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An Overview on Recent Patents and Technologies on Solid Dispersion

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Abstract: The oral bioavailability enhancement of poorly water-soluble medicaments is still one of the most complicated aspects of the formulation development. Various approaches are currently available for solubility and rate of dissolution enhancement such as salt formation, solubilization and reduction of particle size, each with its own limitations and advantages. Solid dispersion is one of the most suitable approaches for the formulation development of poorly water-soluble drugs. The popularity of solid dispersion is evident from the increasing number of patent applications and patents granted in this field during recent years. This article reviews the various approaches for the preparation of solid dispersion such as a solvent melting, hot-melt extrusion method, solvent evaporation method, cryogenic processing approaches etc. from the perspective of patents filed or granted for these techniques. Some of the aspects taken into account before the preparation of solid dispersions are carrier selection and physicochemical testing along with an insight into the molecular arrangement of medicaments in solid dispersion. The manuscript further highlights various commercial patented technology platforms such as Solumer[tm], Hovione and Kinetisol which are based on the concept of solid dispersions.

Keywords: Solid dispersion, patents, dissolution, bioavailability, solubility, patented platform, carrier.

1. INTRODUCTION

The oral route of drug delivery is the most popular, easiest and simplest way of medicament administration. Owing to accurate dosage, smaller bulk, greater stability and ease of production of oral solid dosage forms have various benefits over other types of orally given dosage formulations. These solid oral dosage forms prepared with some excipients will affect the physicochemical properties of the medicament. The poor solubility and dissolution rate is the biggest hurdle in the biological performance of Poorly Water-Soluble (PWS) medicaments. The solubilization behavior of the drug is the key factor for the determination of oral bioavailability. Several approaches are available for the solubility enhancement as well as enhancement of the bioavailability and dissolution rate such as salt formation, solubilization, particle size reduction each with its own advantages and limitations. Solid Dispersions (SDs) implement the principle to medicament discharge by creating a mixture of a PWS medicament and highly soluble carriers used. SD approach has been broadly utilized to get better dissolution rate, solubility and oral assimilation of PWS [1-3].

2. SDS/SOLID STATE DISPERSIONS

SD is an easy and appropriate approach in comparison to a chemical approach for improvement in the solubility of PWS medicament [4]. Chiou defined SD as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method". The SDs may also be called as solid-state dispersions (Chiou and Riegelman, 1971) [5]. For instance, it is a molecular blend of the medicament and hydrophilic polymer in which the dispersed compounds may be in individual entity or in clusters. Chemical approaches will include the salt formation and development of prodrugs [6].

SDs are more therapeutic compliant by patients than other solubilization products. SDs efficiently reduce the size of the particle with a consequential enhancement in the medicament discharge in comparison to micronization or milling process in which the size of the particles is 2-5µm in the limited range. Further dispersion is also defined as "product formed by converting a fluid medicament-carrier combination to the solid-state". SDs of medicaments, therefore, fulfill active agent bioavailability and solubility of PWS medicament also increases in the medicament action and reduces side effects in the body [7-9].

2.1. Mechanism Responsible for the Improvement in Solubility from SD

The following is the underlying mechanism for improvement of the dissolution rate of PWS medicament by SD.

2.1.1. Reduced Particle Size

When the SD is exposed in the aqueous media, the polymer is dissolved and the medicament release is in the

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form of fine particles of colloids. This results in an improved surface area which leads to a high rate of dissolution of PWS medicaments.

2.1.2. Drug in an Amorphous State

PWS crystalline medicaments present in the amorphous form are having higher solubility. The energy required to break the crystal lattice in amorphous form during dissolution is negligible [10-13].

2.1.3. Particles with High Porosity

Particles in SD are found to have high porosity. This increased porosity of SD particles speeds up the release of medicament. Enhancement in porosity depends on polymer properties *i.e.* linear carriers have larger and more porous particles as compared to reticular particles.

2.14. Particles with Improved Wettability

A strong contribution to the improvement of solubility of medicament related to the medicament wettability enhancement has been verified in solid dispersion. A polymer having surface activity, *i.e.*, cholic acid and bile salt, can increase the wettability property of medicament results in improved dissolution profile [14-16].

2.2. Benefits

- The bioavailability is enhanced by SD without altering the active target by the chemical or the formulation approach [17].
- SDs are easy to manufacture and scale-up [18].
- Reduction in particle size in solid dispersion results in an improvement in surface area and the rate of dissolution is enhanced. Due to this, there is an increment in the bioavailability [19].
- The carrier utilized in the SD plays a vital function in enhancing the wettability of the particles. Improved wettability results in increased solubility; thus, it improves the bioavailability [20].
- In SDs, medicaments occur as a supersaturated solution (metastable polymorphic form). Thus, the drug present in the amorphous form increases the solubility of the particles [21].
- Solubilization and particle size reduction are the formulation approaches, among others. The formulation in SDs confers rise to a solid dosage form instead of liquid dosage form [22].
- SDs are much efficient than the particle size reduction methods since the limit of the reduction of particle size would be around 2–5 mm which is insufficient for enhancement in the solubility and bioavailability of the drug and drug discharge in the small intestine [23,24].

2.3. Drawbacks

- SDs are not extensively utilized in commercial products, essentially because throughout processing (mechanical stress) or storage (temperature and humidity stress), the amorphous state might endure crystallization [25-27]. Moisturization affect while storing will effect the stability of amorphous pharmaceuticals [28, 29].
- Moreover, all the polymers used in SDs can absorb moisture which might result in the partition of phase, growth of the crystals, transformation of the amorphous into the crystalline state and transformation of a metastable crystalline form to the more stable form while storing results in diminishing the solubility and dissolution rate [30, 31].

2.4. Classification of SDs

Based on the carrier physical state, SDs are classified in two main categories *i.e*. amorphous SD and crystalline SD. Based on their composition, the SDs can also be categorized into four generations, as shown in Fig. (**1**).

2.5. Techniques/Methods for SDs

There are various methods for the preparation of solid dispersion as described in Fig. (**2**).

2.5.1. Melting Method

In this approach, medicament and the carrier are melted collectively under specific temperature which is above the eutectic point after that, the liquid is cool down or solidified by dissimilar methods such as dispersing on thin layer of stainless steel cooled by the air or pouring water in a petridish inside a desiccator, ice bath agitation and immersion into the liquid nitrogen. The solid comes out which is trampled, sieved, minced to decrease the size of the particle. The benefit of the approach is that it does not require any solvent. Eric Gorman *et al.* discovered an SD of hepatitis C drugs by using different polymer *i.e.* copovidone, polyvinylcaprolactum polyvinyl acetate, polyethylene glycol, hydroxypropyl methylcellulose acetate, HPMC phthalate and cellulose acetate phthalate in the ratio of 5:1 and 1:5 [32]. Yunxia *et al.* invented a new stable ternary solid dispersion composition with enhanced bioavailability comprising of about 1-50% wt. of one or more PWS active pharmaceutical ingredients from BCS class II and IV, 11- 50% wt. of at least one water-soluble polymers and about 20-99% wt. of crosslinked polyvinylpyrrolidone where the solid dispersion is capable of inhibiting crystallization of API in the solid-state and aqueous gastrointestinal tract (GIT) medium [33].

2.5.2. Hot Melt Extrusion Method

Medicament and the carrier are mixed by heating, after that, the melting mixture is homogenized and squeezed out in the form of pellets, tablets, rods and uniformly mixed with another ingredient. Amalgamate the mixture with a force by revolving the bolts leads to the disaggregation of medicament inside the polymer which results in the formation of homogenous dispersion. The extruded systems consist of one or more melted carriers and other additives like plasticizers and other pH modifiers. An advantage in comparison to the other liquefying methods is the short resistance duration of the medicament and carrier at an elevated temperature within the extruder which will reduce the danger of degradation of the thermolabile medicaments and is a chief benefit of this

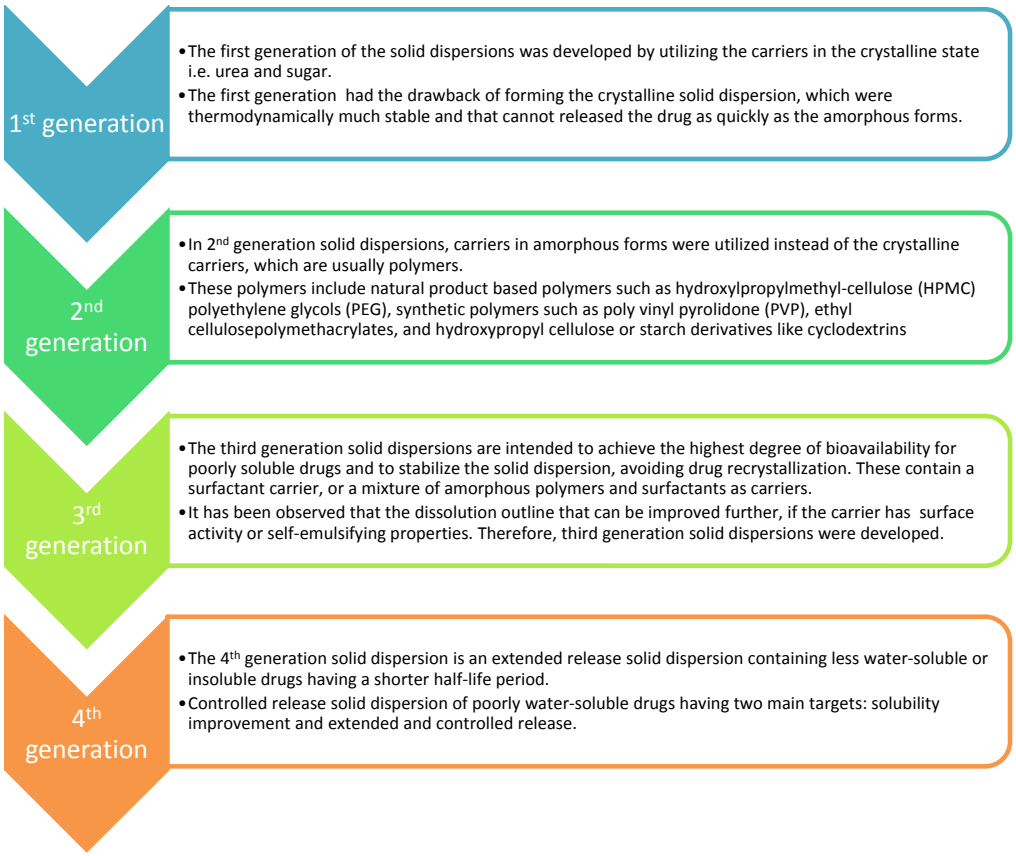

Fig. (1). Generations of solid dispersion. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

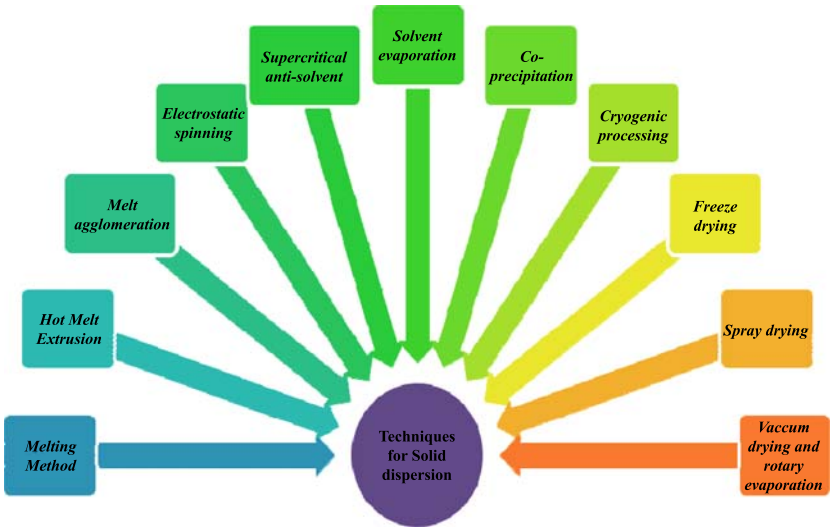

Fig. (2). Various techniques/methods used in preparation of solid dispersion. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

method. Nomera *et al*. states that solid dispersion of the less soluble medicaments are prepared by hot-melt extrusion method having enhanced solubility and assimilation properties of the API [34]. Kawasaki *et al.* invented a solid dispersion comprising of cilostazol, methacrylic acid copolymer S and methacrylic acid copolymer L where the cilostazol is retained in an amorphous state in a gastrointestinal tract for a certain period after oral administration [35].

2.5.3. Melt Agglomeration

In this technique, two methods are used to formulate the solid dispersion. One is by spraying the medicament on melt binder with ingredients and second is melting of binder, medicament and ingredients above the melting point of binder. This technique is beneficial in the uniform blending of medicament but larger particle size causes segregation and results in an adhesive mass. Chen *et al.* invented an SD of

ospemifene with a hyfophile carrier *i.e*. crospovidone hypromellose acetate succinate, polyvinyl pyrrolidine /vinyl acetate copolymer, HPMC, eudragit in the ratio of 1:1 to 1:20(w/w) [36]. Kulkarni *et al.* stated that the present innovation relates to SD of rifaximin which increases the rifaximin solubility, improves GI availability and process of formulating solid dispersion [37].

2.5.4. Solvent Evaporation Method (Solvent Method)

SD is obtained by evaporating the solution of the solvent consisting of medicament and the carrier. Some of the polymers are being used as carriers in this technique owing to the high melting point of the polymers. An important prerequisite of this technique is the ample solubility of medicament and the carrier in the cosolvent or solvents. The solvents used are ethanol, acetone, methanol, methylene chloride, ethyl acetate, water and the mixtures. Several surfactants such as SLS and Tween 80 were utilized to boost up the solubility of medicaments and carriers used in the solvents. On the other hand, the incorporation of the solvents considered is having a large excess of solvent which may trigger a major alteration in the configuration of the matrix. Therefore, the methods are developed for the fast removal of the solvent such as hot plate heating, drying in vacuum, etc [38]. Stefinoric *et al.* discovered an SD of naloxegol salts in amorphous form and a matrix compound *i.e*. organic polymer and silicon-based inorganic absorbent [39].

2.5.5. Vacuum Drying and Rotary Evaporation

Solvent removal is the task which will take place while working on this technique. The heating procedure, which can increase the mobility of molecules, results in the phase separation. After this process, the resultant of SDs might be stock up in the vacuum desiccator which leads to complete removal of residual solvent. Therefore, the recrystallization of medicaments and the phase separation can, without much of a stretch, occur during the whole process. Kulkarni *et al.* also discussed the melt agglomeration method. Guo *et al.* developed a SOMCL-9112 pharmaceutical formulation with high bioavailability, to meet the needs of clinical administration under the premises of achieving adequate medicament loading and stability [37]. In one invention, the SOMCL-9112 solid dispersion can form stable mixed micelles with an average particle size of about100 nm in a simulated gastrointestinal fluid, and the solubility of SOMCL-9112 can be increased from about 10.mu.g/ml to more than 300 .mu.g/ml. The medicament solubility is also improved [40].

2.5.6. Spray Drying

This approach allows extremely rapid evaporation of solvent that results in the fast conversion of an active pharmaceutical ingredient (API)-polymer solution to the solid API- polymer particles. In this process, the solution of medicament and polymer is evaporated by spraying the solution as fine droplets into a chamber under controlled conditions of heat, humidity and airflow. Air is used as a drying medium and separation of the product after completion of drying takes place. Particle size manufactured by the spray drying will modify the size of the droplets through a projecting spout to meet the advance applications or processing requirements. Stefinovic *et al.* discussed the same solvent evaporation method [39].

2.5.7. Freeze-Drying

The process comprises immersing the carrier and the API solution in liquid nitrogen until it was completely frozen and the frozen solution is then lyophilized. Benefit of the study is that this approach will minimized phase separation risk. Temtem *et al.* reveal a technique for delivering amorphous SDs in a nanoparticulate structure through dissolvable controlled co-precipitation, utilizing microfluidization/ microreaction innovation technology to advance high vitality blending/communication at a micro and/or molecular level between the streams engaged with the procedure. Feed streams, solvent and anti-solvent, are sustained to an intensifier siphon at independently controlled rates and compelled to communicate to small scale and additionally nano-scale inside a microreactor. The present creation additionally uncovers undefined SDs obtained by the strategy for the development just as pharmaceutical pieces containing the equivalent [41].

2.5.8. Cryogenic Processing Approaches

Cryogenic processing approaches such as Spray Freeze Drying (SFD) and Ultra-Rapid Freezing (URF) can also be used for the preparation of SD. SFD allows a drop-down in the particle size of medicament without intense mechanical stress or frictional force results in the dilapidation of the API by thermal stress. SFD is an exceptionally encouraging method in which the polymer solution and the medicament apply in the form of tiny droplets on/into the cold dry air or liquefied nitrogen and the frozen droplets were later desiccate in the lyophilization chamber. In URF, a medicament and the carrier solution are applied onto a solid cryogenic surface and particles which are frozen, are gathered and the solvent is eliminated *via* lyophilization. As cooling is rapid, the API nucleation crystals are reduced or totally evaded, produce amorphous morphology after lyophilization. The cryogenic processing approach includes many other benefits in contrast to the traditional methods. For thermolabile medicaments, melting method and spray drying are not suitable. Berg *et al.* present invention related to an ultra-rapid freezing device for cooling the specimen sample (flash freezing apparatus), in particular to ultra-rapid freezing devices suitable for ultra-rapid freezing of biological samples. The invention further samples frozen ultra-rapid related (flash freezing) method, and more particularly to an ultra-rapid freezing method of the biological sample. The present invention is applicable to ultra-rapid freezing of artificial (synthetic) Sample or biological (Biological) sample [42].

2.5.9. Supercritical Anti-Solvent (SAS)

SAS strategy utilizes the supercritical CO_2 as a dissolving solvent or antisolvent. Therefore, this approach is esteemed as an environmentally well-arranged technique where no natural solvent is required. In supercritical fluids, pressure and temperature are more critical factors. The main features of the gas such as low surface tension, low high diffusivity and viscosity impart to liquids during the management of stress of the supercritical fluids allow the exact management of the solubilization of various medicaments. When CO_2 was used as a solvent, carriers and medicament are dissolved into the supercritical CO_2 and spray from the spout inside an expansion chamber having lower pressure. The rapidly growth induced speedy nucleation of the medicaments dissolved and the carriers lead in the development of the SD particle with

an alluring distribution of size in a brief span of time. Sing *et al.* disclose a method for preparing an azilsartan SD by a supercritical anti-solvent method. SD of the medicament and the water-soluble carrier is PVP-K30. By this method, the azilsartan is dispersed in the PVP-K30 in an amorphous form, so that the dissolution rate of the azilsartan can be increased and the stability thereof can be improved [43].

2.5.10. Co-Precipitation Method

It is an appropriate approach to formulate SDs of PWS medicaments, which are having poor solubility and high melting points in organic solvents which cannot be operated by melting and other solvent methods. In this approach, medicament and polymers are completely dissolved into an organic solvent by incorporating antisolvent that leads to precipitation of medicament and the polymer. This suspension is then filter-out and washed off to evacuate leftover solvents. The material of co-precipitation acquired after the filtration and drying is referred to as microprecipitated bulk powder (MPD). The advantages behind this study are that it does not need any increased temperatures which results into the decomposition of medicament and the carrier. Shirish Kumar Kulkarni *et al.* same as discussed above in the melt agglomeration method [37]. The present innovation identifies with SD, rifaximin, which builds the solubility of rifaximin and improves GI accessibility. It additionally identifies with pharmaceutical structures involving an SD of rifaximin [44].

2.5.11. Electrostatic Spinning

In this approach, the medicament and polymer solution is kept in a spinneret, which is linked to a microsyringe pump of high voltage between 5-30 kV. This pump is attached with a tip of the needle to raise a charge on the solution surface. A set electrical potential is applied diagonally having a fixed distance between spinneret and collector. At the point, while the electrical forces surmount the surface tension of the solution in the air interface, the polymer jet is evicted [45]. Once it comes outside, then these jet are charged and goes straightaway for some space and then they will travel along the spiral path owing to whipping instability. The fibers collected will fabricate a non woven fabric which is utilized in the oral dosage forms *via* incorporating the materials into the capsule. The benefits behind the strategy are that it is related to the enormously large surface area/unit mass of fibers which will smoothen the rapid and proficient solvent evaporation methods lead to the amorphous dispersion formulation. As a result, the dissolution rate of API was improved significantly *via* amorphization and nanosizing methods. Farah *et al.* disclose a pharmaceutical composition comprising of SD of telmisartan in a novel pharmaceutical carrier (PEG-32-stearate). More particularly, the invention relates to a pharmaceutical composition comprising the SD of BCS class II drugs in Gelucires [46]. Yunxia *et al*. discussed the solvent melting method [47].

2.6. Carriers Used for SDs

Carrier is an inactive substance that acts as a vehicle for an active substance, or we can say that by incorporating the carrier to any PWS medicament, solubility may be enhanced. The features of the carrier have a reflective impact on the dissolution properties of the medicament which is dispersed. Table **1** demonstrates different class of carriers which are used in solid dispersion.

A carrier should meet the following prerequisites for the improvement of the dissolution rate of a medicament:

- Rapid dissolution is the features of freely water-soluble
- Nontoxic and pharmacologically inert
- Heat stability for the melt method
- Solubility in a diversity of solvents
- Rather than improving the aqueous solubility of the medicament
- Chemically compatibility with the medicament
- Form only weakly associated complexes with the medicament

Table 1. Different class of carrier used [48].

Type of Carrier	Carrier Examples
Acids	Citric acid, Tartaric acid, Succinic acid, Phosphoric acid
Sugars	Dextrose, Mannitol, Sorbitol, Sucrose, Maltose, Galactose, Xylitol, Lactose, Soluble Starch, Chitosan, Galactomannan, British Gum, Amylodextrins
Polymer material	PVP, PEG4000, PEG6000, Methylcellulose, CMC, HPC, Xanthan Gum, Guar Gum, Sodium Alginate, MC, HPMC, Dextrin, β-CD, HPβ-CD, Eudragit® L100 sodium salts
Surfactant	Polyethylene Stearate, Poloxamer, Deoxycholic acid, Tween and Spans, docusate sodium, Myrj-52, Pluronic F68, SLS, Vitamine E, Gelucire 44/14
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthenes

2.7. Characterization of SDs

Standard Dissolution methods verified the dissolution improvement of PWS medicaments in SDs. Properties including the physical condition of medicaments, the medicament–carrier interaction, physical and chemical stability of medicaments can also be assessed. As a result, many instrumental and analytical approaches are used to determine the properties of SD. The degree of crystallinity and the crystalline state of medicaments were prominently characterized. The number of amorphous medicaments can be determined indirectly from the extent of crystallinity in the sample. The crystalline nature of medicaments is generally characterized *via* thermoanalytical approaches such as Differential Scanning Calorimetry (DSC), powder X-Ray Diffraction (PXRD), Confocal Raman Spectroscopy and Modulated Differential Scanning Calorimetry (MDSC). Table **2** specifies the different characterization techniques. Other instrumental approaches such as solid-state nuclear magnetic resonance, Fourier Transformed Infrared Spectroscopy (FTIR) and Thermal Gravimetry Analysis (TGA) are utilized for studying the stability of chemical and interaction of molecules of

Table 2. Characterization techniques of SD.

S. No.	Methods	Introduction	Refs.
1.	Thermal Analysis Approaches	• It involves a cluster of approaches in which the physical parameters is assessed as a function of temperature, while the substance used is subjected to a controlled temperature programme • Approach will give a valuable information of the carriers and stability of medicament including the physical and chemical processes in SDs to chose the processing and the preparatory parameters while formulation of the SD.	[49]
2.	PXRD	• PXRD is a broadly utilized technique to distinguish and classify crystallinity of the medicaments in SDs. • This approach would perceive a material of long-range order as well as interpret the pointed peaks diffraction which can indicate that the Crystallinity of the compound with a characteristic fingerprint region. • The fingerprint specificity and the medicament crystallinity can be independently identified from the crystalline state of the carrier and which will distinguish it as a crystalline state and amorphous state of medicaments in SDs. However the crystallinity under 5–10% fraction might not be detected *via* PXRD.	[9]
3.	DSC	• Differential Scanning Calorimetry (DSC) is the most dependable thermoanalytical technique. • It is a thermal method to find out the temperature and heat flow linked with compounds transitions.With the help of DSC we can find and monitor melting temperatures and study the thermal behavior of various compounds. • Methods in which energy is produced or required can be observed quantitatively with the help of DSC. • Interactions between drugs and carrier cause the changes in the exothermic and endothermic peaks.	[50]
4.	XRD	• In this technique of analysis, the intensity of the XRD (or reflection) from a sample is calculated as the functions of the angles of diffraction. • The diffraction technique is especially important in identifying the compounds or formation of complexes since spectrum or lattices parameters are markedly different from that of pure components. • The major problem while using the diffraction technique is to study about inability of dispersion systems to differentiate between the amorphous precipitation from molecular dispersion if the lattice parameters of the solvent component are not altered.	[51]
5.	FT-IR	• FT-IR can be employed for the characterization of the possible interactions in between medicament and carrier in the solid-state on FT-IR spectrophotometer via using traditional KBr pellet method. • In this technique, SD weighs about 10 mg of the sample is mixed with the anhydrous KBR of equal weight and samples (Pure medicament, carrier, SD) then spectra are obtained using FTIR spectrophotometer.	[52]
6.	SEM	• SEM is useful in ascertaining the morphology, particle size of solid particles and sometimes polymorphism of medicament. • The fine dispersion of medicament particles in the carrier matrix may be visualized. The application of the electron microscope approach, however usually limited to chemicals with high resolution.	[53]

Table 3. Evaluation parameters of SD.

S. No.	Methods	Introduction	Refs.
1.	*In vitro* dissolution Studies	• Dissolution is carrying out to decide the rate and dissolution extent in USP- type II paddle apparatus at 37±0.20C. Aliquots of 5 ml from the dissolution medium are withdrawn at a different time interval which is filtered through filter paper and analyzed for medicament contents by measuring the absorbance at fixed wavelength using UV spectrophotometer and replenished by an equal volume of fresh dissolution medium.	[54, 55]
2.	*In vivo* bioavailability enhancement study	• The *in vivo* study of the selected optimized formulation shall be performed on one animal from reported animals like Wister rats, Sprague- dawley rats and albino rats. • The *in vivo* study will help to determine the enhancement of the solubility and bioavailability of selected BCS class II medicament. • The bioavailability shall be determined *via* the pharmacokinetic/ pharmacological method or in-situ animal modeling as deemed appropriate wherever possible, *in vivo* studies may be replaced with an *in vitro* study.	[54, 55]
3.	*Ex vivo* permeability	• The *Ex-vivo* study of the selected optimized formulation shall be performed on one animal from reported animals like Wister rats, Sprague-Dawley rats and albino rats. The *in vivo* study will help to determine the improvement of the solubility and bioavailability of selected BCS class II medicament. • *Ex vivo* environments allocate experimentation on an organism's cells or tissues under more controlled circumstances that is possible *in vivo* experimentation work (in alive creature), at the expenditure of varying the "natural" environment.	[56]

the carrier and the medicament. Approaches of microscopy like optical microscopy, Atomic Force Microscopy (AFM) Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are also utilized for the qualitative characterization of the crystallinity of the medicament, molecular miscibility, phase separation and surface morphology of SDs. Table **3** focuses on the different evaluation parameters of SD.

2.8. Patents on SD Technology

Bountiful techniques that have been described in academics and patent literature for innumerable products and processes are involved in the SD technology. The restrictions of conventional techniques of SD are provoking the researchers to restructure them which results in the number of patents in the area of Solid dispersion [77]. There is an account of some of the recent patents in the field of solid dispersions as shown in Table **4**.

2.9. Recent Patentented Technology Platform

Patented Platform know-hows are considered a valuable apparatus to fix the productivity and quality of drug product development. The essential thought is that a platform, in blend with a hazard-based methodology, is the most deliberate

Table 4. Patents on SD.

S. No.	Patent No. & Year	Summary of Invention/ Method	Medicaments Used	Carrier Used	Refs.
1.	CN108186578A (2018)	SD of the medicament is prepared by polymeric carrier by copolymerisation method.	Ritonavir	VA 64	[57]
2.	CN108175751A (2018)	The present invention includes bufotalin solid dispersion that is obtained by mixing bufotalin, a hydrophilic carrier and a deposition inhibitor and processing a mixture through solid disperse preparation technology. A medicament loading amount is 1-30%. The bufotalin solid dispersion does not use an organic solvent which is safe and efficient. The obtained bufotalin solid dispersion can increase a dissolution rate of three components medicament loading mount is high, the stability of the bufotalin is good.	Bufogenin	-	[58]
3.	CN108042496A (2018)	In this, the curcurbitacin B SD consists of cucurbitacin B and a carrier material. The cucurbitacin B solid dispersion is quick in dissolution and high in bioavailability. The cucurbitacin B solid dispersion is relatively simple in production equipment, easily controlled in quality, short in cycle and cost-saving, and has extremely good application prospects.	Curcurbitacin B	Hydroxypropyl methyl cellulose, polyethylene glycol caprolactam or polyethylene - polyvinyl acetate - polyethylene glycol	[59]
4.	CN108096205 (2018)	The invention discloses an apixaban tablet. The apixaban tablet is formed through the tableting of apixaban solid dispersion and auxiliary ingredients. The apixaban solid dispersion is formed by apixaban and mannitol and the auxiliary ingredients comprise microcrystalline cellulose, polyvinylpolypyrrolidone, superfine silica powder and the weight ratio of apixaban to microcrystalline cellulose to polyvinylpoly pyrrolidone to the superfine silica powder is 1 to (30-60) to (5-10) to (1-5).	Apixaben	Mannitol, micro crystalline cellulose, polyvinylpoly pyrrolidone and superfine silica powder	[60]
5.	US20180147154A1 (2018)	The invention relates to a method for stabilization of rotigotine. In this SD comprising of PVP and a non-crystalline form of rotigotine where the ratio of weight of rotigotine to PVP is in a range from about 9:3.5 to about 9:6.	Rotigotine	Polyvinylpyrrolidine	[61]
6.	CN108261401 (2018)	The present invention discloses the SD of antiparasitic medicament along with dispersion carrier, antioxidant & ethanol. The ivermectin tablets prepared by an ivermectin solid disperse system have the advantages of a high dissolution rate and good stability.	Ivermectin	Anhydrous powdered sugar, lactose, sucrose, starch, maltodextrin, and microcrystalline cellulose one or more, and / or the antioxidant is parabens, butyl hydroxyanisole or dibutylhydroxytoluene	[62]
7.	CN107213127B (2017)	Invention will provide a stable, dissolution & improved in bioavailability by SD of the medicament	Ruige pirfenidone	Sorbitol and povidone	[63]

Table (4) contd….

S. No.	Patent No. & Year	Summary of Invention/ Method	Medicaments Used	Carrier Used	Refs.
8.	CN108210472A (2017)	Invention will increase the *in vivo* bioavailability and dissolution rate of the medicament *via* SD	Cilnidipine	Hydroxypropyl cellulose and hydroxy propyl methylcellulose phthalate	[64]
9.	WO2018127088A1 (2018)	Lurasidone SD preparation method comprises of melting treatment of a mixture containing lurasidone, a medicinal hot melt carrier, optionally an acidic regulator and plasticizer. Lurasidone is present in a form of free base.	Lurasidone	Povidone, copovidone, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol	[65]
10.	JP2017222728A (2017)	Fenofibrate SD is prepared by melting with PVP and then pass through the sieves	Fenofibrate	PVP	[66]
11.	KR101856911B1 (2017)	The present invention is the pelruby sustained-release SD formulation of the propene containing Eudragit® RL PO, Eudragit® RS PO, and amino Clay (aminoclay) as a pharmaceutical composition to provide.	Pelubiprofen	Eudragit® RL PO, Eudragit® RS PO, and aminoclay	[67]
12.	US10004719B1 (2017)	A spray-dried SD in which the pharmaceutical compound is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer. Further disclosed are methods for preparing such a solid dispersion and using it for treating hepatitis C virus infection and a pharmaceutical formulation containing the same.	Heterocyclic compound	Poloxamer 188, PVP K30, PVP VA64, HPC-L, or HPC-SSL.	[68]
13.	US20170157095 (2017)	In order to resolve the low solubility of by adding a specific carrier and using SD technology, the dissolution of an active ingredient is effectively increased.	Allisatan isoproxil	Hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, hydroxy propyl methyl cellulose cellulose acetate succinate.	[69]
14.	US20170273999 (2017)	In this invention method of producing an SD that can improve the solubility of a hardly soluble polyphenol in water.	Polyphenol	-	[70]
15.	US10265270B2 (2019)	This invention relates to a hot-melt extrusion method of solid dispersion of decoquinate medicament. In this hot melt extrusion method, the composition comprises 5-30% of decoquinate, 60-90% of a polymeric carrier and 0-10% of a surfactant	Decoquinate	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, copovidone, povidone or polyethylene glycol	[71]
16.	US20170368031 (2017)	This invention relates to SD formulations that may be beneficial for the ailment of diseases and disorders caused by the hepatitis C virus ("HCV").	Elbasvir	Hydroxypropyl methylcellulose	[72]
17.	US20170028007 (2017)	The SD is used for preparing a medicament for treating urinary tract calculi.	Desmodium stracifolium	-	[73]
18.	WO2015152544A1 (2015)	An amorphous *SD* comprising a medicament with enhanced solubility, stability, bioavailability and oral formulation (*e.g*., a tablet)	Taxane	Polyvinylpyrrolidone K-30	[74]
19.	US20160213684 (2016)	The present invention relates to a novel galenic form of a Selective Progesterone Receptor Modulator (SPRM)	Ulipristal acetate	Polyethylene glycols, N-vinyl-2-pyrrolidone polymers, N-vinyl-2-pyrrolidone	[75]
20.	US20160017164 (2016)	The present invention concerns an SD of pigment in the granular form that is suitable for colouring aqueous compositions.	Cold water-soluble modified starch	-	[76]
21.	WO2017041679A1 (2017)	The present invention belongs to the field of pharmaceutical preparations and particularly relates to a process for preparing tadalafil the solid dispersion pharmaceutical excipients. Tadalafil further relates to a pharmaceutical composition of solid dispersion containing amorphous and preparing the method for treating male erectile dysfunction medicament.	Tadalafil	Hydroxypropylmethyl cellulose, hydroxy propyl cellulose, povidone, poly ethylene glycol, ethylcellulose, liposomes, methacrylic acid copolymer	[77]
22.	KR101561406B1 (2015)	Telmisartan medicament is mixed with NaOH and PVP	Telmisartan	Polyethylene glycol almond glycerides, polyethylene glycol Caprylic / capric glycerides	[78]

technique to impact earlier learning for the given technology. In addition, SD innovation has been developing every day in this manner. Various pharmaceutical and medicament conveyance consortium is currently engaged in providing patented SD technology. An innovative medicament delivery platform generates accompanying patient benefits which will add a new competitive recompense for a medicament [79]. Fig. (**3**) focusses on the different patented technologies in solid dispersion.

Following is a brief account of various patented technology platforms.

Fig. (3). Various patentented technologies on solid dispersion.

2.9.1. Solumer[tm]

SoluBest has built up one of a kind SD innovation for essentially improving the bioperformance of inadequately soluble medicaments. This versatile and robust technological platform alluded to Solumer™ that can be applied towards a wide range of marketed medicaments and molecules in development. SoluBest has developed a proprietary platform for the creation of medicament-polymer SDs in which the lipophilic medicament is homogeneously interwoven within a multi-polymer matrix. Due to association with the amphiphilic polymer, solumerized medicaments exhibit modified physico-chemical properties (*e.g*. decreased enthalpy and temperature of melting) compared to the crystalline lipophilic APIs. Some commercial patented technology platform products are solufeno, tricor 145 and soluresveratrol [80].

2.9.2. Hovione

Spray drying and Hot-Melt Extrusion (HME) are the two technologies most widely used for the formulation of Amorphous Solid Dispersions (ASDs). Both processes utilize a range of polymer excipients that have been approved for use in medicament formulations. Hovione is a developing company that focuses on four primary aspects, *i.e*. performance in the GI tract, physical stability, chemical stability/compatibility between the ingredients and manufacturing scale-up. For spray-dried ASDs, the solvent must be compatible with both the API and the polymer matrix. With all ASDs, the formulation must also be physically and chemically compatible. Hovione has been providing SD services to the pharmaceutical industry for nearly 15 years. During that time, a significant amount of effort was undertaken to leverage all prior experience for each new SD project. Employing a Quality-by-Design (QbD) approach to understand the fundamentals of the SD process and build models for the prediction of spray-dried particle properties under various processing conditions is essential to process design and scale-up, and QbD adds predictability and significantly reduces the risk involved in process development, scale-up and right-first-time clinical batch manufacturing [81].

2.9.3. KinetiSol

This is from DisperSol Technologies, which is based on a commercial plastic compounding process that was developed into a GMP pharmaceutical process by the company. The solvent-free, fusion-based process requires high shear and is typically completed within 20 seconds at the lab and commercial scale. Frictional and shear energies combined with high-intensity mixing lead to a rapid transition to the molten state. Some commercial patented technology platform products of amorphous SD are Kaletra®, Norvir®, Prograf®, Spranox®, Zelboraf®, Intelence®, Incivek®, and Kalydeco® [82].

2.9.4. Meltrex® Technology Platform

Meltrex TM is a patented SD developing technology. The fundamental elements in this technology is used as a special twin-screw extruder and existence of the two self-governing hoppers in which temperature may vary over a wide range of temperature. This technique allows a compact drug residence time in the extruder and a continuous mass flow and avoids the thermal stress of the medicament and carriers. In addition to this, the purpose of the method is to protect medicaments from hydrolysis and oxidation by the entire elimination of oxygen and moisture from the mixture. Some of the commercially patented technology platform products which come under the melt extrusion are Troglitazone® (Parke Davis)*, Kaletra® Meltrex® (Abbott), NuvaRing® (Oragnon), Implanon® (Schering-Plough), Zoladex® (AstraZeneca) and Ozurdex® (Allergan) [83].

2.10. Future Perspectives and Approaches in SD

Solid Dispersions create a lot of curiosity for the pharmaceutical scientists owing to its simplicity and scalability for the product developments of PWS medicaments. Though SD are investigated for such an elongated time recently, there is a lot of hope for the scientists and the researchers in this area.

Recent advancements of carriers in the area of SD:

- Appropriate use of novel carriers
- Incorporation of novel additives such as super disintegrants, pH modifiers and surfactants
- Development and categorization of novel research methods
- Elucidate the mechanism of thermodynamic of many procedures in the dissolution, formulation, preparation, and storage conditions [84-86].

Some new inert carriers are now being reported in recent years. One such carrier is AEROPERL® 300, which is a highly adsorptive carrier, a granulated form of colloidal silicon dioxide consisting of particles with a mean diameter of approximately 30 μm. It can absorb liquid formulations and turn them into free-flowing powders which than can easily be used for direct tableting processes [87].

Apart from these, the focus of the scientist is on the innovation of newly surface-active/self-emulsifying carriers and vehicles/ingredients to avoid recrystallization of medicaments and physical/chemical stability of both medicament and carrier in SD during the development of their ER dosage forms. Kinetisol Dispersing (KSD) is a newly elevated energy mixing process for SD preparation, in which, the drug and carrier are processed by utilizing a series of rapidly rotating blades through a combination of kinetic and thermal energy without the aid of external heating sources. This brings new hope for the development of more SD products in the future [82].

CONCLUSION

Solubility enhancement techniques have turn into an essential feature in bringing PWS medicaments effectively in the market. Among which solid dispersion is one such technology which has led to an endorsement of a variety of products to market by enhancing drug solubilization. It is well-thought-out as one of the most successful methods in which product is easilydeveloped and the issues related to low bioavailability of water-insoluble medicaments are solved. Though some of the issues related to the instability and scalability remain the same, some novel and optimized manufacturing approaches having high potential to overcome the issues associated with low soluble medicaments are now being reported. In the preparation of SD, indulgent properties of the carrier and selecting a suitable method play crucial roles in the success of the formulation. Development of improved and advanced equipment, analytical techniques, technologies and the emergence of various alternative polymers may help in the future to find solutions and make the SD approach practically more feasible at large scale. Furthermore, the dispersion of BCS class II drugs in drugs belonging to BCS class I may be used as a potential carrier-free new solid dispersion approach for improving the dissolution and bioavailability of PWS drugs, with an overall improvement in the efficacy of drugs. The multiple advantages offered by SD appeal both industries as well as academics and will witness more patents being filed in this area. Although there are several approaches for the development of SDs, recently a lot of patents are being filed/granted for melt extrusion/melt agglomeration techniques.

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