercritical carbon dioxide was found to be a novel useful complexation method of drugs into B-cyclodextrin.	57. Van Hees et al., 1999.
50. Felodipine	SAS	Amorphous solid dispersion with high dissolution rate	60. Wong et al., 2005
51. Griseofulvin	SAA	No drug degradation and a solvent residue (acetone) less than 800 ppm was measured. A faster dissolution and a better reproducibility of the dissolution profile were observed	Reverchon E et al., 2004
52. Griseofulvin	RESS	Two different morphologies of were observed : quasispherical particles and needles.	17(new) Reverchon E et al., 1995
53. Terbutaline	SAS	No chemical degradation and very narrow volumetric particle size distributions were produced	19(new) Reverchon E et al., 2003

a non-expensive process, solvents already in use in the pharmaceutical protocols and a non-polluting antisolvent. A large selection is reported in Table 3.

Conclusion:

Supercritical fluid technology is considered an innovative and promising way to design drug delivery systems and/or to improve the formulation properties (like solubility) of many drug candidates. SCFs can be used to formulate drug carrier systems, due to their unique solvent properties, which can be altered readily by slight changes in the operating temperature and pressure. The advantages offered my this technology include the formulation of poorly water-soluble compounds, obtaining particles of uniform size and shape, avoiding multistep processes, and reducing the excessive use of toxic organic solvents. SCF technology was successfully applied in the laboratory to prepare microparticles and nanoparticles or liposomes that encapsulate drug in a carrier, inclusion complexes, solid dispersions, microporous foams, and powders of macromolecules. Hence these technologies are expected to form a basis for the commercialization of many water-insoluble drugs in their solid-dispersion formulations in the near future.

List of abbreviations:-

ASES Aerosol Solvent Extraction System

CAN-BD Carbon dioxide Assisted Nebulization-Bubble Drying

GAS Gas AntiSolvent
MCP mixture critical point
PCA Precipitation by Compressed Antisolvent
PF-RESS Pre-Filtering Rapid Expansion of Supercritical Solutions
PGSS Particles from Gas Saturated Solution
RESOLV Rapid Expansion of a Supercritical solution into a Liquid Solvent
RESS Rapid Expansion of Supercritical Solutions
RESS-SC Rapid Expansion of Supercritical Solutions-Solid Cosolvent
SAA Supercritical Assisted Atomization
SAE Supercritical Antisolvent Extraction
SAS Supercritical AntiSolvent
SAS-EM Supercritical AntiSolvent with Enhanced Mass transfer
SC-CO2 supercritical carbon dioxide
SCF supercritical fluid
ScMM Supercritical Melting Micronization
SEDS Solution Enhanced Dispersion by Supercritical fluids
SEM Scanning Electron Microscope
SFE Supercritical Fluid Extraction
SFED Supercritical Fluid Expansion Depressurization
SFEE Supercritical Fluid Extraction from Emulsions

References:

[1] A.Rawat, V. Jaitely, P. Kanaujia, V. Mishra and P. Singh. Supercritical Fluid Technology perspectives and industrial application. The Eastern Pharmacist. 1994; 12: 35-43.

[2] Castor TP, Chu L. Methods and apparatus for making liposomes containing hydrophobic drugs. United States Patent No. 5,776,486 (1998).

[3] Chen A.-Z., Pu X.-M., Kang Y.-Q., Liao L., Yao Y.-D., Yin G.-F. (2006). Preparation of 5 fluorouracil-poly(L-lactide) microparticles using solution-enhanced dispersion by supercritical CO2. Macromol. Rapid Commun. 27, 1254-1259.

[4] Dana E. Knox, Solubilities in supercritical fluids, New Jersey Institute of Technology, Newark, NJ 07102-1982, USA.

[5] Della Porta G., De Vittori C., Reverchon E. (2005). Supercritical assisted atomization: a novel technology for microparticles preparation of an asthma-controlling drug. AAPS PharmSciTech [Electronic Resource] 6, E421-8.

[6] Dohrn R, Bertakis E, Behrend O, Voutsas E and Tassios D. Melting point depression by using supercritical CO2 for a novel melt dipersion micronization process. J of Molecular Liquids 131- 132, 2007,53-59.

[7] Dong-Han Won, Min-Soo Kim, Sibeum Lee, Jeong-Sook Park, Sung-Joo Hwang , Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process, International Journal of Pharmaceutics 301 (2005) 199–208.

[8] Drug Delivery Applications of Supercritical Fluid Technology , Issue Date: Vol. 2 No. 1 January/February 2002.

[9] Ernesto Reverchon and Iolanda De Marco, Supercritical antisolvent micronization of Cefonicid: thermodynamic interpretation of results, The Journal of Supercritical Fluids Volume 31, Issue 2, October 2004, Pages 207-215.

[10] Ernesto **Reverchon**, Iolanda De Marco and Giovanna Della Porta, Rifampicin microparticles production by supercritical antisolvent precipitation. International Journal of Pharmaceutics Volume 243, Issues 1-2, 28 August 2002, Pages 83-91.

[11] H. Krober and U. Teipel, Materials processing with supercritical antisolvent precipitation: process parameters and morphology of tartaric acid, The Journal of Supercritical Fluids Volume 22, Issue 3, April 2002, Pages 229-235.

[12] Hamsaraj Karanth,1 Vikram Subraya Shenoy,1 and Rayasa Ramachandra Murthy1, Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report. AAPS PharmSciTech 2006; 7 (4) Article 87.

[13] Hile DD, Amirpour ML, Akgerman A, Pishko MV. Active growth factory delivery from poly (D,L-lactide-co-glycolide) foams prepared in supercritical CO2. J Controlled Rel. 2000; 66(2-3): 177-185.

[14] J. Ker, S. Sr, Knez and P. Sen, ar-Bo, Micronization of drugs using supercritical carbon dioxide, International Journal of Pharmaceutics Volume 182, Issue 1, 10 May 1999, Pages 33-39.

[15] Jaarmo S., Rantakylä M., Aaltonen O. (1997) Particle tailoring with supercritical fluids: production of amorphous pharmaceutical particles, Proceedings of the 4th International Symposium on Supercritical Fluids, Sendai, Japan, vol. A.

[16] Jeong-Soo Kim, Min-Soo Kim, Hee Jun Park, Shun-Ji Jin, Sibeum Lee, Sung-Joo Hwang, Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using spray-drying and SAS process, International Journal of Pharmaceutics, 359 (2008) 211–219.

[17] Juppo AM, Boiddier C, Khoo C. Evaluation of solid dispersion particles prepared with SEDS. Int J Pharm. 2003;250:385Y401.

[18] Kakumanu VK, Bansal AK. Supercritical fluid technology in pharmaceutical research. CRIPS. 2003;4:8Y12.

[19] Kamihara H, Asai T, Yamagata M, Taniguchi M, Kobayashi T. Formation of inclusion complexes between cyclodextrins and aromatic compounds under pressurized carbon dioxide. J Ferment Bioeng. 1990;69:350-353.

[20] Kerc J, Srcic S, Knez Z, Sencar-Bozic P. Micronization of drugs using supercritical carbon dioxide. Int J Pharm. 1999;182:33Y39

[21] Kikic I., Alessi P., Eva F., Moneghini M., Perissutti B. (2006). Supercritical antisolvent 79 precipitation of atenolol: The influence of the organic solvent and of the processing approach. J. Supercrit. Fluids 38, 434-441.

[22] Kim JH, Paxton TE, Tomasko DL. Microencapsulation of naproxen using rapid expansion of supercritical solutions. Biotechnol Prog. 1996;12(5):650-661.

[23] Kordikowski A., Shekunov T., York P. (2001). Polymorph control of sulfathiazole in supercritical CO_2. Pharm. Res. 18, 682-688.

[24] Lin SY, Kao YH. Solid particulates of drug-b-cyclodextrin inclusion complexes directly prepared by a spray-drying technique. Int J Pharm. 1989;56:249-259.

[25] Liu G, Nagahama K. Solubility and RESS experiments of solid solution in super critical carbon dioxide. J Chem Eng of Jpn. 1997;30:293Y301.

[26] M. Perrut, J. Jung and F. Leboeuf, Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes Part I: Micronization of neat particles Pharmaceutics Volume, 6 January 2005, Pages 3-10.

[27] Majerik V, Charbit G, Badens E, Horvath G, Szokonya L, Bosc N and Teillaud E. Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. J of Supercritical Fluids 40,2007, 101 110.

[28] Manna L, Banchero M, Solta D, Ferri A, Ronchetii S and Sicrdi S. Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO2. J of Supercritical Fluids 2006 article in press.

[29] Maren L. Seibold, analysis of pharmaceutical/polymer solid dispersions produced by supercritical carbon dioxide-assisted techniques,

[30] Markku Rantakyla, Particle production by supercritical antisolvent processing techniques.2004.

[31] Martin T.M., Bandi N., Shulz R., Roberts C.B., Kompella U.B. Preparation of budesonide and budesonide-PLA microparticles using supercritical fluid precipitation technology. AAPS PharmSciTech 3, E18.

[32] Min-Soo Kim , Shun-Ji Jin , Jeong-Soo Kim , Hee Jun Park , Ha-Seung Song , Reinhard H.H. Neubert , Sung-Joo Hwang , Preparation, characterization and in vivo evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process, European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 454–465.

[33] Moneghini M, Kikic I, Voinovich D, Perissutti B, Filipovic-Grcic J. Processing of carbamazepine-PEG 4000 solid dispersions with supercritical carbon dioxide: preparation, characterization, and in vitro dissolution. Int J Pharm. 2001;222(1):129-138.

[34] Muhrer G, Meier U, Fusaro F, Albano S and Mazzotti M. Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: generation of drug microparticles and drug-polymer solid dispersions. Int. J. Pharm. 308,2006, 69-83.

[35] Muhrer G. and Mazzotti M. (2003). Precipitation of Lysozyme Nanoparticles from Dimethyl Sulfoxide Using Carbon Dioxide as Antisolvent. Biotechnol. Prog. 19, 549-556.

[36] Munuklu P. and Jansens P.J. (2007). Particle formation of edible fats using the supercritical melt micronization process. J. Supercrit. Fluids 43, 181-190.

[37] Petra Senar-Bo, Stane Sr, Zeljko Knez, and Janez Ker, Improvement of nifedipine dissolution characteristics using supercritical CO_2, International Journal of PharmaceuticsVolume 148, Issue 2, 28 March 1997, Pages 123-130.

[38] Phillips EM, Stella VJ. Rapid expansion from supercritical solutions: application to pharmaceutical processes. Int J Pharm. 1993;94:1Y10.

[39] Quan Ling Suo, Wen Zhi He, Yan Chun Huang, Chun Ping Li, Hai Long Hong, Yun Xia Li and Ming Da Zhu Micronization of the natural pigment-bixin by the SEDS process through prefilming atomization Powder Technology

Volume 154, Issues 2-3, 6 July 2005, Pages 110-115.

[40] R.D.Gupta, A Review : Supercritical Fluid Extraction Technology; 2008.

[41] Rehman M., Shekunov B.Y., York P., Lechuga-Ballesteros D., Miller D.P., Tan T., Colthorpe P. (2004). Optimisation of powders for pulmonary delivery using supercritical fluid technology. Eur. J. Pharm. Sci. 22, 1-17.

[42] Reverchon E. (2002). Supercritical-Assisted Atomization to produce micro- and/or nanoparticles of controlled size and distribution. Ind. Eng. Chem. Res. 41, 2405-2411.

[43] Reverchon E. and Antonacci A. (2006). Chitosan Microparticles Production by Supercritical Fluid Processing. Ind. Eng. Chem. Res. 45, 5722-5728.

[44] Reverchon E. and Antonacci A. (2006). Cyclodextrins micrometric powders obtained by supercritical fluid processing. Biotechnol. Bioeng. 94, 753-761.

[45] Reverchon E. and Della Porta G. (1999). Production of antibiotic micro- and nanoparticles by supercritical antisolvent precipitation. Powder Technol. 106, 23-29.

[46] Reverchon E., Della Porta G., Spada A. (2003). Ampicillin micronization by supercritical assisted atomization. J. Pharm. Pharmacol. 55, 1465-1471.

[47] Sarkari M., Darrat I., Knutson B.L. (2003). CO_2 and fluorinated solvent-based technologies for protein microparticle precipitation from aqueous solutions. Biotechnol. Prog. 19, 448-454.

[48] Sellers S.P., Clark G.S., Sievers R.E., Carpenter J.F. (2001). Dry powders of stable protein formulations from aqueous solutions prepared using supercritical CO2- assisted aerosolization. J. Pharm. Sci. 90, 785-797.

[49] Sencar-Bozic P, Srcic S, Knez Z, Kerc J. Improvement of nifedipine dissolution characteristics using supercritical CO2. Int J Pharm. 1997;148:123Y130.

[50] Sievers R.E., Huang E.T.S., Villa J.A., Engling G., Brauer P.R. (2003). Micronization of water-soluble or alcohol-soluble pharmaceuticals and model compounds with a low temperature Bubble Dryer. J. Supercrit. Fluids 26, 9-16.

[51] Subramaniam B, Rajewski RA, Snavely K. Pharmaceutical processing with supercritical carbon dioxide. J Pharm Sci. 1997;86:885Y890.

[52] Sunkara G, Kompella UB. Drug delivery applications of supercritical fluid technology. Drug Del Technol. 2002;2:44Y50.

[53] T. Van Nijlen, K. Brennan, G. Van den Mooter, N. Blaton, R. Kinget and P. Augustijns,, Improvement of the dissolution rate of artemisinin by means of supercritical fluid technology and solid dispersions. International Journal of Pharmaceutics Volume 254, Issue 2, 26 March 2003, Pages 173-181

[54] Tandya A., Dehghani F., Foster N.R. (2006). Micronization of cyclosporine using dense gas techniques. J. Supercrit. Fluids 37, 272-278.

[55] Tservistas M, Levy MS, Lo-Yim MYA, O'Kennedy RD, York P, Humphery GO, Hoare M. The formation of plasmid DNA loaded pharmaceutical powders using supercritical fluid technology. Biotech Bioeng. 2000; 72(1): 12-18.

[56] Van Hees T, Piel G, Evrard B, Otte X, Thunus T, Delattre L. Application of supercritical carbon dioxide for the preparation of a piroxicam-beta-cyclodextrin inclusion compound. Pharm Res. 1999;16(12):1864-1870.

[57] Verreck G, Chun I, Peeters J, Rosenblatt J, Brewster ME. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. Pharm Res. 2003;20:810Y817.

[58] William K. Snavely , Bala Subramaniam , Roger A. Rajewski , Michael R. Defelippis , Micronization of insulin from halogenated alcohol solution using supercritical carbon dioxide as an antisolvent, Journal of Pharmaceutical Sciences, Volume 91 Issue 9, Pages 2026 – 2039.

[59] Wong D H, Kim M S, Lee S, Jeong S P and Hwang S J. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int. J. Pharm. 301,2005, 199-208.

[60] Yun-Ping Chang, Muoi Tang and Yan-Ping Chen , Micronization of sulfamethoxazole using the supercritical anti-solvent processm, Journal of Materials Science, Volume 43, Number 7 / April, 2008.