Solid Dispersion with innovative Sintering Technique in Pharmaceutical Industry: An Ultimate Solution for development of dosage form of Poorly Aqueous Soluble Drugs

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Abstract:
The Solubility of poorly water soluble drug have critical impact on drug dissolution and their absorption. Most of the newly discovered drugs have poor or very limited aqueous solubility, causes a serious challenge to the successful development & commercialization of new drug product or dosage form in the pharmaceutical industry. Numbers of techniques are available for the solubility enhancement but all individual techniques have its own limitations during its commercialization. A well-known Solubility enhancement technique like Solid dispersions provides dispersion of poorly soluble drug in a suitable inert carrier at a molecular level and form amorphous and highly soluble compounds. The conversion of crystalline compound in to amorphous form or reduction of particle size to its molecular level caused enhanced solubility of poorly soluble by the application of solid dispersion techniques. Although, Solid dispersion has vast potential, but only limited products are commercialized and reported in different literatures due to its poor scalability and low mechanical strength of solid dosage forms like Tablets. Hence, an innovative Sintering technique in combination of solid dispersion produces high mechanical strength and easy scalability in pharmaceutical industry. The sintering is expressed as the joining of adjacent particles in a mass of powder, or in tablets, by the heat application. Conventional sintering technique involves heating of compact mass at a temperature below the melting point of the available solid constituents in controlled environments. The sintering technique with solid dispersion technique has manifold advantages over traditional dry or wet granulation method like minimum quantity of drug polymer ratio,easy tailoring of drug release profile, cost effective, high mechanical strength of dosage forms. Sintering concept not only improves mechanical strength of dosage form, but it also controls the release of medicament on over an extended time period.

Keywords: Pharmaceutical dosage form, Solubility, Solid dispersion, Tablets, Sintering Technique

INTRODUCTION:

The oral route is more popular route in drug delivery due to its diverse superiority including cost effective, ease in ingestion, non-invasiveness, inventiveness, flexibility of dosage form design and most important high patient compliance.Aqueous solubility of API's plays an essential role in drug dissolution or absorption of the drug from the oral dosage form and hence its bioavailability. When a drug is administered orally in solid dosage form, it is designed to undergo series of predetermined stages[1,2]. The first step towards the absorption process is the disintegration or diffusion or erosion (as per immediate release or Modified release dosage form) process from dosage form. The second and in fact the slowest or rate-limiting step is found to be dissolution of drug in the fluid at the absorption site (Figure - 1). The fact that most of the newly discovered API's or new molecular entity(NME) have little or no aqueous solubility, causes a serious challenge to the successful development & commercialization of new drugs in the pharmaceutical industry. Although the pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, but those with aqueous solubility of less than 0.1 mg/ml present unique challenges[2-5].

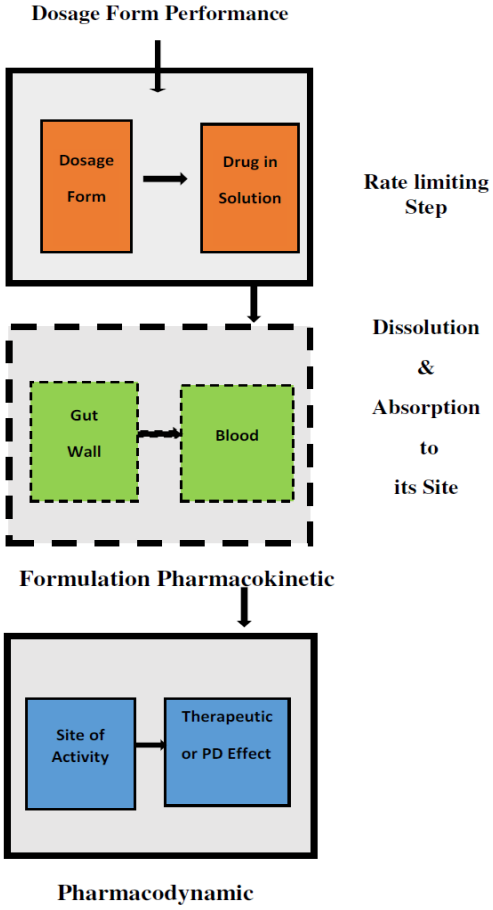

Figure 1. Schematic representation of oral dosage form after ingestion

The solubility of an active ingredient or a new molecular entity (NME) is defined as the amount of drug that goes into solution when equilibrium is established between the drug solute in solution and any excess, un-dissolved drug to produce a saturated solution at a specified temperature. When the highest dose strength of API's is not completely soluble in aqueous media (volume 250 ml over the pH range of 1.2 to 6.8), the NME's is considered as poorly aqueous soluble[6-9]. If an active ingredient or a new molecular entity (NME) does not qualify the above said property, it will not be a viable candidate for new product development. Most of the newly discovered drugs candidates are porn to limited aqueous solubility. Hence, pharmaceutical Industries are not able to furnish rigorous preclinical and clinical studies. Therefore, development of NME's becomes difficult and their potential are not realized or confirmed[7,9]. Drug substances or NME's are generally classified into four categories (Figure-2) upon their solubility and permeability according to the Biopharmaceutical Classification System (BCS)[6-10].

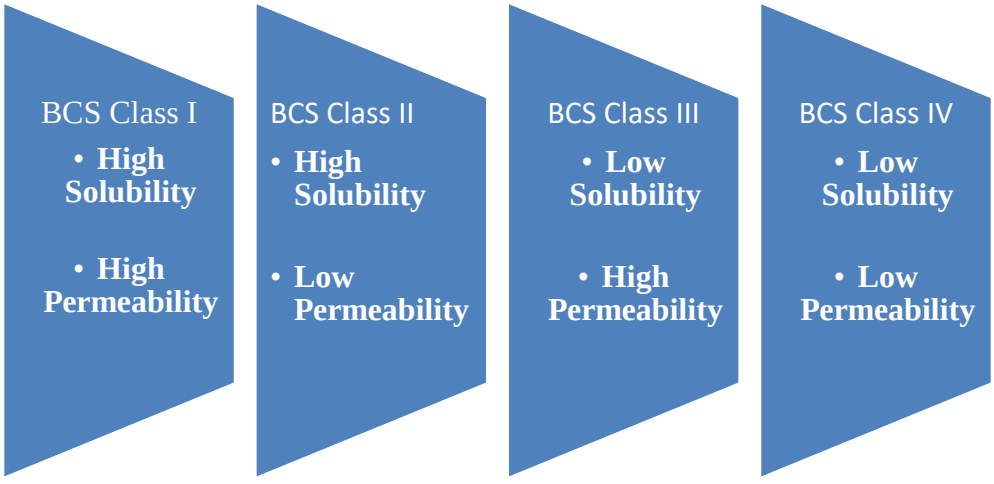

Figure2. Biopharmaceutical Classification System (BCS)

As per BCS classification, Class II & IV drug candidates have poor aqueous solubility and need a solubility enhancement for successful development & commercialization of oral dosage form with enhanced bioavailability. Numerous technologies have been utilized in the recent past. A lot of approaches are being currently used for the solubility enhancement of poorly aqueous soluble drugs [11-14].Some listed widely used approaches (Table-1) are as per following:

Table 1. Various Solubility enhancement approaches

Physical Approaches	***Chemical Approaches***	***Miscellaneous***
Reduction of Particle Size by ➢ Conventional Method(Grinding) ➢ Micronization(Air Jet Milling) ➢ Nanoparticle or Nanosuspension Crystal Habit Modification by ➢ Co-precipitation Method ➢ Polymorphs ➢ Pseudopolymorphs Inclusion Complexation ➢ Kneading Method ➢ Lyophilization ➢ Microwave irradiation Method ➢ Solubilization by Surfactant ➢ Microemulsion Solid Dispersion ➢ Melting /Fusion Method ➢ Physical Kneading ➢ Solvent Evaporation ➢ Hot melt Extrusion ➢ Spray Freeze Drying	➢ Pro drug approach ➢ pH Adjustment ➢ Buffer maintenance ➢ Derivatization, ➢ Salt formation ➢ Polymeric micelles formation ➢ Self-emulsifying systems	➢ Supercritical fluid process, ➢ Adsorption process

Among the various approaches, Solid dispersion is being unfolded for solubility& Stability enhancement. Solid dispersion approach is briefly highlighted in subsequent sections.

Solid Dispersion Technique as a Solubility Enhancement Approach

Aqueous solubility enhancement by Solid dispersion is a unique approach, which improvesolubility, dissolution rate and bioavailability of drugs. Solid Dispersion can be defined as a “dispersion of one or more active ingredients at molecular to microcrystalline level in an inert carrier or matrix at solid state”. Physiologically inert carrier isusedfor the preparation of solid dispersion and it may be readily water-soluble carrier or water insoluble carrier, for fast or modified release preparations respectively [2,3,12].

Sekiguchi and Obi scientists were first introduced the concept of solid dispersion in 1961[15] by utilizing sulfathiazoledrug with Urea as a water-soluble carrier. They formed eutectic mixture by melting the physical mixture of sulfathiazole and urea, followed by a rapid solidification in term of cooling them. The prepared solid dispersion has higher absorption of sulfathiazole as compared to sulfathiazole alone, after its oral administration

Accordingto author Chiou and Riegelman,solid dispersion is defined as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by the melting (fusion), solvent, or melting-solvent method"[16]. Solid dispersion may also be called'solid-state dispersion"[17]. Fusion process also called melts and solvent method are frequently referred to as 'coprecipitates' (Sulfathiazole-PVP dispersion)[18].Various techniques are employed for preparation of solid dispersion which are been briefly and critically reviewed here. In general, Solid dispersions are classified on the basis of their molecular arrangement & Carrier used in the preparations.

Classification of Solid dispersion on the basis of their molecular arrangements:

Author’s Chiou and Riegelman classified the solid dispersion into six groups as per following:

1. SimpleEutectic Mixture

A eutectic mixture consists of two independent constituents, both constituents are completely miscible in the liquid state but they are miscible in the solid state at a little extent[19]. This type of mixtures are prepared by sudden chilling of melted mixture of drug polymer produce a fine crystal.A simple eutectic mixtureis represented in Figure -3, where both component A & B are not miscible in solid state. When this mixture is heated and cooled, itproduces very fine crystals. The large surface area of resulting fine crystals are responsible for improved dissolution rate and so that with improved bioavailability[16,19].

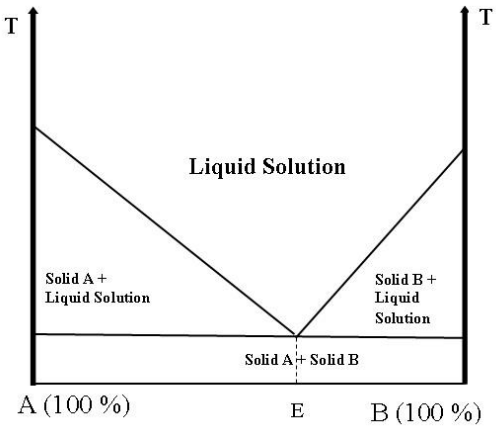

Figure3. Eutectic mixture Phase diagram

2. Solid Solutions

Solid Solutions are similar to liquid solutions. They consistofonly one phase not withstanding of the number of components (two components crystallize together in a homogenous one-phase system). This Solid solution reduces the particle size up to the molecular level. Hence, faster dissolution can be easily attained in comparison to eutectic mixture. Various types of solid solution are shown in Figure 4.[16,19,20].

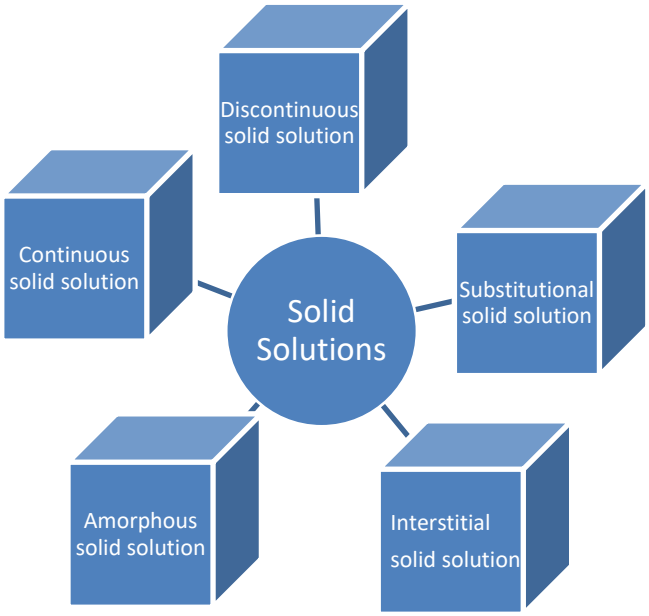

Figure-4: Solid Solutions Types

2.1 Continuous Solid Solutions

Two components in continuous solid solution are miscible or soluble at solid state in all proportions (Figure-5).Any Pharmaceuticalliterature does not support this type of solid solution[16,19].

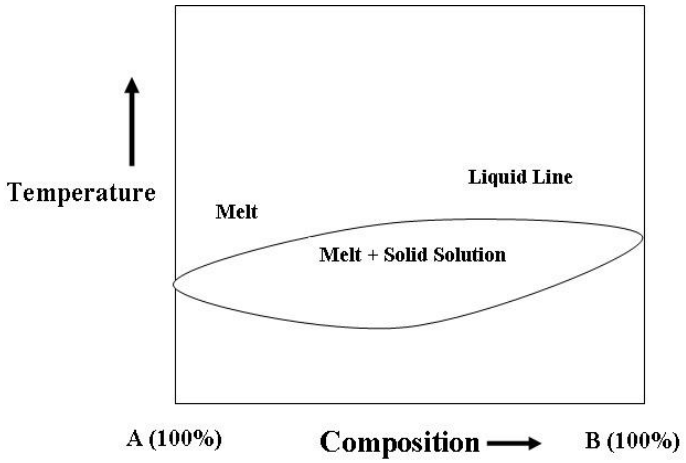

Figure 5. Phase diagram of Continuous Solid Solution for a binary system consisting of content A and B.

2.2 Discontinuous Solid Solutions

In contrast to continuous solid solution, this system has only a limited solubility of a solute in a solvent system[19.] (Figure6).

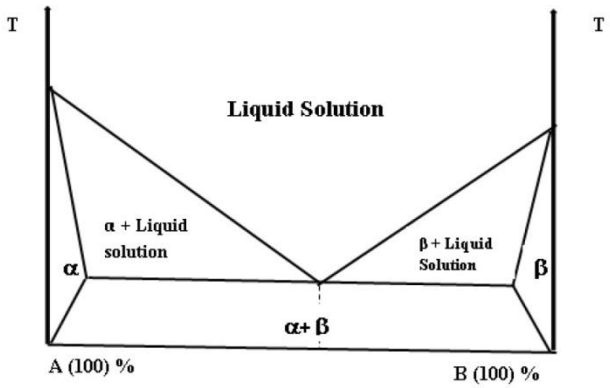

Figure-6: Phase diagram of a Discontinuous Solid Solution for a binary system consisting of content A and B, where $\alpha$and βare regions of solid solution formulation

2.3Substitutional Crystalline Solid Solutions

In this typeof solid solution, some of the solvent molecules are substituted by solute molecules in the lattice of crystalline molecules (Figure7.). This typed of arrangements is only happened when solute molecules sizes are differed below 15% from the lattice of solvent [19].

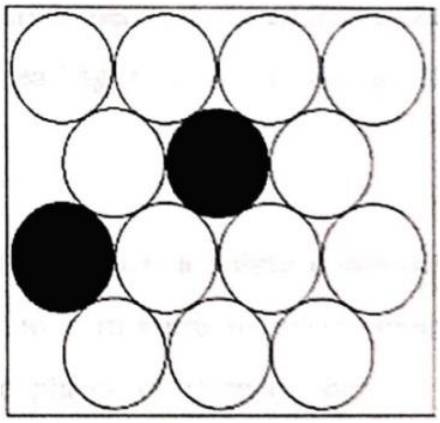

Figure 7. Substitutional Crystalline Solid Solution

2.4 Interstitial Crystalline Solid Solution

In this solid solution, the solute molecules occupy the interstitional space (Figure8) in the solvent lattice [16,19].

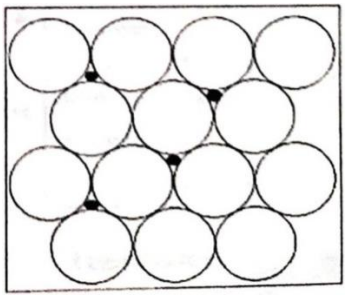

Figure 8. Interstitial Crystalline Solid Solution

2.5 Amorphous Solid Solution

Amorphous Solid Solution is the solid solution where, irregularly and molecularly solute molecules are dispersed within the solvent (Figure-9).Solute molecules plasticize the polymer and amorphous polymer chain network is produced and reduction in its glass transition temperature [16,19].

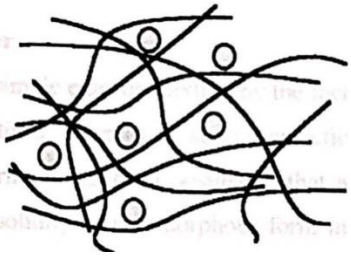

Figure 9. Amorphous SolidSolution

2.6 Glass Solutionand Glass suspension

Solute is dissolved in the Glassy carrier and formsa homogenous glassy system called‘Glass solution’. Whereas 'Glass Suspension' refers to a mixture in which precipitatedparticles are suspended in the glassy solvent. An abrupt quenching of the meltproduces a glassy or vitreous state.Transparency and brittleness below the glass transition temperature (Tg) can characterized this state.This system softens gradually and constantly without a sharp melting point during heating. The lattice energy represents a barrier for rapid dissolution in glass solution. Figure10.shows the volume changes associated with glass formation when a melt is cooled down. Carriers that form glass solution or glass suspension include citric acid, sugars, polyvinylpyrrolidone, urea and polyethylene glycol[16,20,21].

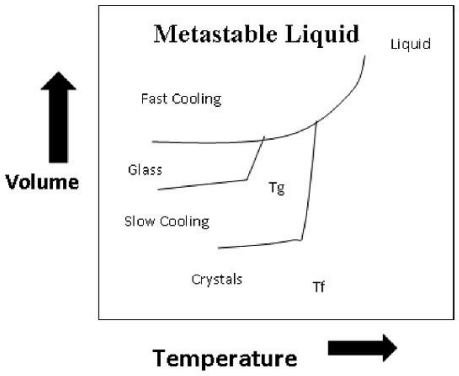

Figure 10. Temperature volume changes associated with cooling of melts

3. Amorphous precipitation in crystalline carrier

This type of solid dispersion shows precipitation of drug in an amorphous form as compared to simple eutectic mixture, whereas drug is precipitated out in crystalline form. It has been postulated that a drugs super-cooling property has more tendency to solidify as an amorphous form in the carrier[16,20,21].

4. Compound and complex formation between drug and carrier

Compound and complex formation (soluble and insoluble) can enhance or reduce the dissolution of drugs. e.g. Quinine-Phenobarbitonsystem increases dissolution, whereas PEG-Phenobarbitonesystem reduces the dissolution [16,20].

5. Any combination of above classes

It is also possible that, solute molecules can exist in combination of above classes in the form of crystalline or amorphous forms[16].

Classification of Solid dispersion based on carrier used:

Solid dispersion is classified in four categories as per the carrier application. Different generation of Solid dispersions is highlighted in Table2.with their major characteristics[21-24].Solid Dispersion are prepared by the use of different category of carriers [21-24], which are highlighted in Table 3.

Table 2. Types of Soliddispersion classification based on carrier system

Types of Solid Dispersion	Applicable Carriers	Characteristics
First Generation	Crystalline Carriers like Sugars, Urea etc	Enhancement of Solubility & dissolution by decreasing size of API particles or increasing their surface area, improving water uptake capacity and change in their polymorphicforms.
Second Generation	Amorphous carrier likes Synthetic or natural polymers; Hydroxypropyl methyl cellulose (HPMC), Polyethylene glycol (PEG), Povidone, Hydroxy ethyl cellulose (HEC), Starch, Cyclodextrin, PVP, EC, HPMCS	Amorphous nature of carrier increases wettability, dispersibility of the crystalline drug and decrease their crystalline nature on dissolution in aqueous media. The low thermodynamic stability of carrier is a main characteristic of high dissolution rate.
Third Generation	Carriers with additional surface-active agents or self emulsifiersexamples include Poloxomer, Gelucire, Soluplus, Sodium Lauryl sulfate, Tween 80 and compritrol	They are used to achieve highest degree of bioavailability, to stabilize solid dispersion and avoid drug recrystallization.
Fourth Generation	A wide range of Water-soluble polymers or water insoluble carrier or swellable carriers like Ethy Cellulose, Carbopol, Polyethylene oxide (PEO), Eudragit and carboxyvinyl polymer	Applicable for drugs having low aqueous solubility, short biological half-life and to obtain a sustained or controlled release pattern.

Table3. Carriersfor the preparation of solid dispersion

Carriers Categories	Examples
Sugars	Sugar alcohols like Lactose monohydrate or Lactose anhydrous,Fructose,Sucrose, Dextrose, Galactose, Maltose, Sorbitol and Xylitol, Amylodextrin, British gum, galactomannan and Mannitol, etc.
Acids	Acids Like Citric, Tartaric, Succinic, phosphoric and/or their combinations etc.
Polymeric materials	Carregeenan, Pectin, Polyvinylpyrrolidone (PVP), Poly(vinyl alcohol) (PVA), polyether compound like Polyethyleneglycol (PEG 6000 or PEG 8000), HydroxyPropyl Methyl Cellulose (HPMC), Gelatin, Ethylcellulose (EC), Methyl cellulose (MC), HydroxyEthyl Cellulose (HEC), HydroxyPropyl Cellulose (HPC), Sodium carboxymethyl cellulose, Sodium Alginate, Galactomannan, Dextrins, Cyclodextrin (CD) and its derivatives, Gum Arabic, Tragacanth, and Guar Gum etc
Insoluble or enteric polymers	Hydroxypropylmethyl cellulose phthalate (HPMCP),Polymethylacrylate (e.g. Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS), Poly DL-aspartic acid and Spheron P40 etc.
Surfactants	Non-ionic surfactantlikePolyoxyethylene stearate, Synthetic block copolymers(Pluronic F 68), water-soluble nonionic triblock copolymers (Poloxamer 407&Poloxamer 188, mixtures of mono, di and triglycerides with PEG esters of fatty acids(Gelucire 44/14), docusate sodium, Texafor AIP, Deoxycholic Acid, Tweens, Spans, Myrj 52, Myrj 51, Myrj59, Polyoxyethylene 40 Stearate (P40S) and Brij 35 etc.
Miscellaneous materials and Combinations	Pentaerythritol, Pentaerythrityltetraacetate, Urea, Urethane, Hydroxyalkyl-xanthines, Dehydroxypropyltheophylline, Nicotinamide, Hydroquinone, Ascorbic Acid, Acetamide, Nicotinic Acid, Succinamide, mixture of sugar like Sugars-PEG and Surfactants like Sterol etc.

Hence, Solid dispersion improves dissolution rate of poorly soluble drugs due to following charactristics[16,20-23,25]:

1. Reduction of API particle size at their molecular level.
2. High dissolution rate due to hydrophilic nature of carrier or high wetting of API molecules.
3. Conversion of crystalline compound into amorphous state.

Method of preparations of Solid Dispersion

There are numbers of approaches for the preparations of solid dispersion, some are briefly and critically tabulated in Table- 4[20,22,23,26-32]:

Table-4: Solid dispersion preparation method

S.No.	Solid dispersion preparation method
1.	Solvent method (including Spray drying and Freeze drying)
2.	Melting/ Fusion method
3.	Solvent-melting method.
4.	Coprecipitation or Coevaporate
5.	Co-milling
6.	Hot-spin-melting
7.	Hot-melt extrusion
8.	Kneading Method
9.	Supercritical fluid process (SCF)
10.	ElectrostaticSpinning Method
11.	Microwave irradiation technique

Some Patented Solid dispersion Technologies are briefly highlighted in Table5.

Table 5. Patented Solid dispersion Technologies

Patented Technologies	Characteristics
Meltrex™	This is a patented technology and trademarks of the Abbott group of companies. This technique is based on Hot-melt extrusion principle and applicable for thermolabile, oxygen sensitive and moisture sensitive drugs. This technology utilizes special designed twin screw extruder attached with two separate hoppers for transferring the material to the extrusion port continuously. This technique has unique advantages of low resistance time of thermolabile drug in extruder and avoids thermal stress. This technique allows a compact closed chamber manufacturing process.So, drugs which are sensitive to heat, oxidative degradation or hydrolysis by moisture can be easily processed [22,26,33,34].
Kinetisol®	KinetiSol® Technology was developed by AustinPx™Georgetownandis a fusion-based technique,where both frictional and shear energies combined for efficient mixing to produce a homogenous mixture of drug-polymer in a molten stage. A computer-control module is used to control temperature and time of process to produces molten matrix. This technique has very low processing time; less than 20 seconds and has capability to produces an amorphous solid dispersion of broader formulation design space (high melting point & poor solvent solubility of active pharmaceutical ingredients), viscous polymer, very low processing time, solvent free process and wide application to challenging molecules[22,26, 29,35].
Solumer®	It is a patented technology of FormulexPharma Innovations Ltd, Israel. Technique is based on interaction of insoluble-lipophilic molecule with polymers resulting in a solid composition. Lipophilic compound dissolves faster and to a higher extent, enhancing the drug solubility and bioavailability in aqueous media. FormulexPharma has been developing more than 10 medical cannabis products using their patented Solumer™ and generic technologies. Five of the products are under the clinical and commercial stages[26].
Hovione	Hovione is a developing company and particularly specializes in process development technology & scale up processofparticle engineering. This technique providesa solution for oral bioavailability, lung delivery, modified release, taste masking and it support proof of concept to commercial large-scale manufacturing. Hovione provides services to the pharmaceutical industry in solid dispersion technologies since last 15 years. It is engaged in various technologies of solid dispersions like HME, Spray drying, Jet milling, Nanoparticles and Spray congealing technologies. It also provides all the way of manufacture to commercial supplies and performs formulation development and production of early clinical supplies. It works on mathematic modeling concept to understand the fundamentals of the solid dispersion process and uses a Quality-by-Design (QbD) approach for successful commercialization[26].
SUBA™	SUBA™ technology is a patented technology of MaynePharma, USA. Technology is based on solid dispersion via spray drying process. This technique improves the aqueous solubility or dissolution rate of poorly water-soluble drugs candidates and converts it in amorphous form as compared to crystalline forms. This technology ultimately enhances the bioavailability of poorly soluble drugs and reduced intra or inters subject patient variability. The novel SUBATM technology is approved in US, Australia, Europe and South American countries as a brand name of TOLSURA® in the US and LOZANOC® in Australia for poorly soluble anti-fungal drug itraconazole[32].

Advantages of Solid dispersion:

Solid Dispersion enhances the dissolution rate and bioavailability of poorly soluble drugs due to following reasons[16, 20, 28, 29,32]**:**

- ✓ Conversion of Crystalline compound in Amorphous form,
- ✓ Reduction of particle size to its molecular level,
- ✓ Improves the wettability of drugs by use ofhydrophilic carrier,
- ✓ Increases porosity of formulation,

There are numerous analytical and instrumental approaches to characterize the solid dispersion and distinguish between amorphous or crystalline nature of materials. The crystalline state and degree of crystallinity of molecules or API's are prominently characterized by instrumental method (like Differential Scanning Calorimtry (DSC), Modulated Differential Scanning Calorimetry (MDSC), powder X-ray diffraction (PXRD)). The chemical interactions of molecules with carrier are characterized by Fourier Transformed Infrared spectroscopy (FTIR) and Thermal Gravimetric Analysis (TGA). The surface morphology, qualitative characterization of crystallinity of solid dispersion is characterized by microscopy like optical microscopy, scanning electron microscopy (SEM) and transmission electron microscopy (TEM).The*In-vitro* dissolution study is the most prominent method to predict *In-vivo* performance of solid dispersion. One single method cannot provide sufficient information regarding the physical nature of solid dispersion systems, but in most of the cases, combination of several methods is required to characterize the solid dispersion.Differentmethodsof characterization and various available approaches are listed in Table 6[16, 32, 36-40].

Table6. Methods of characterization of solid dispersion

S.No.	Characteristics of Solid Dispersion	Instrumental Methods
1.	Drug-Polymer/Carrier Interaction Study	➢ Differential Scanning Calorimetry (DSC) ➢ Fourier Transform Infrared Spectroscopy (FTIR) ➢ Nuclear Magnetic Resonance Spectroscopy
2.	Physical State Study	➢ Differential Scanning Calorimetry (DSC) ➢ Powder X-ray diffraction (PXRD)
3.	Microscopic Study	➢ Optical Microscopy ➢ Scanning Electron Microscopy (SEM)
4.	Structural Study	➢ Fourier Transform Infrared Spectroscopy (FTIR) ➢ Nuclear Magnetic Resonance Spectroscopy ➢ Raman Spectroscopy
5.	Intrinsic Solubility or Dissolution Study	➢ In-Vitro Dissolution Apparatus

Application of Solid Dispersion Solubility Enhancement Technique

- ✓ Rapid dissolution rate [12,14,23],
- ✓ Moleculardispersion of the drug in the carrier system, resulting Solubility enhancement or ultimately enhancement of absorption & bioavailability of drug[11,30],
- ✓ Easy toformulate a Modified Release products (Controlled/Delayed/Sustained products) by the application of dissolution controlling carriers [19, 24],
- ✓ The bitter or unpleased odor of drug can be easily masked by Solid Dispersion techniques using insoluble matrices [24],
- ✓ Solid dispersionstabilizes unstable drug and protect from decomposition [28],
- ✓ Excellent Uniformity of content for potent drugs in the dosage forms [29],
- ✓ Conversion of potent Liquid drug into solid state[29],
- ✓ To improve wettability of drug using carriers[21],
- ✓ Excellent content uniformity[33],
- ✓ Applicable for potent drug [29,33],
- ✓ Dose of drug can be reduced by increasing solubility, absorption and ultimately improved bioavailability [30],
- ✓ Avoidance of polymorphic changes and thereby overcoming bioavailability problems[33],
- ✓ Protection of drug against decomposition by saliva [25,33,36]and
- ✓ Two poorly soluble drugs can be easily formulated when they have Eutectic property [41].

Conclusion & Limitation of Solid Dispersion Solubility Enhancement Technique

Solid Dispersion concept is very versatile for solubility enhancement in comparison to other solubility enhancement techniques. Hence, solid dispersion successfully enhances solubility of poorly aqueous soluble drug, stability of unstable drug and thereby bioavailability by either dispersion of drug at molecular level or production of amorphous formsof drug.

Although, Solid dispersion has vast potential, but only limited products are commercialized and reported in different literatures (Table 6) [20,32, 37, 42-58], due to following limitations [28, 34, 73, 43].

- ➢ Poor scale-up for the manufacturing of dosage form or need specialized equipment for manufacturing of solid dispersion like Hot-melt Extruder, Spray dryer etc.[22,37, 41,59,60],
- ➢ Insufficient mechanical strength of tablet dosage form due to poor compressibility of number of carriersand problem in formulating a dosage forms [20],

- Handling problem (due to Stickiness or Tackiness of carrier)[25],
- Major disadvantage of solid dispersion technique is instability of drugdue to moisture absorption of carrier and phase separation[20, 25],
- Re-crystallization of the amorphous drug and/or transitions occurs between polymers [25],
- Encapsulation in Hard Gelatin Capsule result in delay and erratic release of drug [16], and
- Susceptible to denaturation of gelatin shell when filled in a capsule shell [16].

Table 7. Commercially approved marketed product of Solid dispersion

S.No.	Brand name	API	SD Method	Polymer/ Carrier	Manufacturer	Regulatory Agency/ Approval Year
1	Cymbalta®	Duloxetine	Physical-Kneading	HPMCAS	Eli Lilly	FDA-2004
2	Intelence®	Etravirine	Melting - HME	HPMC	J & J	FDA/EMA-2008
3	Intelence®	Etravirine	Solvent Method - Spray drying		Tibotec	FDA-2008
4	Certican®	Everollimus	Co-precipitation		Novartis	FDA-2010
5	Votubia®	Everollimus	Solvent Method - Spray drying		Novartis	FDA-2010
6	Fenoglide®	Fenofibrate	Melting+Solvent-Spray melt	Poloxomer 188	Santorus	FDA-2010
7	Gria-PEG®	Griseofulvin	Melting - HME	PEG6000	Pedinol	FDA-1982
8	Sporanox®	Itraconazole	Fluid bed layering	HPMC	Janssen Pharma	FDA-1992
9	Onmel®	Itraconazole	Melting - HME		Merz	FDA-2010
10	Lozanoc®	Itraconazole	Solvent Method - Spray drying	HPMCP	Mayne	NA
11	Kalydeco®	Ivacaftor		HPMC	Vertex	FDA/EMA-2012
12	Orkambi®	Ivacaftor		HPMCAS	Vertex Pharm.	FDA-2015
13	Galvusmet®	MetformineHCl	Melting - HME	PEG6000	Novartis	EMA-2007
14	Cesamet®	Nabilone	Solvent Method	Povidone	Valeant	FDA-1985
15	Nivadil®	Nilvadipine	Solvent Method - Spray drying	HPMC	Fujjsawa	NA
16	Noxafil®	Posaconazole	Melting - HME	HPMCAS	Merck	FDA-2013
17	Kaletra®	Ritonavir		Povidone	Abb Vie	EMA-2001
18	Norvir®	Ritonavir			Abbvie	EMA-2009
19	Crestor®	Rosuvastatin	Solvent Method - Spray drying	HPMC	Astra Zeneca	FDA-2002,EMA-2004
20	Prograf®	Tacrolimus	Physical-Kneading		Astellas	FDA-1994
21	Advagraf®	Tacrolimus	Wet granulation		Astellas	FDA-2012
22	Incivek®	Telaprevir	Spray drying	HPMCAS	Vertex	FDA/EMA-2011
23	Samsca®	Tolvaptan	Physical-Kneading	NA	Otsuka	FDA/EMA-2009
24	Rezulin®	Troglitazone	Melting - HME	HPMC	Pfizer	FDA-1997
25	Zelboraf®	Vemurafenib	Co-precipitation	HPMCAS	Roche	FDA-2011
26	Isoptin SR®	Verapamil	Melting - HME	HPMC/HPC	Abbot	FDA-1987
27	Eucreas®	Vildaglaptin		HPC	Novartis	EMA-2007

However, various approaches are reported for theimprovement of solubility in community, but still it remains a challenge for the formulation of dosage forms containing poorly soluble drugs. This article addresseslimitations of solid dispersion technique by the application of Sintering techniques in combination with solid dispersion technique.A combination technique hasindustrial applicability and a rapid dissolution or modified release characteristics after application of water soluble or water insoluble carriers respectively. This article highlights development of tablet dosage form formulation, utilizing Micronizationor grains/particles of Solid Dispersion in combinationwith polymer matrix Sintering Technology with industrial applicability. The Polymer Matrix Sintering Technique is briefly overviewed in this article.

Polymer Matrix Sintering Technology in Pharmaceutical Industry

Sintering can be expressed as the joining of particles(adjacent to each) surfaces in a powder compacts, or in tablets, by the application of thermal effect. Traditional sintering technique imply, heating of compact at a temperature below the melting point of the solid constituents present in compact, in a controlled environment [61-64].

Sintering concept describes the impact of heat on a pharmaceutical compacts preparation to improve the product performance and its applicability in the manufacturing of modified release products, to alter their release profile. The sintering concept consists of following properties[61-71]:

(I) Impact on Powder/ PolymerMicrostructure

The effect of sintering causes different structural changes in microstructure of compacts. Polymer microstructure during sintering can be easily studied by Scanning Electron Microscopy (SEM), Mercury intrusion and Nitrogen adsorption porosimeter. The change in microstructure can be divided in following five stages (Figure 11).

Sintering Process can be divided in five stages:

a) Bonding of Interparticle: - The particles come in closure at their boundaries by physical bonding. This type of bonding happens rapidly on heat application.
b) Neck growth: - Continuing application of heat, resulting formation of easily distinguishable "neck" development leads to enhancement of compact strength.
c) Closeness of Pore: - The pores in compact become more closure and forms isolated pore.
d) Pore Uniformity: - Continuous closeness of pore, produces much more uniform size of pores. Hence, this stage enhances smoothing effect on the pore wall and ultimately improves toughness and strengths.
e) Shrinkage of Pore: - On continuation of Sintering (heating), the number of pores and their sizes are reduced. A shrinkage phenomenon causes densification of powder compacts.

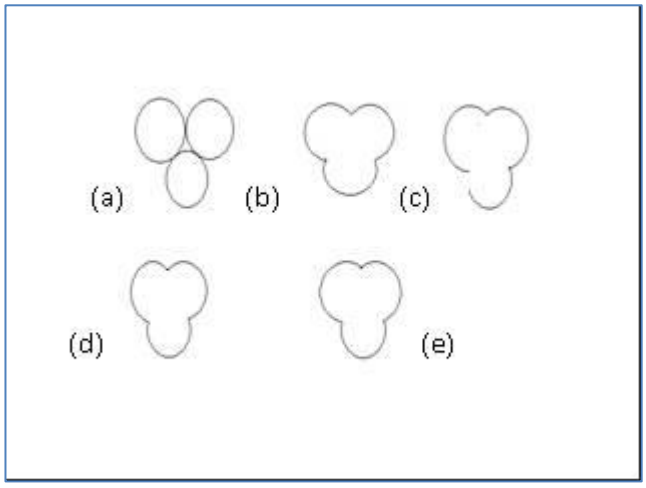

Figure 11. Schematic representation of Sintering Concept in a pharmaceutical compact. [(a) InterparticlesBonding (b) Neck growth, (c) and (d) Pore Uniformity, (e) shrinkage of Pore]

(II) Impact on Powder mechanical strength

The overall mechanical strength of powder or compact is improved as the particle comes in closure to each other.

(III) Impact on disintegration time and dissolution rate

The sintering concept increase onset and duration of disintegration time for powder compacts as the mechanical strength is increased.

Sintering Method

There are two methods for the application of sintering concept in tablet dosage form[61-85]:

1. Heat treatment method or Thermal Sintering or Solid-State Sintering
 i. Microwave sintering Method
 ii. Laser Sintering Method
2. Acetone saturation methods

1. Heat treatment Method or Thermal Sintering or Solid-State Sintering

Heat treatment method involves heating a drug-polymer in a sintering heating system (thermal or microwave or any other)until its particles start to adhere/fuse to each other and forms aamalgamatedbonds. The API's particles are entangling in the matrix, resulting in slow release of the active ingredient from a tablet dosage forms.Thermal sintering can also be provided by Microwave irradiation or by laser technique[61, 64, 67, 72, 78].

2. Acetone Saturation Method

Acetone saturation method imply by holding of tablets in a prefilled saturated non-aqueous solvent based closed chamber for sufficient time durations. The prefilled saturated chamber can be prepared by using desiccators with a volatile solvent like acetone. The solvent vapors move to center of tablets thru capillary and polymer particles solubilize

outer surface of particles and resultingjoining or sintering of particles. Tablets canexpose to different duration of sintering time. After sintering, the tablets are further dried at room temperature or in a closed camber containing calcium chloride to remove the entrapped residual solvent.Final sintered tablets are finally air tightly packed for further evaluation[70, 76, 80, 84].

Future prospective of Solid dispersion technique with Sintering Technology:

Now a day, sintering technologies play a unique importance in the development and production of advanced drug delivery, to satisfy market need of novel drug delivery system. By exploring the use of sintered technique after solid dispersion, may become a key role in the growth of the pharmaceutical field. A recent research is also going on the development of temper resistant dosage form by the use of sintering technique. Resulting tablet dosage form will not only be high mechanical strength owing to sintering technology, but also ensure high solubility of poorly soluble drug because of solid dispersion. Surfactant can also be incorporated in the solid dispersion for further enhancement of dissolution rate of poorly soluble candidates. A process flow diagram for the preparation of Tablet dosage form by this combination technique is shown in Figure 12.

Hence, concurrent utilization of established approaches; solubility enhancement (solid dispersion with an optional surfactant) and Sintering technique will provide following perceptible features of Tablet dosage forms:

- ✓ Two component homogeneous tablets,
- ✓ Improved solubility of poorly water-soluble drugs and improved Gastric absorption of drug,
- ✓ Charged micronized material can be easily handled in solid dispersion process,
- ✓ Segregation, clumping, and other possible physical instabilities during long term storage of micronized material can be easily overcome by solid dispersion technology,
- ✓ Poorly soluble drug at molecular level in the carrier,
- ✓ Poor compressibility of solid dispersion carriers can be easily used in sintering technology. hence, facilitates use of carriers with poor compressibility,
- ✓ No handling problems of sticky carrier (used in solid dispersion preparation) in sintering technology,sinteringcan be performed in a conventional coating pan / machine,
- ✓ Process simplicity,
- ✓ High dissolution rate in medium due to solid dispersion mechanism,
- ✓ Remarkable bioavailability enhancement,
- ✓ Ease to fabricate in any suitable shape or size dosage forms,
- ✓ Improved stability of dosage form at accelerated storage conditions,
- ✓ Sustained release property helps in dose adjustment,
- ✓ Reduced Incompatibility with other components duetosmaller number of components,
- ✓ Surfactant can also improve dissolution while formulating solid dispersion,
- ✓ Potent drugs formulation with excellent content uniformity,
- ✓ Overall efficiency of the productcan be improved,
- ✓ Easy commercialization and scale up of solid dispersion process,
- ✓ Easy approach to formulate a controlled or sustained release products by the use of low solubility carriers in solid dispersion,
- ✓ Sintering Techniques provides sufficient mechanical strength of tablets, which is a limitation of solid dispersion.
- ✓ Pharmaceutical Industrial applicability, economic and commercially viable for the development of modified release dosage form of poorly soluble drugs.
- ✓ Suitable dosage form for pediatrics, elderly, and bed ridden patients and
- ✓ Patient compliance

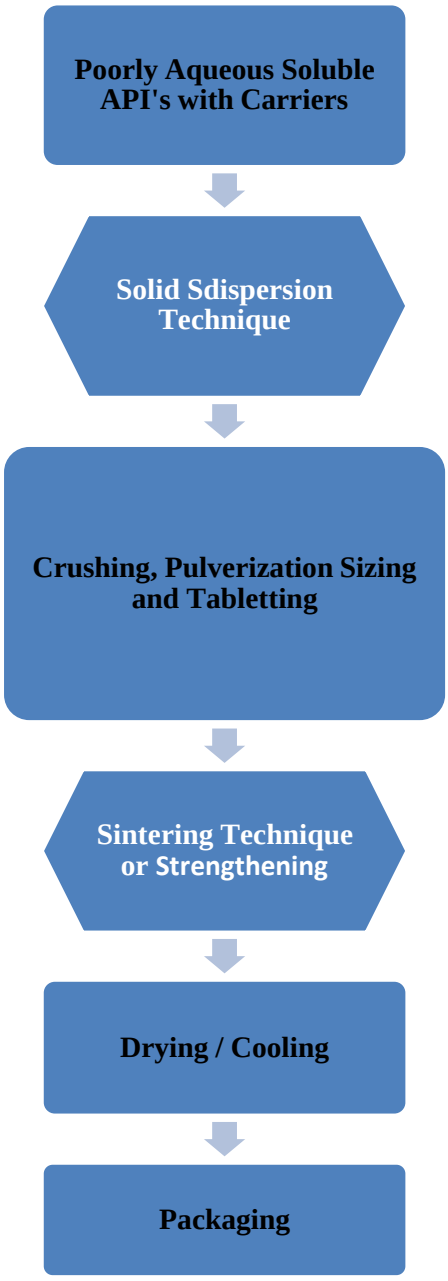

Figure12. Process flow diagram for the preparation of fast or modified Release Tablet by Amalgamating Solid dispersion Technique & Sintering Technology

CONCLUSION:

Most of the newly discovered chemical entities are poorly water-soluble. They have a critical effect on their solubility, dissolution, bioavailability and therapeutic potential. The wide ranges of solubility enhancement approaches are available, which can playasignificantrole in aqueous solubility, dissolution properties and content uniformity of poorly soluble drugs. Out of these approaches, Micronization and Solid dispersion is the most prominent techniques to enhance aqueous solubility of poorly water-soluble drugs but the development of dosage form has quite limitations. Mingling of Sintering Technology with Solubility enhancement techniques like Micronization or Solid Dispersion with release controlling carrier led to development of novel modified release tablet dosage forms. Where, Micronization of drugs can be easily achieved by Air Jet milling and Solid dispersions of drugs withrelease controlling agents can be easily formed into *Modified Release Tablets* by a familiar sintering technology. Developed tablets will improve solubility of poorly soluble drugs owing to Micronization or/ solid dispersion but also control the release of drug for prolong time duration. Concurrent application of well-established approaches- Micronization *(size reduction)*, *dispersion of drug in inert carrier (amorphous formation)*,optional*surfactant*(wettability) and sintering (strengthening) in the current article will obviously ultimately improve the aqueous solubility or dissolution rate of poorly soluble drugs.These techniquesextend anextensive potential for the development of fast or modified release tablet dosage form of sparingly soluble potent drugs.

CONFLICT OF INTEREST:

The authors have no conflict of interest regarding this investigation.

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