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A Review on: Solubility Enhancement by Implementing Solid Dispersion Technique for Poorly Water Soluble Drug

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ABSTRACT

Solid dispersions have been known to be one amongst the recent means of improving the dissolution rate by enhancement of solubility, and hence the bioavailability of poorly water soluble drugs. According, to – Chiou and Riegelman Solid dispersions are "The dispersion of one or more active ingredients in an inert carrier or matrix, where the active ingredients could exist in finely crystalline, solubilized or amorphous state." This review is the brief compilation of the solid dispersion as a technique of solubility enhancement in the current consensus. It deals with the mechanism of solubility enhancement, various techniques of solubility enhancement and the methods of formulation of solid dispersion. The implications of a deeper understanding of the dissolution mechanisms have been discussed, with particular emphasis on optimization of manufacturing methods along with type of polymer used. With the recent development in the screening of potential therapeutic agents, the number of poorly water soluble drugs have risen sharply and gained large interest due to the challenges in the oral solubility of the drug which leads to the major cause for which the techniques are meant to be implemented. One amongst such techniques is the formulation of solid dispersion for the solubility enhancement.

Keywords: Solid dispersion, poorly water soluble drugs,dissolution, solubility enhancement

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HISTORY

In 1961, the concept of solid dispersion first emerged .Solid Dispersions were proposed to increase the dissolution and oral absorption of poorly-water soluble drugs .As early as in 1961, Sekiguchi et al. developed the concept of solid dispersion of poorly water soluble drugs.

Table 1: SOLUBILITY:

Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Therapeutic efficacy of a drug depends on the bioavailability of the drug which in turn depends on the solubility of the drug candidate. For the absorption of the drug at absorption site it must be present in the aqueous state. Thus, the Release of drug is a crucial step for the oral bioavailability of the drug. Basically poorly water soluble drugs with the low gastrointestinal solubility and high permeability (BCS class II) and drugs with low solubility and permeability (BCS class IV) observe the problem of oral solubility and hence bioavailability. Improvement in the release profile of such drugs it is possible to enhance the solubility and thereby the bioavailability of the drug. According to the monograph of European Pharmacopoeia, about 40% of drugs have aqueous solubility of less than 1mg/ml and 32% have an aqueous solubility less than 0.1mg/ml. although aqueous solubility of more than 1% (1g/100ml) does not show any potential. However, the 1% solubility limit is an arbitrary guideline and in no way represents a universal limitation in terms of solubility and absorption relationship. [1, 17]

Mechanism of solubilization

Solubility of the drug may be defined as the maximum concentration of the drug solute dissolved in the solvent under specified condition of temperature, pH and pressure. The drug solubility in a saturated solution is a static property that is relative to the rate of bioavailability.

The solubility of a weak acid or weak base varies with the fraction of pH.

Solubility of weak acid, total solubility (Cs) is given by:

$$Cs = [HA] + [A^-]$$

Where [HA] = intrinsic solubility of non ionized acid
[A-]= the concentration of its anion

The anion concentration can be expressed in terms of dissociation constant Ka

$$Cs = Co + Ka [Co/H+]$$

Where Co= non ionized acid concentration

- This equation indicates that solubility of weak acid increases with increase in the pH solubility is optimal at higher pH.

Solubility of a weak base is given by the expression

$$Cs = Co + [H+/Ka]$$

- It indicates that the solubility of a weak base decreases with increasing pH and the solubility is optimal at the lower pH.

Thus, solubility is the intrinsic factor of the drug candidate which affects absorption of drug in the body fluids and its oral bioavailability. As the absorption of a drug occurs at the pH at which it remains in the unionized state so the drug must be soluble at a particular body fluids pH from where drug can absorb and show its action. [17]

Some traditional and novel approaches to improve the solubility are:

1. Particle Size Reduction
2. Solid Dispersion
3. Nanosuspension
4. Supercritical Fluid Technology
5. Cryogenic Technology
6. Inclusion Complex Formation Techniques
7. Floating Granules

SOLID DISPERSION

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms.

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and

Sodium Lauryl Sulphate used. There are various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility.[1,2]

Various techniques for the solubility enhancement:[5]

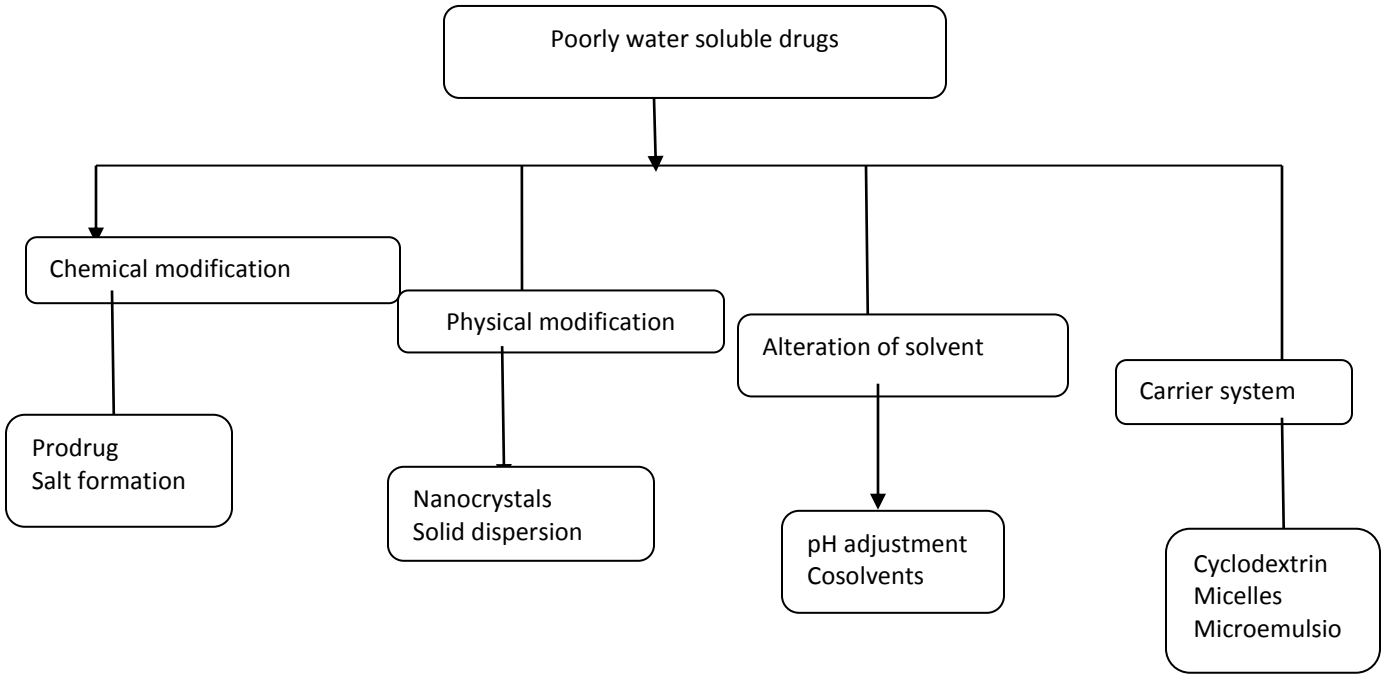

Fig 1: Flowchart Showing Techniques For Solubility Enhancement

PHYSICOCHEMICAL CLASSIFICATION OF SOLID DISPERSIONS

Solid dispersion can be classified as follows:

a) Simple eutectic mixture
b) Solid solution
c) Glass solution
d) Complex formation
e) Amorphous precipitation in a crystalline carrier

a) Simple eutectic mixture:

A simple eutectic mixture can be described as an intimately blended physical mixture of two crystalline components, which are completely miscible in the liquid state, but not in the solid state. When a mixture of A and B with composition E is cooled, A and B crystallize out

simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other.

Differential thermal analysis (DTA) of binary mixtures normally exhibits two endotherms, but a binary mixture of eutectic composition usually exhibits a single endotherm. In the case of a simple eutectic system, the thaw points of binary mixtures of varying compositions are equal to the eutectic temperature of the system.

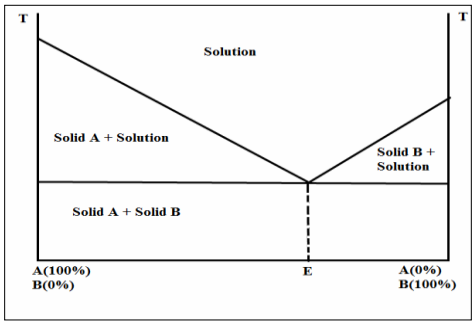

Figure2: Phase diagram for eutectic systems.

b) Solid solutions

Solid solution consists of a solid solute dissolved in a solid solvent. The particle size in solid solution is reduced to molecular level. As the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Solid solutions have also improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility.
Solid solutions can be classified by their miscibility characteristics (continuous or discontinuous) or by the way in which the solute/solvent molecules are distributed in the lattice (interstitial, substitutional or amorphous).

i) *Continuous solid solutions:*

In a continuous solid solution the components are totally miscible with one another in all proportions in both the liquid and solid state. The lattice energy of the continuous solid solution at all compositions is higher than that of the respective pure components in the solid state, because the hetoromolecular bonding strength is higher than the homomolecular one in order to form a continuous solid solution. **Figure 2** shows the hypothetical phase diagram of a continuous solid solution.

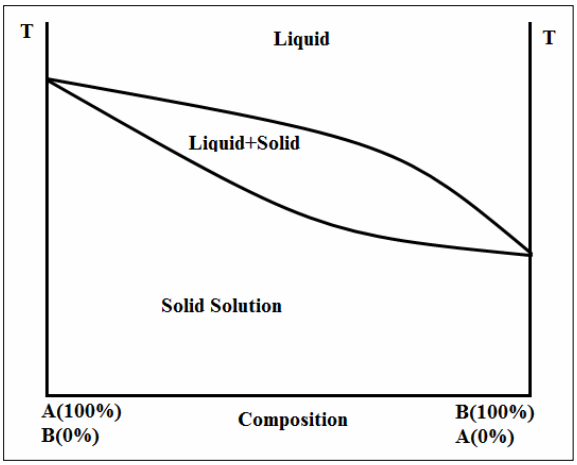

Fig 3: Continuous solid solutions.

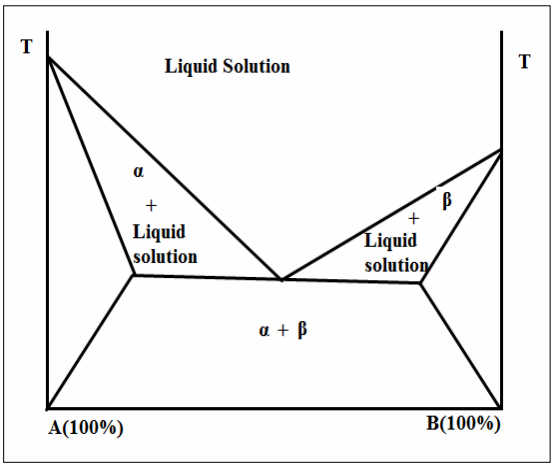

Fig 4: Discontinuous solid solutions.

ii) *Discontinuous solid solution :*

In discontinuous solid solutions, the miscibility or solubility of one component in the other is limited. In figure 3 α and β shows the regions of true solid solutions. The region labelled α is a solid solution of B in A that is component A would be regarded as the solvent and B as the solute. Similarly the region labelled β is a solid solution of A in B. Below a certain temperature, the mutual solubilities of the two components start to decrease.

iii) *Substitutional solid solution:*

In substitutional solid solutions the solid molecules replace the solvent molecule in the crystal lattice of the solid solvent.

iv) *Interstitial solid solution :*

In interstitial solid solutions the dissolved molecules occupy the interstitial spaces between the solvent molecules in the solvent crystal lattice.

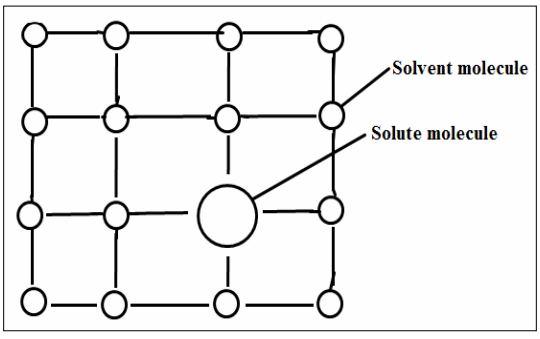

Fig 5: Substitutional solid solutions

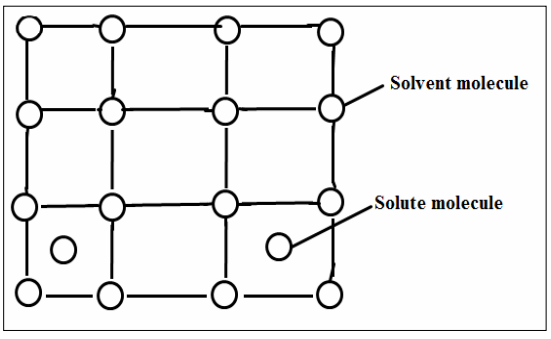

Fig 6: Interstitial solid solutions.

v) *Amorphous solid solutions:*

The solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Polymer carriers are particularly to form amorphous solid solutions as the polymer itself is present in the form of an amorphous polymer chain network.

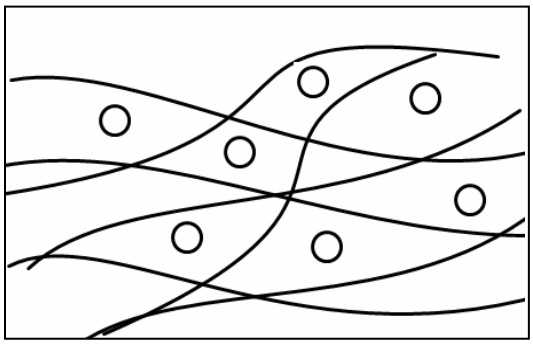

Fig7: Amorphous solid solutions.

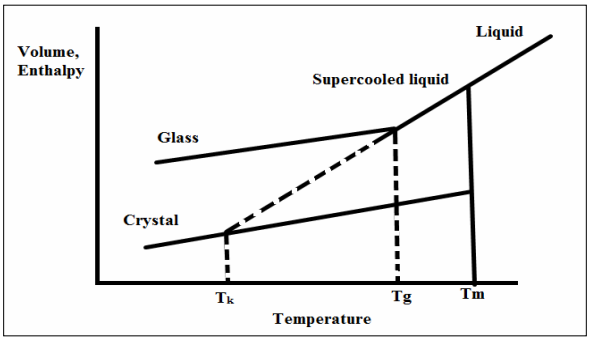

Fig8: Variation between enthalpy&temperature

c) Glass solutions :

A glass solution, also known as an amorphous solution, is a homogeneous system in which a glassy or a vitreous form of the carrier solubilises drug molecules. The glassy or vitreous state is characterized by transparency and brittleness below the glass transition temperature (T_g). The temperature at which a glassy polymer becomes rubbery on heating and a rubbery polymer reverts to a glassy one on cooling is called the glass transition temperature, T_g. The glass transition is not a sharp transition but a gradual transition and is the mid value of the temperature region of transition between brittle and soft. The main advantage of glass solutions over solid solutions is that they do not possess a strong lattice as true solid solutions and hence they do not present this barrier to rapid dissolution. An important disadvantage of glass solutions is that the glassy state is metastable compared to the crystalline state, and depending on its physicochemical properties and storage conditions a glass can convert into a crystalline solid.

d) Complex formation :

These are dispersions in which a drug forms a complex with an inert water soluble carrier in the solid state. The availability of the drug depends on the solubility and stability constant of the complex and the absorption rate of the drug. The dissolution rate of the drug and oral absorption are believed to be enhanced by formation of a water soluble complex with a high dissociation constant. Cyclodextrins are frequently used complex carriers.

e) Amorphous precipitation in a crystalline carrier:

Instead of simultaneous crystallization of the drug and the carrier (eutectic system), the drug may also precipitate in an amorphous form in the crystalline carrier. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.[1,12]

METHOD OF PREPARATION OF SOLID DISPERSIONS

i) Melt method
ii) Solvent evaporation method
iii) Melt evaporation method
iv) Melt extrusion method
v) Melt agglomeration method
vi) Lyophillisation technique
vii) Use of surfactants
viii) Electrospinning
ix) Super critical fluid technology

i) Melt method:

Hot melt method may be used for the dispersion of relatively low melting point with the various carriers for the improvement of solubility of the drug. various carriers such as PEG, Mannitol, Propylene glycol, PVP etc may be used for the formulation of the solid dispersions. In the Hot melt method, carriers are melted at a particular temperature in a china dish and the drug is then dispersed into the molten mixture with a constant stirring. The molten mixture is then poured and cooled immediately to obtain the formed dispersion.[10]

ii) Solvent evaporation method:

Solid dispersions containing 10 and 50% w/w of chlorodiazepoxide was prepared by dissolving accurately weighed amounts of PVP K30 and drug in ethanol. After complete dissolution, the solvent was evaporated under reduced pressure at 60°C in a desiccator. Subsequently, the solid mass was ground and the particle size fraction of <250 µm was obtained by sieving. The sieved ground powders were stored in an oven for at least 48 h. All dispersions were kept at room temperature in a screw-capped glass vial until use. Similar procedure was carried out to prepare chlordiazepoxide solid dispersions containing eudragit E.[14]

iii) Melt Extrusion Method:

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing

zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185°C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm.[23]

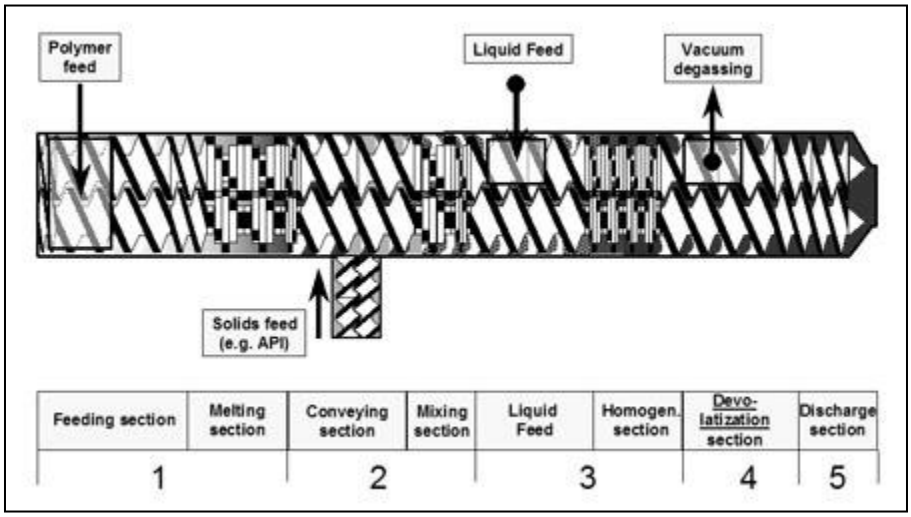

Fig 9: Extruder for the preparation of solid dispersion

iv) Melt Evaporation Method:

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polymer without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polymer. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

v) Melt agglomeration Method:

This study investigated Atomized Melt Agglomeration (AMA) technique in a fluidized bed with top spray atomization of molten carrier, aiming to obtain agglomerates with appropriate tablet pressing characteristics and to improve the dissolution characteristics of a poorly water-soluble drug, lumefantrine. Agglomerates were prepared by the AMA technique using a fluidized-bed system. The temperature of molten carrier was maintained 20±50˚C above its melting point during process. The LMF and lactose were taken into the column of fluidized

bed processor and agglomerated using either PEG 6000 (LMF-PEG) or Poloxamer 188 (LMF-PLM).[15]

vi) Lyophilization of solid dispersions:

Solid dispersion containing different ratio (1:1, 1:3 and 1:5 ***w***/w) of (GLC) and PXM was prepared by the freeze drying method.GLC was weighed and dispersed into 100 mL of PXM solution, the dispersion being stirred with the help of a magnetic stirrer. 25% liquid ammonia was added drop wise and stirred until a clear solution was obtained. The sample was freezed to a temperature of -45˚C and lyophilized in a freeze dryer at a temperature of - 40˚C and vacuum of 90 x 10-3 Mbar. The freeze dried mass was then sifted through 60 mesh sieve and stored in air-tight containers **u**ntil further evaluation.[13]

vii) Use of Surfactants:

Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition and thereby enhancing solubilization. This property is used for enhancing the solubility of poorly water soluble drug by preparing solid dispersion by melt extrusion method. Solid dispersions of a poorly soluble drug were prepared using PVP-K30, Plasdone-S630, and HPMC-E5 as the polymeric carriers and surfactants as plasticizers. The solid dispersions were produced by hot melt extrusion temperatures 10 degrees C above and below the glass transition temperature (Tg) of the carrier polymers using a 16 mm-Haake Extruder. The surfactants tested in this study included Tween-80 and Docusate Sodium. [21]

viii) Super critical fluid technology:

Supercritical carbon dioxide was used as a solvent to load chlorpheniramine maleate (CPM) into Eudragit polymers (E) for controlled release. CPM was loaded into E in ratio of 1:10 using supercritical carbon dioxide as the solvent at various pressures (780 to 5000 psi), temperatures (22°C to 55°C), processing time (0 to12 hours), and the drug polymer ratio (1:1 to 1:10) to form solid dispersions. This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor's dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS).[20]

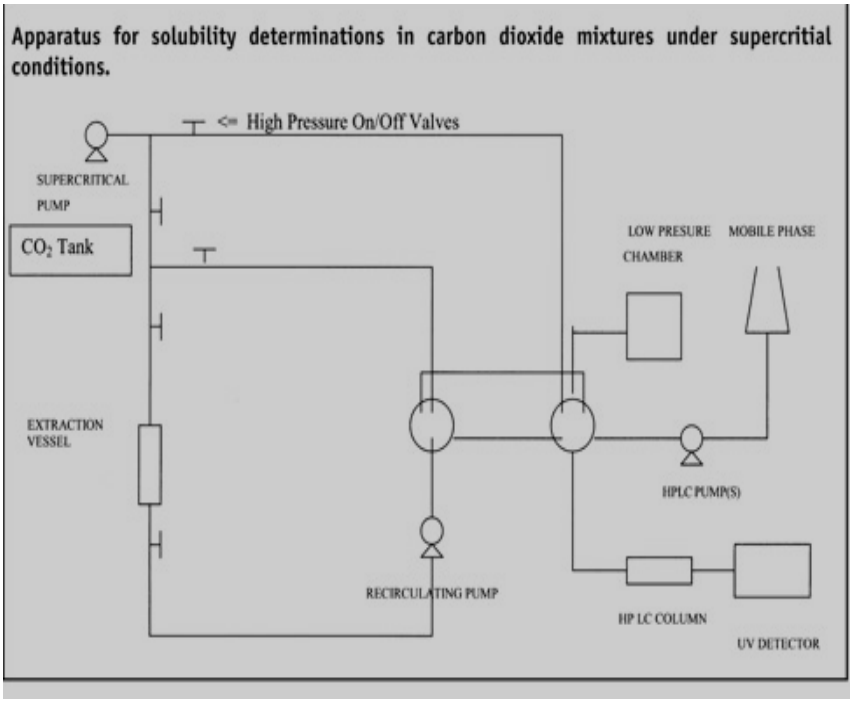

Fig 10: Schematic diagram for super critical fluid technology.

Table2: List of some of the solid dispersion of poorly water soluble drugs prepared by different methods:

Drug	Polymer	Method	Solvent used
Fenofibrate	PEG6000, Poloxamer 407	Melt evaporation, Lyophillization	Chloroform
Glipizid	PEG6000, Mannitol PVPK30	Fusion(melt)method, Solvent evaporation method	Dichloromethane
Acyclovir	PEG6000,PVPK30	Solvent evaporation method	Methanol
Valdecoxib	PVP	Kneading	Water
Flurbiprofen	HPC	Solvent evaporation method	Ethanol
Efavirenz	PEG6000	Solvent evaporation method	Acetone(min.vol.)
Chlordiazepoxide	PVPK30, Mannitol	Co-precipitation method	Ethanol
Itraconazole	Eudragit	Melt method	-
Furosemide	Sodium starch glycolate	Kneading method	Water:ethanol
Tolbutamide	PEG 6000, β-cyclodextrin	Melt method	-

Table 3: Marketed formulation of solid dispersion:[18]

Drug	Brand Name	Company Name	Polymer
Griseofulvin	Griseofulvin tablets	Dorsey/Sandoz and Novartis	PEG
Nelfinavir mesylate	Viracept®	Agouron Pharmaceuticals	
Ritonavir	Norvir®	Abbott Laboratories	
Amprenavir	agenerase	Glaxosmithkline	
Calcitriol	Rocaltrol	Roche	
Cyclosporine	A/I neoral	Novaritis	
Indomethacin	Indomethacin	Eisai Co	
Nabilone	Cesamet	Eli –Lily and Co.	PVP
Troglitazone	Rezulin	Parke Davis	
Lopinavir-Ritonavir	Kaletra	Abott laboratories	PVP-vinylacetate
Itraconazole	Spronox	Janssen Pharmaceutica	Hypromellose
Etravirine	Intelence	Tibotec,yardley	Hypromellose ,MCC
Ibuprofen	Ibuprofen	Abott laboratories	
Verapamil	IsoptinSR-E240	Abott laboratories	
Nimodipine	Nimotop	Bayer	

REFERENCES

[1] Ghaste R Panditraj, Chougule DD, Shah RR, Ghodake DS. Solid Dispersion: An Overview. 2009. (www.pharmainfonet.com).

[2] Chiou WL, Riegelman S. J Pharm Sci 1970;60(9)

[3] Abu TM Serajuddin. J Pharm Sci 1999; 88(10):

[4] Craig Duncan QM. International J Pharm 2002; 231: 131–144.

[5] Tiwari R, Tiwari G, Srivastava B, Rai Awani K. International Journal of PharmTech Research 2009; 1(4): 1338-1349.

[6] Kumar Anuj, Sahoo Sangram Keshri, Padhee Kumud ,Kochar Prithi Pal Singh, Satapathy Ajit , Pathak Naveen. International Journal of Comprehensive Pharmacy 2011; 2(03): 1-7.

[7] Sinha Shilpi, Baboota Sanjula, Ali Mushir, Kumar, Anil and Ali, Javed. J Disp Sci Technol 2009; 30(10): 1458 -1473.

[8] Samba Moorthy U, Madan Mohan Kumawat, Rohit Reddy.T, Someshwar.K, Kumaraswamy D. International Journal of Pharmacy and Pharmaceutical Sciences.2011;3(1): 116-122

[9] Kumar Averineni Ranjith, Shavi Gopal Venkatesh, Usha. Yogendra Nayak, Armugam Karthik, Ranjan Om Prakash, Ginjupalli Kishore, Pandey Sureshwar. International Journal of Drug Delivery 2010; 2(1): 49-57.

[10] Monica Rao, Yogesh Mandage, Kaushik Thanki, Sucheta Bhise. Dissolution Technologies.2010; 1(1): 27-34.

[11] K R Bobe , C R Subrahmanya, Sarasija Suresh, D T Gaikwad , M D Patil, T S Khade , B B Gavitre, V S Kulkarni And U T Gaikwad. International Journal of Comprehensive Pharmacy.2011 ;1(02): (1-6)

[12] Rajnikant C. Patel, Saiyad Masnoon, Madhabhai M. Patel, and Natvarlal M. Patel. www.pharmainfo.net.
[13] Kalyanwat Renu, Patel Sushma. International Journal of Drug Formulation & Research 2010, Vol. 1 (Iii): 1-14.
[14] Farzana S. Bandarkar, Ibrahim S. Khattab. Int J Pharm Pharm Sci.2011; 3(2): 122-127.
[15] Ali Nokhodchi, Roya Talari, Hadi Valizadeh, Mohammad Barzegar Jalali. International journal of Biomedical Science 2007; 3(3)
[16] Sachin Gahoi, Gaurav K Jain, Mayank Singhal, Musarrat H Warsic, Neha Mallick, Roop K Khar, Farhan J Ahmad. Journal of Pharmacy Research 2011; 4(5):1520-1523.
[17] Shikha Aggarwal, G D Gupta, And Sandeep Chaudhary. International Journal of Pharmaceutical Science and Research.2010; 1(8): 1-13.
[18] Anuj Kumar, Sangram Keshri Sahoo, Kumud Padhee, Prithi Pal Singh Kochar, Ajit Satapathy and Naveen Pathak. International Journal Of Comprehensive Pharmacy 2011; 3 (03):1-7.
[19] Tapan Kumar Giri, Amit Alexander and Dulal Krishna Tripathi. International Journal of Pharmaceutical & Biological Archives 2010; 1(4): 309-324.
[20] Surender Verma, Aruna Rawat, Mahima Kaul and Sapna Saini. International Journal of Pharmacy and Technology 2011; 3 (2):1062-1099.
[21] Dr Emilio Squillante, Dr Ketan A Mehta. Drug Development and Delivery 2008;2(5)
[22] Alazar N, Ghebremeskel Chandra Vemavarapu, Mayur Lodaya. International Journal of Pharmaceutics 2007; 328(2):119-129.
[23] Bee T and Neub N. Manufacturing Chemist 2011;1:36-38
[24] Kim EJ, Chun MK, Jang JS, In-Hwa Lee IH, Lee KR, Choi HK. European J Pharm Biopharm 2006; 64: 200–205.
[25] Rabasco AM, Ginrs JM, M Fernfindez-Arrvalo M and Holgado MA. International Journal of Pharmaceutics 1991;67:201-205.