

REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES FOR HYDROPHOBIC DRUGS

Anuj Kumar*, Sangram Keshri Sahoo, Kumud Padhee, Prithi Pal Singh Kochar, Ajit Satapathy and Naveen Pathak

Department of Formulation Research & Development, Jagsonpal Pharmaceuticals Limited, Rudrapur, Uttarakhand, India.

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ABSTRACT

Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drugs. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development.

Keywords: Solubility, cyclodextrin, nanosuspension, hydrophobic drugs, bioavailability.

INTRODUCTION

Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.¹

Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water soluble drug. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form. This review is intended to discuss the various traditional and novel techniques for solubility enhancement of hydrophobic drugs for oral pharmaceutical formulation.

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of hydrophobic drugs. 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

Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent which cause increase in solubility.²

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds. Also, this traditional methods are often incapable of reducing the particle size of nearly insoluble drugs (<0.1mg/mL).³⁻⁵

Micronization is another conventional technique for the particle size reduction. Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility⁵. Decreasing the particle size of these drugs which cause increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for

*Corresponding Author:

Anuj Kumar
Department of Formulation Research & Development,
Jagsonpal Pharmaceuticals Limited, Rudrapur,
U.S. Nagar, Uttarakhand, India.
Contact no: +91-9557957692, Email: anujkumar_a5@rediff.com

drugs having a high dose number because it does not change the saturation solubility of the drug.

These processes were applied to griseofulvin, progesterone, spironolactone and diosmin, fenofibrate. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy.^{6,7}

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.⁸ 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, Plasdones-5630. Many times surfactants may also be used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate are used.

The solubility of celecoxib⁹, halofantrine¹⁰, ritonavir¹¹ can be improved by solid dispersion using suitable hydrophilic carriers. There are various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility.

Hot melt method (fusion method): The main advantages of this direct melting method is its simplicity and economy. The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms.¹² In this method, the physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tableting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system.¹³

An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermostability of the drug and carrier.

Solvent Evaporation Method: Tachibana and Nakumara¹⁴ were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β -carotene in the highly water soluble carrier polyvinylpyrrolidone. Many investigators studied solid dispersion of meloxicam¹⁵, naproxen¹⁶ and nimesulide¹⁷ using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poorly water soluble drugs.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, some

disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms.

Hot melt extrusion: Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

Nanosuspension

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs.¹⁸ This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.^{18,19}

There are various methods for preparation of nanosuspension include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedge).^{20,21}

Precipitation Techniques: In precipitation technique the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.²²

Nanosuspension of Danazol²³ Naproxen^{23,24} prepared by precipitation technique to improve their dissolution rate and oral bioavailability.

Media milling (Nanocrystals or Nanosystems): The method is first developed and reported by Liversidge et al. (1992) the nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media

with the drug resulting into breaking of microparticulate drug to nanosized particles.^{25, 22}

Dissolution rate and bioavailability of poorly soluble drugs such as Cilostazol²⁶, Danazol²³ Naproxen^{23,24} have been improved by reducing their particle size by nanocrystal techniques.

High pressure homogenization: High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required.²⁷ DissoCubes technology is an example of this technology developed by R.H. Müller using a piston-gap-type high pressure homogenizer, which was recently released as a patent owned by Skye Pharm plc.⁸ Other technologies and patents which are based on the homogenization processes are shown in Table 1.²⁷

Table 1. Overview of the technologies and patents/patent applications on which the various homogenization processes are based²⁷

Nanocrystal	Company	Patent/patent application
Hydrosol	Novatis (prev. Sandoz)	GB 22 69 536 GB 22 00 048
Nanomorph™	Soligs/Abbott	D 1963 7517
Nanocrystal™	Élan Nanosystems	US 5,145,684
Dissocubes®	SkyePharma	US 5,858,410
Nanopures	PharmaSol	PCT/EP00/0635
NANOEDGE™	Baxter	US 6,884,436

Dissolution rate and bioavailability of poorly soluble drugs such as Spironolactone²⁸, Budesonide²⁹ and Omeprazole³⁰ have been improved by reducing their particle size by high pressure homogenization.

Combined precipitation and homogenization (Nanoedge): The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (Homogenisation). They are in completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step. (Table 2)

Table 2. Current marketed pharmaceutical products utilizing nanocrystalline formation.³¹

Product	Drug Compound	Company	Nanoparticle Technology
RAPAMUNE	Sirrolimus	Wyeth	Elan Drug Delivery Nanocrystals
EMEND	Aprepitant	Merck	Elan Drug Delivery Nanocrystals
TriCor	Fenofibrate	Abbott	Elan Drug Delivery Nanocrystals

Supercritical Fluid (scf) Process

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and

critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power.^{32,33} Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing particle engineering via SCF technologies for particle size reduction and solubility enhancement.^{34,35} Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS), Rapid Expansion of Supercritical Solutions (RESS), Gas Anti Solvent Recrystallization (GAS) and aerosol supercritical extraction system (ASES)^{36, 37} (Table 3)

Table: 3. Pharmaceutical compounds converted in amorphous form by using Super Critical Fluid based techniques to improve their dissolution & oral bioavailability

Drug Used	Method	References
5 fluorouracil	SEDS	Chen A. et al., 2006 ³⁸
Tetracycline	SAS	Reverchon et al.,1999 ³⁹
Tartaric acid	PCA	H. Krober et al., 2002 ⁴⁰
Sulphamethoxazole	SAS	Yun et al., 2008 ⁴¹
Pheytoin	GAS	Muhrer G. et al., 2006 ⁴²
Naproxen	RESS	43. Kim JH. Et al., 1996 ⁴³

Cryogenic Techniques

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, ultrasonic nozzle), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydrofluoroalkanes, N₂, Ar, O₂, organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying⁴⁴, atmospheric freeze drying⁴⁵, vacuum freeze drying and lyophilisation⁴⁶.

Spray freezing onto cryogenic fluids: Briggs and maxwell⁴⁷ invented the process of spray freezing onto cryogenic fluid. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of aqueous solution.

Spray freezing into cryogenic fluids (SFL): The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability⁴⁸. It incorporates direct liquid – liquid impingement between the atomized feed solution and cyogenic liquid to provide more intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and

free-flowing micronized powders. Hua et al⁴⁹ produced the rapid dissolving high potency Danazol powders by using Spray Freezing into liquid process.

Spray freezing into vapor over liquid (SFV/L): Freezing of drugs solution in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability.⁵⁰ During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.

Ultra-Rapid Freezing (URF): Ultra-rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leading to instantaneous freezing and subsequent lyophilization for removal of solvent forms micronized drug powder with improved solubility. Ultra rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug-carrier solid dispersions and solid solutions. This technique has been investigated for the solubility enhancement of repaglinide.⁵¹

Inclusion Complex Formation Based Techniques

Among all the solubility enhancement techniques inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs.

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α -Cyclodextrin, β -Cyclodextrin, and γ -Cyclodextrin.⁵²

Solubility and oral bioavailability of Glipizide⁵³, Rofecoxib⁵⁴, Piroxicam⁵⁵ and Carvedilol⁵⁶ can be improved by using cyclodextrins inclusion complex. There are various technologies adapted to prepare the inclusion complexes of poorly or poorly water soluble drugs with cyclodextrins.

Kneading method: This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required.⁵⁷ Parik et al.⁵⁸ have reported the dissolution enhancement of nimesulide using complexation method. In laboratory scale kneading can be achieved by using a mortar and pestle⁵⁹⁻⁶¹. In large scale the kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.

Lyophilization/ Freeze drying technique: In order to get a porous, amorphous powder with high degree of

interaction between drug & CD, lyophilization/ freeze drying technique is considered as a suitable^{62,63}. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique are considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent.⁶⁴

Microwave irradiation method: This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 °C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40 °C for 48 hrs. Deshmukh et al.⁶⁵ have developed inclusion complexes of ziprasidone hydrochloride with beta-cyclodextrin and hydroxypropyl beta-cyclodextrin to design the fast dissolving formulation using various superdisintegrants. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product.⁶⁶⁻⁶⁸

Supercritical Antisolvent technique: This method has been introduced in the late 1980s. Since the first experiences of Hannoy et al in 1879, a number of techniques have been developed & patented in the field of supercritical fluid-assisted particle design. In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, nonflammable, inexpensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds.³⁶ In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug cyclodextrin complexes. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power⁶⁹⁻⁷³. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid

solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow.^{74,75}

Floating Granules

Patel Rajanikant et al.⁷⁶ utilized a novel approach for dissolution enhancement of ibuprofen by preparing floating formulation.

Ibuprofen, a weakly acidic, non-steroidal anti-inflammatory drug having high permeability through stomach because it remains 99.9% unionized in stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid - 1.2). Ibuprofen is mostly permeable through stomach but due to its solubility limitation it can't enter into systemic circulation and gastric emptying time is 30 min to 2 hr. After this time ibuprofen goes into small intestine where it is solubilized but can't permeate through its membrane (Ibuprofen having pH dependent solubility and permeability). It was logically decided to design such formulations which remain in stomach for more than 2 hrs because drug was not completely soluble within 2 hrs hence to dissolve completely in stomach region, this can be achieved by making floating dosage form.

Floating ibuprofen granules were prepared by fusion method. 200 mg ibuprofen divided into 50 mg and 150 mg, 350 mg gelucire 44/14 melted and 50 mg ibuprofen

REFERENCES

- Rinaki E, Valsami G, and Macheras P; Quantitative Biopharmaceutics Classification System; the central role of dose/solubility ratio. *Pharm. Res.* 2003; 20:1917.
- Adam M Persky and Jeffrey A Hughes; Solutions and Solubility. <http://www.cop.ufl.edu/safezone/prokai/pa5110/pha5110.htm>
- Blagden N, Gavan P T, York P; Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, *Adv. Drug Del. Rev.* 2007; 59(30): 617-630. 33.
- Aulton M E, *Pharmaceutics: The science of dosage form design*, 2nd edition, London: Churchill Livingstone; 2002: 113-138.
- Dubey R; Pure drug nanosuspensions impact of nanosuspension technology on drug discovery and development. *Drug Del. Tech.* 2006.
- Chaumeil J C; Micronization: a method of improving the bioavailability of poorly soluble drugs, 1998; Apr; 20(3):211-5.
- Vogt M, Kunath K, Dressman J B; Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations, *Eur J Pharm Biopharm.* 2008 Feb; 68(2):283-8.
- Sekiguchi K, Obi N; Studies on absorption of eutectic mixtures. I. A comparison of the behaviour of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, *Chem. Pharm. Bull* 1961; 9: 866-872.
- Gupta P, Vasu Kumar Kakumanu and Bansal A K; Stability and Solubility of Celecoxib-PVP Amorphous Dispersions: A Molecular Perspective, *Pharmaceutical Research*, 2004, 21, 1762-1769.
- Ahmad M Abdul-Fattah, Hridaya N Bhargava; Preparation and in vitro evaluation of solid dispersions of Halofantrine, *International Journal of Pharmaceutics*, 2002, 235, 17-33.
- Sinha S, Ali M, Baboota S, Ahuja A, Kumar A and Ali J, Solid Dispersion as an Approach for Bioavailability Enhancement of Poorly Water-Soluble Drug Ritonavir, *AAPS PharmSciTech*, 2010: 18 March.
- Sekiguchi K, Obi N; Studies on absorption of eutectic mixtures. I. A comparison of the behaviour of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, *Chem. Pharm. Bull* 1961; 9: 866-872.
- Chiou W L, Riegelman S; Pharmaceutical Applications of Solid Dispersion Systems. *J. Pharm Sci* 1971; 60: 1281-1302.
- Tachibana T, Nakamura A; A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of beta-carotene by polyvinylpyrrolidone, *Kolloid-Z. Polym.*, 1965; 203, 130-133.
- Chaumeil J C; Micronisation: a method of improving the bioavailability of poorly soluble drugs, *Methods and Findings in Experimental and Clinical Pharmacology*, 1998; 20,211-215.
- Blagden N, Matas M. de, Gavan P.T., York P, Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, *Advanced Drug Delivery Reviews*; 2007; 10 May.
- Nanosuspension drug delivery Technology and application - Nanotech - Express Pharma Pulse.htm, <http://www.expresspharmapulse.com/>
- Muller R H, Jacobs C and Kayer O; Nanosuspensions for the formulation of poorly soluble drugs. In: F Nielloud,

- G Marti-Mestres (ed). Pharmaceutical emulsion and suspension. New York, Marcel Dekker, 2000; 383-407.
19. Nash R A; Suspensions. In: J Swarbrick, JC Boylan (ed). Encyclopedia of pharmaceutical technology. Second edition vol. 3. New York, Marcel dekker, 2002; 2045-3032.
 20. Chowdary K P R and Madhavi B L R, Novel drug delivery technologies for insoluble drugs. *Ind. Drugs*. 2005; 42(9): 557-563.
 21. Patravale V B, Date A A and Kulkarni R M; Nanosuspension: a promising drug delivery strategy. *J. Pharm. Pharmacol.* 2004; 56, 827-40.
 22. Muller R H, Bohm B H L and Grau J Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. In D. Wise (Ed.) Handbook of pharmaceutical controlled release technology. 2000; 345-357.
 23. Merisko-Liversidge E, Liversidge G G and Cooper E R; Nanosizing: a formulation approach for poorly-water-soluble compounds. *Eur. J. Pharm. Sci.* 2003; 18,113-20.
 24. Liversidge GG and Conzentino P, Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. *Int. J. Pharm.* 1995; 125:309-13.
 25. Patravale V B, Date A A and Kulkarni R M; Nanosuspensions: a promising drug delivery strategy. *J. Pharm. Pharcol.* 2004; 56:827-840.
 26. Jinno J I, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, Toguchi H, Liversidge G G, Higaki K and Kimura T; Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. *J. Control Rel.* 2006; 111:56-64.
 27. Keck C M and Muller R H; Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. *Eur. J. Pharm. Biopharm.* 2006; 62:3 16.
 28. Langguth P, Hanafy A, Frenzel D, Grenier P, Nhamias A, Ohlig T, Vergnault G and Spahn-Langguth H; Nanosuspension formulations for low-soluble drugs: Pharmacokinetic evaluation using spironolactone as model compound. *Drug. Dev. Ind. Pharm.* 2005; 31:319-29.
 29. Müller R H and Jacobs C; Production and characterization of a budesonide nanosuspension for pulmonary administration. *Pharm. Res.* 2002; 19:189-94.
 30. Möschwitzer J, Achleitner G, Pomper H and Müller R H; Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology. *Eur. J. Pharm. Biopharm.* 2004; 58:615-9.
 31. Chingunpituk J, Nanosuspension Technology for Drug Delivery, *Walailak J Sci & Tech* 2007; 4(2): 139-153.
 32. Phillips E M, Stella V J; Rapid expansion from supercritical solutions: application to pharmaceutical processes. *Int. J. Pharm.* 1993; 94:1-10.
 33. Subramaniam B, Rajewski R A, Snaveley K; Pharmaceutical processing with supercritical carbon dioxide. *J. Pharm. Sci.* 1997; 86: 885-890.
 34. Sunkara G, Kompella U B; Drug delivery applications of supercritical fluid technology. *Drug. Del. Technol.* 2002; 2: 44-50.
 35. Manna L, Banchemo M, Solta D, Ferri A, Ronchetti S, Sicrdi S; Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO₂. *J. Supercritical Fluids.* 2006; 78: 67-69.
 36. Dohrn R, Bertakis E, Behrend O, Voutsas E, Tassios D; Melting point depression by using supercritical CO₂ for a novel melt dispersion micronization process. *J. Mole. Liq.* 2007; 131-132.
 37. Wong D H, Kim M S, Lee S, Jeong S P, Hwang S J; Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. *Int. J. Pharm.* 2005; 301: 199-208.
 38. Chen A-Z, Pu X-M, Kang Y-Q, Liao L, Yao Y-D, Yin G-F; Preparation of 5 fluorouracil-poly(L-lactide) microparticles using solution-enhanced dispersion by supercritical CO₂. *Macromol. Rapid Commun.* 2006; 27:1254- 1259.
 39. Reverchon E and Della Porta G; Production of antibiotic micro- and nanoparticles by supercritical antisolvent precipitation. *Powder Technol.* 1999; 106:23-29.
 40. Krober H and Teipel U; 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.
 41. Chang Y-P, Tang M and Chen Y-P; Micronization of sulfamethoxazole using the supercritical anti-solvent process, *Journal of Materials Science*, Volume 43, Number 7 / April, 2008.
 42. 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.
 43. Kim J H, Paxton T E, Tomasko D L; Microencapsulation of naproxen using rapid expansion of supercritical solutions. *Biotechnol Prog.* 1996;12(5):650-661.
 44. Leuenberger H; Spray freeze drying: The process of choice for low water soluble drugs. *J Nanoparticle Res* 2002; 4:111-119.
 45. Mumenthaler M, Leuenberger H; Atmospheric spray-freeze, drying: A suitable alternative in freeze-drying technology. *Int J Pharm* 1991; 72:97-110.
 46. Williams RQ et al. Process for Production of Nanoparticles and Microparticles by Spray Freezing into Liquid US Patent, 20030041602, 2003.
 47. Briggs A R, Maxwell T J; Process for preparing powder blends. Patent US 3721725, 1973.
 48. Rogers T L et al. A novel particle engineering technology: Spray-freezing into liquid. *Int J Pharm* 2002; 242:93-100. 32. Buxton IR and Peach JM. Process and apparatus for freezing a liquid medium. US4470202, 1984.
 49. Hua J, Keith P, Johnston B, Robert O, Williams A; Rapid Dissolving High Potency Danazol Powders Produced by spray freezing into liquid process. *Int J Pharm* 2004; 271; 145-154.
 50. Buxton I R and Peach J M; Process and apparatus for freezing a liquid medium US4470202, 1984.
 51. Purvis T, Mattucci M E, Crisp M T, Johnston K P, Williams R O; Rapidly Dissolving Repaglinide Powders Produced by the Ultra-Rapid Freezing Process. *AAPS Pharm sci* 2007; 8(3):1-9.

52. Uekama K, Hirayama F, and Irie T; Cyclodextrin Drug Carrier Systems, Chem. Rev., 1998, 98, 2045 -2076.
53. Adel M. Aly, Mazen K. Qato, and Mahrous O. Ahmad, Enhancement of the Dissolution Rate and Bioavailability of Glipizide through Cyclodextrin Inclusion Complex, Pharmaceutical Technology JUNE 2003.
54. Rawat S, Jain S K; Rofecoxib-beta-cyclodextrin inclusion complex for solubility enhancement, Pharmazie. 2003 Sep; 58(9):639-41.
55. Doijad R C, Kanakal M M, Manvi I V; Studies on Piroxicam-beta-Cyclodextrin Inclusion Complexes. *Indian Pharmacists*. VI: 2007: 94-98.
56. Wen X, Tan F, Jing Z, Iiu Z; Prepration and study of the 1:2 Inclusion Complex of Carvedilol with β -cyclodextrin. *J. Pharm. Biomed. Anal.* 34: 2004:517-523.
57. Baboota S, Bhaliwal M, Kohli K; Physicochemical Characterization, *in-vitro* Dissolution Behaviour, and Pharmacodynamic Studies of Reficoxib- Cyclodextrin Inclusion Compounds. Prepration and Properties of Reficoxib hydroxypropyl β - Cyclodextrin Inclusion Complex: a technical note. *AAPS Pharm. Sci. Tech.* 6(1) Article 14: 2005; E 83-E 89.
58. Parikh R K, Mansuri N S, Gohel M C, Sonlwala M M; Dissolution enhancement of Nimesulide Using Complexation and Salt Formation Techniques. *Indian Drugs*. 2005; 42:149-53.
59. Fernandes C M, Veiga F J B; Effect of the Hydrophobic Nature of Triacetyl- β -cyclodextrin on the Complexation with Nicardipine Hydrochloride: Physicochemical and Dissolution Properties of the Kneaded and Spray-dried Complexes. *Chem. Pharm. Bull.* 50(12):2002:1597-1602.
60. M, Rangoni C, Maestrelli F, Corti G, Mura P; Development of Fast-Dissolving Tablets of Flurbiprofen Cyclodextrin Complexes. *Drug Dev. Ind. Pharm.* 31: 2005:697-707.
61. Cunha-Filho, M S S, Dacunha-Marinho B, Torres-Labandeira J J, Martinez-Pacheco R, Landin M; Characterization of β -Lapachone and Methylated β -Cyclodextrin Solid-state Systems. *AAPS Pharm Sci. Tech.* 8:2007:1-10.
62. Cao F T, Guo J, Ping Q; The Physicochemical Characteristics of Freeze-Dried Scutellarin-Cyclodextrin Tetracomponent Complexes. *Drug Dev. Ind. Pharm.* 31: 2005:747-56.
63. Rodriguez-Perez A I, Rodriguez-Tenreiro C, Alvarez Lorenzo C, Concheiro A, Torres Labardeira J J; *J. Nanosci. Nanotechnol.* 6: 2006:3179-86.
64. Tsinontides S C, Rajnaik P, Pham D, Hunke W A, Placek J, Reynolds S D; Freeze drying-Principles and Practice for Sucessful Scale up to Manufacturing. *Int. J. Pharm.* 28(1): 2004:1-16.
65. Deshmukh S S, Potnis V V, Shelar D B, Mahaparale P R; Studies on Inclusion Complexes of Ziprasidone Hydrochloride with beta-cyclodextrin and Hydroxypropyl beta-cyclodextrin. *Indian Drugs*. 44:2007:677-682.
66. Wen X, Tan F, Jing Z, Iiu Z. Prepration and study of the 1:2 Inclusion Complex of Carvedilol with β -Cyclodextrin. *J. Pharm. Biomed. Anal.* 34:2004:517-523.
67. Shin-ichi Y, Katsuhiko I, Keiichi M, Hideo T, Akira O. Evaluation of ophthalmic suspensions using surface tension. *Eur. J. Pharm. Biopharm.* 57:2004:377-382.
68. Saharan V A, Kukkar V, Kataria M, Gera M, Choudhary P K; Dissolution enhancement of drugs. Part I: Technologies and effect of carriers. *Int. J. Health. Res.* 2(2):2009:107-124.
69. Tirucherai G S, Mitra A K; Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovier. *AAPS Pharm. Sci. Tech.* 4:2003: E45.
70. Hees T V, Piel G, Evrard B, Otte X, Thunus L, Delattre L; Application of supercritical carbon dioxide for the preparation of piroxicam- β -cyclodextrin inclusion compound. *Pharm. Res.* 16:1999: 1864- 1870.
71. Charoenchaitrakool M, Dehghani F, Foster N R; Utilization of supercritical carbon dioxide for complex formation of ibuprofen and methyl- betacyclodextrin. *Int. J Pharm.* 239: 2009:103-112.
72. N Bandi W, Wei C B, Roberts, L P, Kotra, U B, Kmpella; Preparation of budesonide and indomethacin-hydroxypropyl β -cyclodextrin (HPBCD) complexes using a single- step, organic solvent free supercritical fluid process. *Eur. J Pharm Sci.* 24: 2004: 159-168.
73. Rodier E, Lochard H, Sauceau M, Letourneau J-J, Freiss B, Frages J; A three step supercritical process to improve the dissolution rate of Eflucimibe. *Eur. J Pharm Sci.* 26: 2005;184-193.
74. Al-Marzouqui A H, Jobe B, Dowaidar A F, Maestrelli F, Mura P; Evaluation of supercritical fluid technology as preparative technique of benzocainecyclodextrin complexes-Comparison with conventional methods *J. Pharm. Biomed. Anal.* 43:2007:566-74.
75. Vamsi KM, Gowrisankar D; Role of Supercritical fluids in the Pharmaceutical Research-A Review. *Indian J. Pharm. Edu. Res.* 41 (1): 2007:10-17.
76. Patel Rajanikant, Patel Nirav, Patel N M, Patel M M; A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules, *Int. J. Res. Pharm. Sci.* Vol-1, Issue-1, 57-64, 2010.