

## RECENT APPROACHES OF SOLID DISPERSION: A NEW CONCEPT TOWARDS ORAL BIOAVAILABILITY

SABITRI BINDHANI\*, SNEHAMAYEE MOHAPATRA

Department of pharmaceuticals, Faculty of School of Pharmaceutical Sciences Siksha "O" Anusandhan University, Khandagiri, Bhubaneswar - 751 030, Odisha, India. Email: [sabitribindhani@soa.ac.in](mailto:sabitribindhani@soa.ac.in)

Received: 17 October 2017, Revised: 10 November 2017 and Accepted: 27 November 2017

## ABSTRACT

Solid dispersion (SD) has been a major advanced technology in overcoming dissolution and bioavailability problem of poorly soluble compounds. Formulation of SD in water-soluble carrier has becoming more researched over the past four decades for solubility and relative bioavailability enhancement. By reduction of the size of the drug particle to the minimum level which will enhance drug wettability and ultimately bioavailability will be definitely improved. This review article elaborates recent advanced technology and characterization of SDs and also discusses the problems and their solution for the development of better formulations.

**Keywords:** Solid dispersion, Poorly water-soluble drug, Problems and solution, Preparation and characterization, Future perspective and strategies.

© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2018.v11i2.23161>

## INTRODUCTION

The progress in the treatment of diseases has been evident with an upsurge in development of new drugs. An estimated 40% of these drugs are poorly water soluble especially those belonging to the biopharmaceutics classification system Class II and IV. Although most of the drugs have encouraging experimental data obtained *in vitro*, the *in vivo* results have been disappointing [1]. The attributes include:

1. Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration
2. Drug distribution to other tissues with high drug toxicities (anticancer drugs)
3. Poor solubility of drugs
4. Fluctuations in plasma levels due to unpredictable bioavailability
5. High interpatient variability.

The enhancement of oral bioavailability of such poorly water-soluble drugs is a biggest challenge in the pharmaceutical development [2].

Many solubilization techniques have been described that either change the nature of the solvent environment (cosolvent systems, emulsions, and micellization) or the chemical identity of the dissolved solute (salt formation, complexation, and prodrugs). Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered [3]. Solid dispersions (SDs) contribute by slowing devitrification, enhancing wettability and modulating the properties of the solvent [4]. The development of SDs is most practically viable approaches to enhance the bioavailability of poorly soluble drugs due to high drug loading (e.g. 250 mg per tablet in Incivek) and/or containing drugs with high susceptibility to crystallize indicating high melting point (e.g. 291°C of ivacaftor in kalydeco) Table 1.

## CLASSIFICATION OF SD

Based on the physical state of the carrier the SD is categorized as crystalline SD and amorphous SD. It is classified into a first generation, second generation, third generation, and fourth generation.

## First generation

In the first generation, crystalline carriers were generally used in SDs. Urea and sugars are considered as a first crystalline carrier in the preparation of SD. Urea was used as a first crystalline carrier to form eutectic mixture with sulfathiazole (Sekiguchi and Obi) [5]. Okonogia *et al.* [6] had tried to enhance the dissolution of ofloxacin by using

carrier, urea, and mannitol by SD technique. He had observed that the dissolution rate of ofloxacin was manifold in urea than mannitol based SDs due to the reduction of crystallinity of ofloxacin.

## Second generation

The second generation contains amorphous carrier instead of crystalline one. They have the ability to produce amorphous SD in which drug and carrier are uniformly miscible and soluble to originate a homogenous molecular interaction [7]. Povidone, polyethylene glycol (EG) polymethacrylate is fully synthetic polymer and natural product based polymer include cellulose derivative, such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose or hydroxypropylcellulose (HPC), or starch derivatives like cyclodextrin. Kohri *et al.* [8] had described that the dissolution of all formulation of albendazole has been improved using HPMC and hydroxypropyl methylcellulose phthalate (HPMCP). Table 2 summarizes that nowadays HPMC and HPMCP have been successfully applied in many marketed SD product.

## Third generation

In the third generation, new technology has been adopted to overcome the drawbacks such as precipitation and recrystallization using self-emulsifier and surface active agent. The utilization of these carriers not only improves the dissolution profile but also the physical and chemical stability of the drug. The surfactant used in SD is poloxamer, gelucine44/14 [10], solupus [9], inutec sp1 [13], compritol 888 ATO [11] sodium lauryl sulfate (SLS), d-alpha tocopheryl PEG 1000 succinate (TPGS-1000) [14], polyoxyethylene hydrogenated castor oil, Tween 80, and sucrose laurate is used in SD. Ali *et al.* [12] had investigated that both ibuprofen and ketoprofen dissolution has been enhanced using poloxamer 407 and 188. An inulin derivative inutec sp1 which was discovered as a novel carrier in the research of Van den Mooter [13] de Waard *et al.* [15] observed that the dissolution of sucrose glass based SD by taking SLS was strongly increased compared to a standard tablet.

## Fourth generation

In the fourth generation, the aim of introducing SD is for solubility enhancement and extended release in a controlled manner. In this system, the poorly water-soluble drug is dispersed in either water-soluble carrier or water-insoluble carrier [16]. The water-insoluble carrier used in SD is ethyl cellulose, eudragit RS, eudragit RL, HPC, polyethylene oxide (PEO), and carboxyvinyl polymer (carbomer). Cui *et al.* [17] had formulated sustained release nifedipine (NTR)

Table 1: FDA approved medicines that use solid dispersion technologies

Product	Drug	Polymer	Dose (mg)	API Tm(°C)	Dispersion method
Novir	Ritonavir	PVP-VA64	100	122	Hot melt extrusion
Kaletra	Lopinavir/ritonavir	PVP-VA64	200/50	125/122	Hot melt extrusion
Incivek	Telaprevir	HPMC-AS	250	246	Spray drying
Nivadil	Nilvadipine	HPMC	4	173	Solvent evaporation method
Zelboraf	Vemurafenib	HPMC-AS	210	272	Co-precipitation
Kalydeco	Ivacaftor	HPMC-AS	150	291	Spray drying
Intelence	Etravirine	HPMC	100	265	Spray drying
Onmel	ITZ	HPMC	200	166	Hot melt extrusion
Prograf	Tacrolimus	HPMC	5	128	Spray drying
Zortress	Everolimus	HPMC	0.75	115	Spray drying

ITZ: Itraconazole, FDA: Food and drug administration, HPMC: Hydroxypropyl methylcellulose, AS: Antisolvent

Table 2: Successfully prepared marketed solid dispersion product using HPMC and HPMCP

Product	Drug	Type of carrier	Dosage form
Intelence	Etravirine	HPMC	Tablet
Zelboraf	Vemurafenib	HPMC AS	Tablet
Incivek	Telaprevir	HPMCAS-M	Tablet
Crestor	Rosuvastatin	HPMC	Tablet
Nivadil	Nilvadipine	HPMC	Tablet
Rezulin	Troglitazone	HPMC	Tablet
Prograf	Tacrolimus	HPMC	Capsule
Sporanox	ITZ	HPMC	Capsule
Certican	Everolimus	HPMC	Tablet
Isoptin SR-E	Verapamil	HPC/HPMC	Tablet
Cesamet	Nabilone	PVP	Tablet
Gris-PEG	Griseofulvin	PEG	Tablet
Afeditab CR	Nifedipine	Poloxamer/PVP	Tablet
Fenoglide	Fenofibrate	PEG	Tablet
Kaletra	Lopinavir/Ritonavir	PVPVA	Tablet

HPMC: Hydroxypropyl methylcellulose, HPMCP: Hydroxypropyl methylcellulose phthalate, AS: Antisolvent, HPC: Hydroxypropylcellulose, PVP: Polyvinylpyrrolidone vinyl acetate, PEG: Polyethylene glycol, ITZ: Itraconazole

microsphere using HPMC - 55 and Aerosil for improving dissolution of NTR while Eudragit RSPO and ethyl cellulose were used as the retarding agent to control the release of the drug.

#### ADVANTAGES OF SD

In contrast to other technique, such as salt formation, particle size reduction, and solubilization for enhancement of bioavailability. SD flash many more valuable advantages to become one of the most promising strategies:

1. SD technique can reduce the size of the particle for enhancement of bioavailability.
2. Due to supersaturation, the size of the precipitated particle cannot be affected. So that the dissolution rate is always higher [18].
3. It will improve the drug wettability by increasing the water absorption capacity.
4. It will reduce agglomeration by incorporating surfactant and emulsifier.
5. The crystalline structure of the drug is reduced to amorphous form.
6. It improves the porosity by rapid evaporation of solvent.
7. It improves dissolvability in water of a poorly water-soluble drug in pharmaceutical.
8. By incorporating polymer and other excipients, it will improve mask of the taste of the drug substance.
9. To promote and develop release of sustained release dosage form.
10. It stabilizes the unstable product.

#### DISADVANTAGES OF SD

During storage and processing (temperature and humidity stress) the amorphous state may undergo recrystallization due to the presence of

moisture in amorphous which effect on storage stability of amorphous particle [19].

The physical state, i.e., its crystallinity and dissolution characteristic of a drug must be affected due to phase separation, crystal growth, or a change from metastable form to stable form [20].

During formulation sometimes it may form hard lump which is very difficult to break on a large scale. In melting method, drug and carrier produce thermal instability. Solvent residue is present after solvent evaporation method.

#### APPROACHES TO OVERCOME THE COMMON OBJECTION ARISE FROM SD

1. To prevent crystallization and phase separation, the polymer must be miscible with drug. If the polymers have high glass transition temperature (T<sub>g</sub>) compared to API, the molecular mobility is decreased, and the miscibility is increased [21].
2. Vasanthavada *et al.* [22] had investigated that the phase separation rate proportional to the drug-polymer interaction and the drug content of the dispersion by taking griseofulvin-polyvinylpyrrolidone (PVP) and ibuprofen-PVP SDs.
3. Surfactants and emulsifier also reduce crystallinity by improving miscibility of drug and polymer.
4. Surface active agent can also increase the solubility of drug and carrier in an organic solvent in the solvent method.
5. Surface active agents also increase drug wettability and inhibit the precipitation process by adsorbing the surface of drug particle and forming micelles encapsulating drugs.
6. Mura *et al.* [23] explained the effect of non-ionic surfactant including SLC, dioctyl sulfosuccinate on the ketoprofen-PEG. They had shown that the dissolution rate of ketoprofen-PEG is improved.
7. There are many techniques developed to increase solidification process (cooling and solvent removal) such as ultrarapid freezing to prevent recrystallization of drugs.

#### PREPARATION TECHNIQUES

SD is a very highly efficient technique whose methods have been developed from various years. Nowadays some novel techniques have been introduced for preparation of SD. SD is prepared by three methods such as melting method, solvent evaporation method, and solvent melting method.

#### MELTING TECHNIQUE

The melting method involves the preparation of physical mixture by melting drug into the water-soluble carrier at a temperature above eutectic point. Then, the melted liquid is going to be solidified, crushed, pulverized, and sieved [24]. Kolašinac *et al.* [25] had investigated that solubility and dissolution rate of desloratadine have been increased by using poloxamer p. 188 and poloxamer p. 407 by applying melting method at low temperature (70°C). There are several methods which

are developed to overcome its limitation. They are hot melt extrusion method, Meltrex™ and melt agglomeration method.

#### Hot melt extrusion method

It is a complete system in which both the drug and carrier are simultaneously melted, homogenized and extruded in the form of tablets, rods, pellets, and blended with different intention [26]. Ye *et al.* [27] had described a Novel Method of Continuously Preparing Nanocrystal SDs of poorly soluble drug Efavirenz. They had combined high pressure homogenization and hot melt extrusion (HME) which was proved to be a promising novel method for the production of nanocrystals SD. Desai *et al.* [28] had formulated solid solution of Ritonavir for enhancement of solubility by hot melt extrusion method. They had shown that the solubility of Ritonavir was increased by formulating a solid solution with a novel polymer Soluplus due to its low hygroscopicity and low glass transition temperature which made it suitable for hot melt extrusion.

#### Meltrex™

It is an advanced technology which is based on the principle of hot extrusion technology. This process is applied those drugs which are sensitive to oxidation and hydrolysis because oxygen and moisture can be eliminated during the process. In this system, the two independent hoppers and a special twin screw extruder allow conveying the extruded mass continuously throughout the extrusion channel [29]. The temperature of all barrels may be controlled from low temperature (30°C) to high temperature (250°C).

#### Melt agglomeration

It is a feasible method in which the carrier acts as a meltable binder. Melt agglomeration is processed in three ways in a rotary processor. It is processed by adding the molten carrier containing the drug to the heated excipients [30] or adding the molten carrier to a heated mixture of drug and excipients or heating a mixture of drug, carrier, and excipients to a temperature within or above the melting range of the carrier. Helle *et al.* [31] had produced SD of a poorly water-soluble drug, Lu-X by melt agglomeration of Lactose monohydrate and Lu-X with Rylo MG12, Gelucire 50/13, PEG 3000, or poloxamer 188. The result showed that the agglomerates containing SD had improved dissolution rates compared to physical mixtures and pure drug.

#### SOLVENT EVAPORATION TECHNIQUE

In this method, the drug and carrier are solubilized in an organic solvent. The solvent used in this method is ethanol, methanol, acetone, ethyl acetate, and methylene chloride [32]. Some surfactants are used such as Tween 80 and SLS which increases the solubility of drug and carrier in solvents. For fast removal of solvent from solution, some of the methods have been developed such as centrifugal spinning method, electrostatic spinning method, supercritical antisolvent (SC-AS) method, SC fluid technology, spray freeze-drying (SFD), ultra rapid freezing, freeze-drying, spray drying, coprecipitation method, and fluid bed coating. In Table 3, Different solvent evaporation technique are used in recent article for improvement of bioavailability of different poorly soluble drug.

#### Centrifugal spinning technique

Centrifugal spinning method is an alternative technique to fabricate nanofibers from various material and high cost [33]. In this method, the spinning fluid is lodged in rotating spinning head. When the speed of rotation reached a critical value, the centrifugal force reduces the surface tension of spinning fluid. So that a liquid jet is ejected from the nozzle tip of the spinning head. Then, the liquid jet undergoes stretching process and is deposited on the collector to produce solidified nanofibers. It is simple and produces rapid fabrication of nanofibers for various applications

Jiang *et al.* [34] had used a centrifugal spinning method instead of electrospinning method due to difficulty in high scale-up of carbon

nanofibers. They had prepared tin-containing carbon nanofibers from tin chloride polyacrylonitrile precursor solutions with an excellent reversible capacity of 607 mAh g<sup>-1</sup> and high specific capacity of 430 mAh g<sup>-1</sup>. Hence, they had investigated that this method shown great potential in large-scale nanofibers production.

#### Electrostatic spinning technique

Electrostatic spinning method is a finest technique and considered a combination of SD technology and nanotechnology. In this process, when electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed and collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandrel. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. Paaver *et al.* [35] had used electrospinning technique, for preparing HPMC based polymeric nanofibers of a poorly water-soluble drug Piroxicam (PRX). They had concluded that electrospinning can be used to fabricate supersaturating controlled release-SD (CR-SD) nanofibers of PRX and HPMC and to stabilize the amorphous state of PRX.

#### SC-AS method

The SC ant solvent technique is a very impressionable technique for micronization of drug product. In this method SC-CO<sub>2</sub> is used as solubilizing solvent or antisolvent. The SC-CO<sub>2</sub> is quickly mixed up with an organic solvent which causes precipitation of solutes by ant solvent effect [36]. Then SC-CO<sub>2</sub> efficiently extracts organic solution to obtain completely solvent-free products. This method can also be used to encapsulate or coprecipitate different active compounds and carrier materials, thus producing micro composites and microcapsules.

#### SC fluid technology

Supercritical fluid technology exhibits magnificent opportunities to improve the drug delivery sector. This method uses CO<sub>2</sub> as solvent whose temperature and processor are above the critical point. Under lower pressure, the rapid nucleation of the dissolved drug and carrier in CO<sub>2</sub> leads to the formation of SD particle with a desirable size distribution in a very short time. Gang *et al.* [37] had applied supercritical fluid technology for improving the dissolution and bioavailability of silymarin using a carrier, polyvinylpyrrolidone K17 and supercritical CO<sub>2</sub>. The result was shown that the bioavailability of silymarin was increased using SC fluids. The ability to rapidly vary the solvent (or antisolvent) strength and, thereby, the rate of supersaturation and nucleation of dissolved compounds is exploited as an alternative technology for particle formation under various names that are essentially based on three key process concepts:

1. Precipitation from SC solutions-rapid expansion of SC solution (RESS);
2. Precipitation from saturated solutions using SCF as an antisolvent-gas antisolvent, precipitation with compressed antisolvent, SC antisolvent, aerosol solvent extraction system (ASES), and solution enhanced dispersion by SC fluids process; and
3. Precipitation from gas-saturated solutions - particles from gas-saturated solutions (PGSS).

The applicability of RESS for preparation of SDs is limited by the very low or negligible solubility of most drugs and polymers in the commonly used SC CO<sub>2</sub>. In the PGSS process, the rapid cooling and expansion of CO<sub>2</sub> produces fine particles with a narrow particle size distribution and, thereby, avoids the comminution step.

#### SFD

SFD is one of the most efficient technique that originates stable and unique powder product. This method increases freezing temperature and reduces the particle size of the drug particle without using frictional and mechanical forces. Shaofeng *et al.* [38] had used the spray-freeze-drying technique by preparing HPC based microparticles (MSM) loaded

**Table 3: Recent article on preparation of solid dispersion for poorly soluble drug using different solid dispersion technique**

Drug	Carrier	SD technique	Reference
Silymarin	Polyvinylpyrrolidone K17	SC fluid technology	Gang et al. [37]
Polypeptide-K valsartan	Trehalose, tween-80 PEG 6000 HPMC 100KV	Spray drying Freeze-drying	Kaur et al. [41] Wei-Juan et al. [40]
Curcumin	Eudragit® EPO	Solvent evaporation method	Li et al. [59].
Tadalafil	PVP/VA 630, Mallic acid or meglumine and Aerosil 200	Solvent evaporation method	Choi et al. [54]
Poorly soluble drug	HPC	Spray freeze drying	Shaofeng et al. [38]
Pseudomonas podoviridae phage PEV2	Trehalose, mannitol, l-leucine	SFD and spray drying	Leung et al. [63]
Paracetamol	Ethyl cellulose, mesoporous silica	Fluid bed system	Hacene et al. [60]
ITZ, OLZ PRX	Sucrose	Centrifugal spinning method	Marano et al. [61]

HPMC: Hydroxypropyl methylcellulose, HPMCP: Hydroxypropyl methylcellulose phthalate, AS: Antisolvent, PVP: Polyvinylpyrrolidone vinyl acetate, PEG: Polyethylene glycol, HPC: Hydroxypropylcellulose, PRX: Piroxicam, SC: Supercritical, SFD: Spray freeze drying, PVPVA: Polyvinylpyrrolidone vinyl acetate, PEG: Polyethylene glycol, OLZ: Olanzapine, ITZ: Itraconazole, SD: Solid dispersion

poorly soluble drug nanocrystals. They had concluded that the spray-freeze-dried composite particles with HPC ratio of 1:2, 1:1, and 2:1 possessed excellent redispersibility and produced cage-like MSM.

#### Ultra rapid freezing

In this technique, the frozen particles are collected by applying drug-polymer solution to a solid cryogenic substrate. Then, the solvent is removed by lyophilization. Badens *et al.* [39] compared SFD with SC ant solvent method on Oxeglitazar. They investigated that SFD shown lower crystallinity and higher dissolution rate.

#### Freeze-drying

This process involves immersing the drug carrier solution in liquid nitrogen until the solution at frozen state. Then, the frozen solution is then lyophilized. The best advantage is that it reduces the risk of phase separation and disadvantage is that the most of the organic solvent do not stay frozen due to low freezing temperature. Wei-Juan *et al.* [40] had improved the dissolution rate and oral bioavailability of Valsartan using PEG 6000 (PEG 6000) and HPMC 100KV as hydrophilic polymers, without using any organic solvents. It was shown that the Valsartan SDs exhibited significantly higher values of  $AUC_{0-24h}$  and  $C_{max}$  in comparison with the pure drug.

#### Spray drying

It is one of the most efficient technologies for manufacturing of SD. In this technique, the drug carrier solution is passed through the nozzle and atomized into very fine droplets with the increased surface area. These droplets are going for evaporation process and produce SDs commercially available spray dryer such as incivek and intelence which is utilized for production of SDs. Kaur *et al.* [41] had presented the formulation of SD containing polypeptide-k to enhance its aqueous solubility using trehalose and Tween-80 they had concluded that the optimized batch of formulation had exhibited higher solubility in water as well as various aqueous buffers as compared to pure polypeptide-k. Ramesh *et al.* [42] had enhanced the dissolution rate of Etravirine by converting it from crystalline to amorphous form by spray drying method. They had used various polymers such as Solupus and Povidone which convert it into highly soluble amorphous form. They had suggested that spray drying method is an efficacious method which enhances the solubility as well as the release rate of Etravirine.

#### Fluid bed coating

In this method, the solution mixture of drug and carrier is sprayed through a nozzle onto the surface of nonpareil pellet in a fluid bed coating. Li *et al.* [43] had prepared resveratrol (RES) mesoporous silica MSM SD by fluid bed coating method. They had found that RES mesoporous silica MSM shown higher drug loading and more complete dissolution in comparison with solvent equilibrium method.

#### MELTING SOLVENT METHOD

It is a combinational technique of the melting method and solvent method. In this combo technique, first, drugs are dissolved in suitable solvent and mixed with a molten carrier. Then remove the solvent and solidified to form SD. The benefit of this technique is that it protects the drug from thermal degradation by lowering the temperature and mixing time.

#### Surface-active carriers

A surface-active carrier may be preferable in almost all cases for the SD of poorly water-soluble drugs. The surface-active and self-emulsifying carriers for SD of poorly water-soluble drugs have been of great interest in recent years. Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-1000 succinate TPGS. Gelucire 44/14 (Gattefosse' Corp, Gennevilliers, France) has commonly been used in SD for the bioavailability enhancement of drugs [44-46]. Gelucire 44/14 is a mixture of glycerol and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopoeia as lauroyl macroglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value. Vitamin E TPGS national formulary Eastman, Kingsport, TN) is prepared by the esterification of the acid group of *d*-R-tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point, however, is relatively low (38°C), and it may require mixing with other carriers to increase melting temperatures of formulations.

#### CHARACTERIZATION OF PHYSICOCHEMICAL PROPERTIES:

Many instrumental and analytical techniques are used to characterize the physicochemical properties of SD. They are differential scanning calorimetry (DSC), Modulated DSC (MDSC), powder X-ray diffraction (PXRD), and other technique such as Fourier transformed infrared spectroscopy (FTIR), attenuated total reflection (ATR)-FTIR spectroscopy, Solid state nuclear magnetic resonance, and thermal gravimetry analysis (TGA).

#### DSC

It is a thermoanalytical technique which is used to measure the temperature and heat flow associated with a transition in material as a function of time and temperature [47]. Berndl *et al.* [48] had investigated that the endotherm of SD of Itraconazole is which means that it assumes lower endotherm property which led to bioavailability improved.

#### MODULATED MDSC

Modulated DSC is a novel thermal technique which provides an exciting new way to significantly increase the basic understanding of material

properties. Guinot and Lavillar [49] had described that this method was successfully used to detect and quantify amorphous phase transition. It has significant benefits over conventional DSC. These include:-

- More accurate measurement of crystallinity of semi-crystalline polymer.
- Thermal conductivity is measured.
- Determination of heat flow and heat capacity in a single experiment.
- High resolution is detected without compromising sensitivity.
- Weak transition can be detected as compared to standard DSC.

#### PXRD

It is used to indicate phase identification, crystallinity, phase transition, and determination of crystal structure of a drug in SD. It provides diffraction peaks that indicate crystalline compound with characteristic fingerprint region. The drug crystallinity can be individually identified from the carrier crystallinity and differentiate the amorphous and crystalline state of the drug in SD [18].

#### SPECTROSCOPY (FTIR)

It is a technique which is used to investigate the physical and chemical interaction between drug and carrier. FTIR identified hydrogen bonding between drug and carrier which is more important to describe its physical state and stability of the drug. Miyazaki *et al.* [50] investigated the crystalline state of NTR enantiomer in the presence of PVP, HPMCP, and HPMC. FTIR result was shown that hydrogen bonding between PVP and NTR crystal in PVP based is lowered as compared to HPMC and HPMCP based SD.

#### ATR-FTIR

Nowadays IR measurement are performed in ATR mode. It is a simple and novel technique of sampling in which all types of samples (e.g. solids, liquid, powders, pastes, pellets, slurries, and fibers) are placed undiluted on the ATR crystal. The measurement is typically performed within a few seconds. The advantages of ATR-FTIR technique on conventional FTIR technique is fast sampling with no preparation, excellent sample to sample reproducibility, and minimal operator induced variation. Hifumi *et al.* [51] had presented the novel application of ATR-FTIR spectroscopic imaging to study the drying process and dissolution behavior of polymer-based film of ibuprofen. Fig. 1 shows analysis of the purified membrane protein by ATR-FTIR method.

#### THERMAL GRAVIMETRY ANALYSIS (TGA)

It is a thermal analysis technique which provides information about the stability of the drugs and carrier as well as their physical and chemical process involved in the preparation of SD. Frizon *et al.* [52] investigated the thermal stability of Loratadine using TGA method. The result shown that Loratadine has been stable up to 203°C and has no chemical interaction between drug and polymer.

#### SOLID STATE NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

It is a technique which provides detailed structural information about SD of pharmaceutical small molecules. It is a characterization tool for elucidating the structure of amorphous SD. It is used for identification, characterization and quantification of various solid forms of drug candidates (polymorphs, hydrates, solvate, salt, cocrystal, amorphous, mesomorphous, etc.) during drug development [53].

Hence, physicochemical evaluation is essential for SD to investigate the pharmaceutical applicability and thoroughly understand the pharmaceutical mechanism of drug dissolution enhancement and physicochemical stability.

#### FUTURE PERSPECTIVE AND STRATEGIES

Due to the existence of most of the poorly water-soluble drug, the SD has been grown with much interest toward improving dissolution

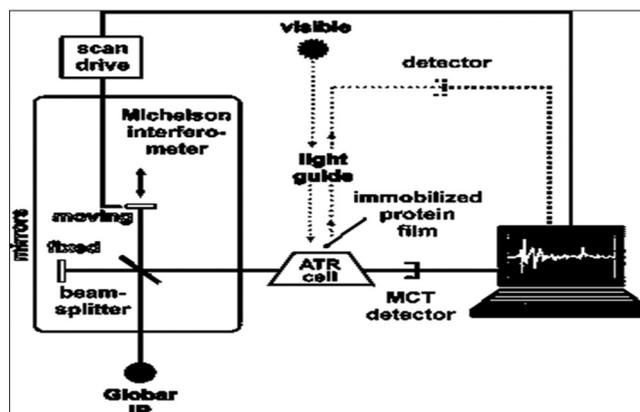


Fig.1: Schematic diagram of attenuated total reflection-Fourier transformed infrared analysis

and bioavailability. Hence, many novel carrier, additives, and new preparation technique are applying for this purpose.

In recent year some novel carrier such as Surplus® inutec sp1 or Kollicoat® IR in SD for improving and expanding the SD. Choi *et al.* [54] had applied solvent evaporation method for improving the solubility of Tadalafil (TDF), using hydrophilic carriers (PVP/VA S-630) and assistants (malic acid or meglumine). It was concluded that the optimal TDF-SD formulation had exhibited a greater dissolution rate (89.1±3.9%) than TDF alone. Nowadays many novel excipients are also used for improving solubility of API. These excipients include super disintegrants, novel surfactants, and pH modifier. Wang *et al.* [55] had prepared *Ginkgo biloba* extract SD (GBE-SD) through HME using a carrier such as Kollidon® VA64/Kolliphor® RH40 (85:15) spray dried powder. The result was shown that the dissolution rate and oral bioavailability of GBE were enhanced. Srinarong *et al.* [56] utilized super disintegrant in SD to prepare tablet. They explained that dissolution rate is enhanced by preventing recrystallization during the dissolution process.

In the fourth generation, centrifugal spinning method is a novel method of CR-SD. It is a highly efficient technique for fabricating nanofibers for the preparation of SD. Marano *et al.* [57] developed microfibrinous to nanofibrinous SD of poorly water-soluble drug in sucrose using temperature controlled centrifugal spinning method. This study was demonstrated that nanofibers based dispersion may possess characteristics that are favorable for the enhanced dissolution and oral absorption of drugs.

Many advanced characterization has been developed such as high-performance DSC, project rapid heat/cool, and chip calorimetry which are applied in SD area. Yu *et al.* [58] investigated the structure and dissolution properties of a SD containing Lansoprazole and PVP. Hence, there are more and more strategies will be needed to overcome remaining problems of SD in future.

#### CONCLUSION

From the above study, SD is one of the efficient technologies for overcoming many problems relating to bioavailability of poorly soluble drug. Still, there has some problem which will be short out by applying novel and current approach. This review focuses on current effort to short out bioavailability problem and explains various new technologies involved for development of SD. The investigation of research will be more on physicochemical properties, interaction of drugs and carrier and characterization technique which will help to elucidate the structure and dissolution properties of SD.

#### REFERENCES

- Karant H, Shenoy VS, Murthy RR. Industrially feasible alternative approaches in the manufacture of solid dispersions: A technical report.

- AAPS Pharm SciTech 2006;7:87.
2. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2001;46:3-26.
  3. Pudipeddi M, Serajuddin AT. Trends in solubility of polymorphs. *J Pharm Sci* 2005;94:929-39.
  4. Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm* 2002;231:131-44.
  5. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem Pharm Bull* 1961;9:866-72.
  6. Okonogia S, Oguchib T, Yonemochi E, Puttipathkachorn S, Yamamoto K. Improved dissolution of ofloxacin via solid dispersion. *Int J Pharm* 1997;156:175-80.
  7. Vasconcelos T, Sarmento B, Costa P. SDs as strategy to improve oral bioavailability of poor water soluble drug. *Drug Discovery Today* 2007;12:1068-75.
  8. Kohri N, Yamayoshi Y, Xin H, Iseki K, Sato N, Todo S, et al. Improving the oral bioavailability of albendazole in rabbits by the solid dispersion technique. *J Pharm Pharmacol* 1999;51:159-64.
  9. Linn M, Collnot EM, Djuric D, Hempel K, Fabian E. Soluplus® as an effective absorption enhancer of poorly soluble drugs *in vitro* and *in vivo*. *Eur J Pharm Sci* 2012;45:336-43.
  10. Damian F, Blaton N, Naesens L, Balzarini J, Kinget R, Augustijns P, et al. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and gelucire 44/14. *Eur J Pharm Sci* 2000;10:311-22.
  11. Jagdale S, Patil S, Kuchekar B, Chabukswar A. Preparation and characterization of metformin hydrochloride - Compritol 888 ATO solid dispersion. *J Young Pharm* 2011;3:197-204.
  12. Ali W, Williams AC, Rawlinson CF. Stoichiometrically governed molecular interactions in drug: Poloxamer solid dispersions. *Int J Pharm* 2010;391:162-8.
  13. Mooter GV, Weuts I, Ridder T De, Blaton N. Evaluation of inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. *Int J Pharm* 2006;316:1-6.
  14. Goddeeris C, Willems T, Houthoofd K, Martens JA, Mooter GV. Dissolution enhancement of the anti-HIV drug UC 781 by formulation in a ternary solid dispersion with TPGS 1000 and Eudragit E100. *Eur J Pharm Biopharm* 2008;70:861-8.
  15. de Waard H, Hinrichs WL, Visser MR, Bologna C, Frijlink HW. Unexpected differences in dissolution behavior of tablets prepared from solid dispersions with a surfactant physically mixed or incorporated. *Int J Pharm* 2008;349:66-73.
  16. Huang J, Wigent RJ, Schwartz JB. Nifedipine molecular dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blends for controlled drug delivery: Effect of matrix composition. *Drug Dev Ind Pharm* 2006;32:1185-97.
  17. Cui F, Yang M, Jiang Y, Cun D, Lin W, Fan Y, et al. Design of sustained-release nitrendipine microspheres having solid dispersion structure by quasi-emulsion solvent diffusion method. *J Control Release* 2003;91:375-84.
  18. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm* 2000;50:47-60.
  19. Van den Mooter G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. *Drug Discovery Today Technol* 2011;9:79-85.
  20. Baird JA, Taylor LS. Evaluation of amorphous solid dispersion properties using thermal analysis techniques. *Adv Drug Delivery Rev* 2012;64:396-421.
  21. Yoshioka M, Hancock BC, Zograf G. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J Pharm Sci* 1994;83:1700-5.
  22. Vasanthavada M, Tong WK (twin), Joshi Y, Kislalioglu MS. Phase behavior of amorphous molecular dispersions II: Role of hydrogen bonding in solid solubility and phase separation kinetics. *Pharm Res* 2005;22:440-8.
  23. Mura P, Moyano JR, González-Rodríguez ML, Rabasco-Alvaréz AM, Cirri M, Maestrelli F, et al. Characterization and dissolution properties of ketoprofen in binary and ternary solid dispersions with polyethylene glycol and surfactants. *Drug Dev Ind Pharm* 2005;31:425-34.
  24. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci* 1971;60:1281-302.
  25. Kolašinac N, Kachrimanis K, Homšek L, Grujić B, Đurić Z, Ibrić S. Solubility enhancement of desloratadine by solid dispersion in poloxamers. *Int J Pharm* 2012;436:161-70.
  26. Verhoeven E, De Beer TR, Schacht E, Van den Mooter G, Remon JP, Vervaet C, et al. Influence of polyethylene glycol/polyethylene oxide on the release characteristics of sustained-release ethylcellulose mini-matrices produced by hot-melt extrusion: *In vitro* and *in vivo* evaluations. *Eur J Pharm Biopharm* 2009;72:463-70.
  27. Ye X, Patil H, Feng X, Tiwari RV, Lu J, Gryczke A, et al. Conjugation of hot-melt extrusion with high-pressure homogenization: A Novel method of continuously preparing nanocrystal solid dispersions. *AAPS PharmSciTech* 2016;17:78-88.
  28. Desai S, Disouza J, Musle K, Avinash H. Solubility enhancement of Ritonavir by hotmelt extrusion. *Int J Pharm Pharm Sci* 2016;8:309-12.
  29. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov Today* 2007;12:1068-75.
  30. Seo A, Holm P, Kristensen HG, Schaefer T. The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int J Pharm* 2003;259:161-71.
  31. Vilhelmsen T, Eliassen H, Schaefer T. Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int J Pharm* 2005;303:132-42.
  32. Takafumi H, Fumie K, Ikuo F. Solid dispersion preparation. *European Patent EP No. 1847260 A3*; 2007.
  33. Zhang X, Lu Y. Centrifugal spinning: An alternative approach to fabricate Nanofibers at high speed and low cost. *J Polym Rev* 2014;54:677-701.
  34. Jiang H, Ge Y, Fu K, Lu Y, Chen C, Zhu J, et al. Centrifugally-spun tin-containing carbon nanofibers as anode material for lithium-ion batteries. *J Mater Sci* 2015;50:1094-102.
  35. Paaver U, Heinämäki J, Laidmäe I, Lust A, Kozlova J, Sillaste E, et al. Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs. *Int J Pharm* 2015;479:252-60.
  36. Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. *Int J Pharm* 2005;301:199-208.
  37. Gang Y, Zhao Y, Feng N, Zhang Y, Liu Y, Dang B. Improved dissolution and bioavailability of silymarin delivered by a solid dispersion prepared using supercritical fluids. *Asian J Pharm Sci* 2015;10:194-202.
  38. Shaofeng W, Ma Y, Luo J, He X, Yue P, Guan Z, et al. Hydroxypropylcellulose as matrix carrier for novel cage-like microparticles prepared by spray-freeze-drying technology. *Carbohydr Polym* 2017;157:953-61.
  39. Badens E, Majerik V, Horvath G, Szokonya L, Bosc N, Teillaud E, et al. Comparison of solid dispersions produced by supercritical antisolvent and spray-freezing technologies. *Int J Pharm* 2009;377:25-34.
  40. Wei-Juan X, Xie HJ, Cao QR, Shi LL, Cao Y, Zhu XY, et al. Dissolution and oral bioavailability of valsartan solid dispersions prepared by a freeze-drying technique using hydrophilic polymer. *J Drug Delivery* 2016;23:41-8.
  41. Kaur P, Singh SK, Garg V, Gulati M, Vaidya Y. Optimization of spray drying process for formulation of solid dispersion containing polypeptide-k powder through quality by design approach. *Powder Technol* 2015;284:1-11.
  42. Ramesh K, Shekar BC, Khadgpathi P. Formulation and evaluation of travertine by spray drying method. *Int J Pharm Pharm Sci* 2015;7:98-103.
  43. Li J, Miao X, Chen T, Ouyang D, Zheng Y. Preparation and characterization of pelletized solid dispersion of resveratrol with mesoporous silica microparticles to improve dissolution by fluid-bed coating techniques. *Am J Pharm Sci* 2016;11:528-35.
  44. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. *In vivo* evaluation of rapid release and sustained release gelucire capsule formulations. *Int J Pharm* 1990;65:85-100.
  45. Dordunoo SK, Ford JL, Rubinstein MH. Preformulation studies on solid dispersions containing triamterene or temazepam in polyethylene glycols or gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug Dev Ind Pharm* 1991;17:1685-713.
  46. Porter CJ, Charman SA, Williams RD, Bkalova MV, Charman WN. Evaluation of emulsifiable glasses for the oral administration of cyclosporin in beagle dogs. *Int J Pharm* 1996;141:227-37.
  47. Shah B, Kakumanu VK, Bansal AK. Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids. *J Pharm Sci* 2006;95:1641-65.
  48. Berndt G, Degenhardt M, Maegerlein M, Dispersyn G. Itraconazole Compositions with Improved Bioavailability. U.S. Patent No. US9149431 B2; 2015.
  49. Guinot S, Leveiller F. The use of MTDSC to assess the amorphous phase content of a micronized drug substance. *Int J Pharm* 1999;192:63-75.
  50. Miyazaki T, Aso Y, Yoshioka S, Kawanishi T. Differences in

- crystallization rate of nitrendipine enantiomers in amorphous solid dispersions with HPMC and HPMCP. *Int J Pharm* 2011;407:111-8.
51. Hifumi H, Ewing AV, Kazarian SG. ATR-FTIR spectroscopic imaging to study the drying and dissolution of pharmaceutical polymer-based films. *Int J Pharm* 2016;515:57-68.
  52. Frizon F, Jd OE, Donaduzzi CM, Mitsui ML, Marchetti JM, Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods. *Powder Technol* 2013;235:532-9.
  53. Paudel A, Geppi M, Mooter GV. Structural and dynamic properties of amorphous solid dispersions: The role of solid-state nuclear magnetic resonance spectroscopy and relaxometry. *J Pharm Sci* 2014;103:2635-62.
  54. Choi JS, Park JS. Design of PVP/VAS-630 based tadalafil solid dispersion to enhance the dissolution rate. *Eur J Pharm Sci* 2017;97:269-76.
  55. Wang W, Kang Q, Liu N, Zhang Q, Zhang Y, Li H, et al. Enhanced dissolution rate and oral bioavailability of *Ginkgo biloba* extract by preparing solid dispersion via hot-melt extrusion. *Fitoterapia* 2015;102:189-97.
  56. Srinarong P, Faber JH, Visser MR, Hinrichs WL, Frijlink HW. Strongly enhanced dissolution rate of fenofibrate solid dispersion tablets by incorporation of superdisintegrants. *Eur J Pharm Biopharm* 2009;73:154-61.
  57. Marano S, Barker SA, Raimi-Abraham BT, Missaghi S, Rajabi-Siahboomi A, Craig DQM, et al. Development of micro-fibrous solid dispersions of poorly water-soluble drugs in sucrose using temperature-controlled centrifugal spinning. *Eur J Pharm Biopharm* 2016;103:84-94.
  58. Yu M, Sun L, Li W, Lan Z, Li B, Tan L, et al. Investigation of structure and dissolution properties of a solid dispersion of lansoprazole in polyvinylpyrrolidone. *J Mol Struct* 2011;1005:70-7.
  59. Li J, Lee IW, Shin GH, Chen X, Park HJ. Curcumin-eudragit® E PO solid dispersion: A simple and potent method to solve the problems of curcumin. *Eur J Pharm Biopharm* 2015;94:322-32.
  60. Leung SS, Parumasivam T, Gao FG, Carrigy NB, Vehring R, Finlay WH, et al. Production of inhalation phage powders using spray freeze drying and spray drying techniques for treatment of respiratory infections. *J Pharm Res* 2016;33:1486-96.
  61. Marano S, Barker SA, Raimi-Abraham BT, Missaghi S, Rajabi-Siahboomi A, Aliev AE, et al. Microfibrous solid dispersions of poorly water-soluble drugs produced via centrifugal spinning: Unexpected dissolution behavior on recrystallization. *Mol Pharm* 2017;14:1666-80.
  62. Hacene YC, Singh A, Mooter GV. Drug loaded and ethylcellulose coated mesoporous silica for controlled drug release prepared using a pilot scale fluid bed system. *Int J Pharm* 2016;506:138-47.