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Review Article

SOLID DISPERSION: A NOVEL MEANS OF SOLUBILITY ENHANCEMENT

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ABSTRACT

Poor solubility of drugs is a major challenge in the formulation development. Solid dispersion is introduced as a novel means for enhancement of solubility. Solid dispersion may be defined as a set of solid products comprising of at least two diverse components, usually hydrophilic matrix and hydrophobic drug. This matrix may be crystalline or amorphous in nature. As per biopharmaceutical classification system class II drugs are with low solubility and high permeability and are the promising candidates for improvement of solubility as well as bioavailability by means of solid dispersion. Practical aspects pertaining to preparation of solid dispersions, like the selection of carrier, drugs molecular arrangement in these preparations are discussed in this article. Proposed article highlights the various preparation techniques of solid dispersion, characterization, available recent technologies, marketed preparation, future prospective etc.

Keywords: Matrix, Solubility, Carrier, Solid dispersion.

INTRODUCTION

The simple and easy way of administration of the drug is through oral route. The oral dosage forms have many benefits compared to other dosage forms like greater stability, accurate dosage, smaller bulk and ease of production. The oral route has been considered as most common and preferred route owing to convenience and easy administration. As a patient's prospect, swallowing a dosage form is a comfortable means of taking medication [1, 2]. Solubility is a major challenge for certain drugs to develop a suitable formulation for administration of drugs orally like Griseofulvin, Digoxin, Phenytoin, Sulphathiazole and Chloramphenicol. With the recent advent of high-throughput screening of potential therapeutics, the numerous drug candidates with poor solubility has increased severely and their formulation for oral delivery poses great challenge to formulation scientists in the pharmaceutical industry [3, 4]. Major problem encountered during oral delivery of certain active agents is poor bioavailability due to inadequate drug absorption. Therefore pharmaceutical research is mainly focused on two prime areas: first to improve the oral bioavailability of active agents including solubility enhancement and dissolution rate of poorly water-soluble drugs and secondly to enhance the permeability of poorly permeable drugs. In the Biopharmaceutical Classification System (BCS) (table 1) drugs with high membrane permeability and low aqueous solubility are categorized as Class II drugs. Therefore, solid dispersion (SD) technologies are particularly useful in the improvement of oral absorption as well as the bioavailability of BCS class II drugs [5].

Table 1: General BCS for orally administered drugs

BCS Class	Solubility	Permeability
BCS I	High	High
BCS II	Low	High
BCS III	High	Low
BCS IV	Low	Low

Solubility

The Solubility is the property of a liquid, solid, or gaseous chemical substance called solute to dissolve in a liquid, solid, or gaseous solvent to obtain a homogeneous solution of the solute in the solvent. The solubility of any substance basically depends on the solvent used in temperature and pressure as shown in (table 2) [6].

Table 2: Solubility aspect of parameter

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practical insoluble	10,000 and over

Importance of solubility

Solubility is one of the significant parameters to attain a preferred concentration of drug in systemic circulation for providing a therapeutic response. Oral intake is the most suitable and frequently employed route of drug delivery owing to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms [7].

Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of the solvent medium as well as temperature and pressure of system [8, 9].

(a) Particle size

It is very much related to solubility and affects surface area to volume. If the particle size is reduced, this ratio gets increased. Greater the surface area greater the interaction with the solvent occurs.

The effect of particle size on solubility can be described by [10].

$$\log \frac{S}{S0} = \frac{2\,\gamma\,V}{2.303\,R\,T\,r}$$

Where,

S, is the solubility of infinitely large particles

S_0, is the solubility of fine particles

V, is molar volume

R, is the radius of the fine particle

T, absolute temp in °K

R, universal gas constant

(b) Temperature

Usually, solubility of a solid solute is increased due to increase in temperature.

(c) Pressure

An increase in pressure causes an increase in solubility and vice versa for gaseous solutes while for solid and liquid solutes it has no effect on solubility [11].

(d) Nature of the solute and solvent

Nature of solute and solvent affect solubility. For example, one gram of lead chloride can be dissolved in 100 grams of water at room temperature; while 200 grams of zinc chloride can be dissolved. This vast difference in solubility is due to the difference in the nature.

(e) Molecular size

Molecular size is also affects the solubility. The bigger the molecule or greater the molecular weight, the less soluble will be the compound. In the case of organic compounds, the quantity of carbon branching will lead to increase in solubility as more branches reduce the size of the molecule [12, 13].

(f) Polarity

It is known that like dissolve like. Generally polar solute dissolves in polar solvents while non-polar solute dissolves in non-polar solvents. Polar solute compound is having both ends to the molecule positive as well as negative. For polar solvent, the positive end of it attracts negative end of the solute molecule. This type of interaction is known as dipole-dipole interaction [14].

(g) Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is a polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility [15, 16].

Techniques for solubility enhancement

There are various techniques that help in increasing the solubility of drugs are as follows [1, 17].

I. Chemical modifications

1. Salt formation

2. Co-crystallization

3. Co-solvency

4. Hydrotropy

5. Solubilization

6. Nanotechnology

II. Physical modifications

1. Particle size reduction

2. Modification of the crystal habit

3. Complexation

4. Solubilization by surfactants

5. Drug dispersion in carriers

• Solid solution

• Eutectic mixtures

• Solid dispersion

Solid dispersion (SD)

There are various techniques for solubility enhancement. Solid dispersion is one of the best approaches for solubility enhancement. The term SD refers to a set of solid products comprising of at least two diverse components, usually hydrophilic matrix and a hydrophobic drug. The matrix may be crystalline or amorphous, and the drug can be dispersed in either form [2, 7, 18, 19].

Advantages of SD

1. Improved drug bioavailability and change in water solubility are possible.

2. More efficient than particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine [20].

3. Increase in dissolution rate and extent of absorption and reduction in pre-systemic metabolism.

4. Transformation of liquid form of drug into solid form.

5. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability [2, 21].

Disadvantages of SD

1. Changes in crystallinity and a decline in dissolution rate with aging [22].

2. Moisture and temperature have deteriorating effect on SD than on physical mixtures.

3. Some SD may not lend them to easy handling because of tackiness.

4. Drawback of SD is their poor scale-up for the purposes of manufacturing [23, 24].

Classification of SD

Researchers have classified SD on various bases, but usually, it can be classified as follows (fig. 1) [2].

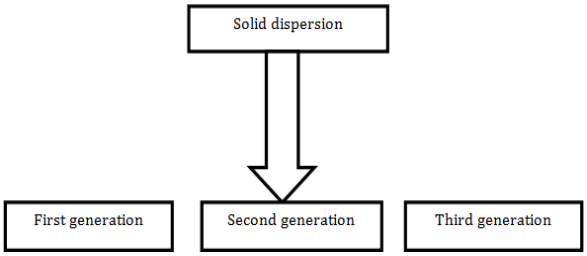

Fig. 1: Generation of solid dispersion

On the basis of carrier employed

SD can be prepared employing various types of hydrophilic carriers. These carriers or polymers affects the final properties of SD including, its state, drug release kinetics, dissolution profile, stability profile, etc. Hence taking in to the consideration the above-mentioned facts, SDmay be further subdivided into three types: [25, 26].

First generation SD (FGSD)

This type of system causes the chances of mixture eutectic development which releases the drug as microcrystals and ultimately improves the solubility. In continuation to successful SD of drugs like Sulphathiazole and Chloramphenicol preparation using urea and sugar as crystalline carrier systems. Hence, SD which is developed by using crystalline carriers is designated as “FGSD” [27].

Second generation SD

Fully synthetic polymers include povidone (PVP), polyethylene glycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins [17, 28].

Third generation SD

Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/141 [20].

Types of SD

Eutectic mixtures

Two compounds which are completely miscible in the liquid state leads to simple eutectic mixture formation but only to a very limited extent in the solid state (fig. 2) [29]. This is usually prepared by rapid solidification of fused melt of two components that shows complete liquid miscibility but negligible solid-solid solution [12, 17].

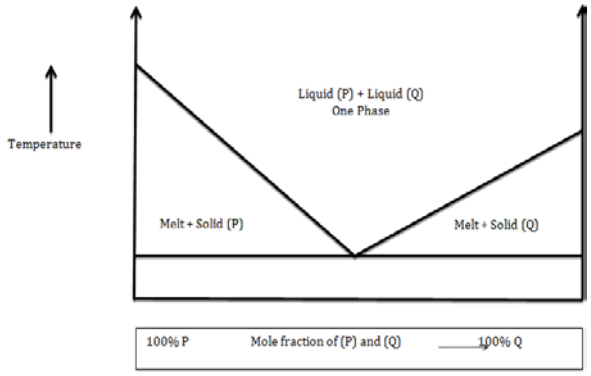

Fig. 2: Simple eutectic mixture phase diagram

Amorphous precipitation in crystalline matrix

This is similar to simple eutectic mixtures but only difference is that drug gets precipitated out in an amorphous form.

Solid solutions

When two components crystallize together in a homogeneous single phase considered as solid solution. They are of two types: Substitutional solid solutions, interstitial solutions. Solid solutions can generally attain quicker dissolution rate than the corresponding eutectic mixture [10, 30].

Glass solutions and suspensions

A homogeneous system which consists of solid solute dissolved in a solid solvent is known as glass solutions. Mixed/heterogeneous groups of crystals are formed because both components crystallize simultaneously. A homogeneous system in which the drug molecule is suspended in a glassy carrier is termed as glass suspensions. Glassy state in glass solution and glass suspension is characterized by transparency and brittleness below the glass transition temperature [14, 19, 31].

Formulation consideration

Polyethylene glycol (PEG)

PEG compounds can be obtained after reaction of ethylene glycol and ethylene oxide. Molecular weights above 300000 are known to as polyethylene oxides [17, 21, 32].

Phospholipids

The complexity of glycerides advances by manipulation of the terminal hydroxyl and phosphate associated head groups to form phospholipids. Commonly used phospholipid head groups are choline, ethanolamine, serine, inositol, inositol phosphate, and glycerol esters [20, 21, 33].

Polyvinyl pyrrolidone (PVP)

It is soluble in water, ethanol, chloroform and isopropyl alcohol and molecular weight ranges from 10000 to 700000. SD prepared by melt method is not suitable for PVP because it melts at a very high temperature above 275 and gets decomposed [17, 22]. The effect of molecular weight of PVP on the rate of dissolution of a drug is more consistent than for PEG. An increase in molecular weight of PVP will decrease the dissolution rate of most drugs. An increase in viscosity of PVP solution due to an increase in molecular weight decreases diffusion of drug molecules from the surface of viscous material into the dissolution medium, lower molecular weight PVP has a short swelling time prior to dissolution resulting in an increase in dissolution rate of the polymer and drug [4, 34].

Cyclodextrins

They are mainly used to enrich solubility, chemical protection, masking of taste and better handling by the transformation of liquids into solids by entrapment.

Selection of solvent for SD

The solvent to be included for the formulation of SD should have the following criteria as shown in (table 3) [17, 6].

Table 3: List of solvent for SD

S. No.	Solvent	Melting point	Boiling point
1	Water	0	100
2	Methanol	-93.9	65
3	Ethanol	-117	78
4	Acetic acid	17	118

Methods of preparation

Melting and solvent evaporation methods are the two major processes of preparing SD.

Melting method

In this method drug is dissolved in a suitable liquid solvent. Then, the solution is incorporated directly into the melt of polyethylene glycol obtainable below 70 °c, without removing the liquid solvent. It has been shown that without significant loss of its solid property 5-10% (w/w) of the liquid compound could be incorporated into polyethylene glycol 6000 [2, 10, 35]. This method consists of the physical mixture of drug and carrier preparation followed by heating until it gets melted. Finally obtained solid mass is then crushed and sieved. Additionally supersaturation of drug or solute can be achieved by quenching the melt quickly from a high temperature [17, 36]. This method is also known as fusion method. Although numerous compounds either drugs or carriers gets decomposed or evaporate during the process due to elevated temperature. Oxidative degradation of drug or carrier can be avoided possibly by heating the physical mixture in a sealed container or melting it under vacuum or in the presence of inert gas like nitrogen [23].

Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated as shown in (fig. 3). The thermal breakdown of drugs or carriers can be

stopped, since organic solvent evaporation occurs at low temperature [37]. A basic process of preparing SD of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, a mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled [2, 26].

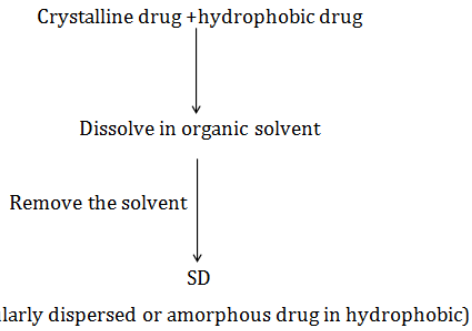

Fig. 3: Preparation of solid dispersion by solvent evaporation method

Melting solvent method (melt evaporation)

Melt evaporation leads to the development of SD by dissolution of drug in a appropriate solvent followed by incorporation of solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The obtained film is dried further till constant weight. The film is further dried to constant weight [7, 38]. This technique possesses unique advantages of fusion as well as solvent evaporation methods.

Hot melt extrusion method

In this method extruder is utilized for intense mixing of components. The components of the extruder are barrel, hopper, a kneading screw, heating jacket, and a die[39]. Generally physical mixture of both the carrier and drug is introduced into the hopper then passed through screw and finally it is extruded from the die (fig. 4). The advantage of the method is to get various shapes and designs of the heated drug-matrix mixture into ophthalmic inserts, implants, or oral dosage form [17, 26].

Other advantage like the continuous production of SD is possible so that large-scale production can easily be achieved. The product produced by this method can easily be handled because any shape can be adopted [40]. Like other methods, miscibility of drug and matrix also creates a problem. Thermolabile compounds can be degraded due to the production of heat generated by the extruder [5, 7].

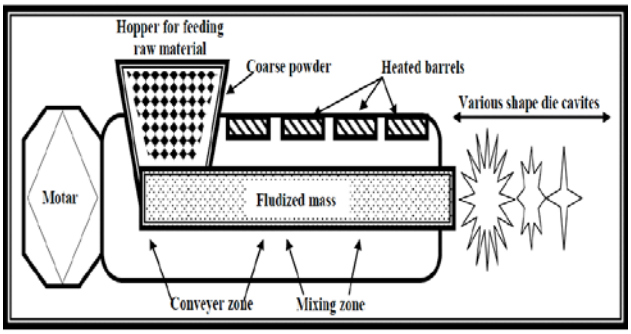

Fig. 4: Hot melt extruder

Fusion method

This is sometimes used interchangeably as the melt method that is appropriate only when the crystalline substances are used as the starting materials. Hence, generally fusion term is chosen [27]. The first SD was developed by this method for pharmaceutical applications. This was a mixture of sulfathiazole and urea which fused and later cooled to get the final dispersion. The eutectic composition was chosen in order to attain to attain concurrent crystallization of drug and matrix during cooling [2, 29, 41].

Supercritical fluid methods

These methods are generally applied with carbon dioxide, which is used either as a solvent for drug and matrix or as an anti-solvent. While supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through nozzle, into an expansion vessel with lowerpressure, and particles are immediately formed (fig. 5)[23, 42]. The mixture causes rapid cooling. In this technique it does not involve the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is rapid expansion of supercritical solution [28].

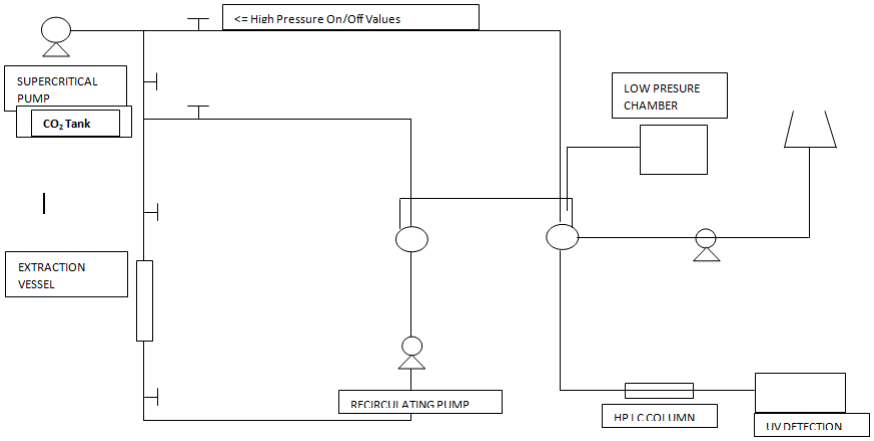

Fig. 5: Schematic diagram for supercritical fluid technology [9]

Spray drying

This method was developed in 1920 in which the manufacture of milk powder was one of the first applications of spray drying. Presently, this technique is having great utility in pharmaceutical industry owing to rapid drying and specific characteristics such as particle size and shape of the final product. In this method atomization of suspensions or solutions into fine droplets is done and drying of particles that may lead to the formation of solid particles [14]. This process permits production of fine, dust free powder [29, 43].

Freeze-drying

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized [1]. The main advantage of this technique is that the drug exposed to minimum thermal stress and low risk of phase separation. Freeze drying technique is poorly explored for making SD [30, 44].

Lyophilization technique

In this technique the drug and carrier are dissolved in a common solvent, frozen and sublimed to attain a lyophilized molecular dispersion [31, 45].

Possible mechanism of SD

The enhancement in dissolution rate because of SD formation, relative to pure drug, varies from as high as 400 fold to less than two-fold. The increase in dissolution rate can be attributed to myriad factors and it is very difficult to show the experimentally importance of one factor in comparison to other. SD improves the dissolution rate of poorly water-soluble drugs by following mechanisms [17, 46].

- Reduction in particle size
- Improvement in wettability and dispersibility
- Change in crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles

Table 4: Applications of pharmaceutical field

Applications of SD	Examples of drugs
Dissolution rate enhancement	Celecoxib, hydrocortisone, ibuprofen, diazepam
Mucoadhesive drug delivery	Piroxicam
Mouth dissolving tablet(MDT)	Celecoxib, oxcarbazepine
Solubility enhancement	Hydrocortisone, carbamazepine, 5-aminosalicylic acid, curcumin
Dry powder for reconstitution	Etravirine
Matrix tablets	Indomethacin
Controlled release	Diclofenac sodium, indometahcin, ketoprofen, nifedipine.
Orodispersible tablets (ODT)	Acelofenac, indomethacin, promethazine hydrochloride

Contribution in the field of SD

Various milestones and turning point in the field of solubility enhancement achieved through usage of SDtechnique since it was put before by Sekiguchi and Obi in1961 is tabulated below (table 5)

Table 5: Historical turning point in the field of SD technology

Year	Author	Contribution	Reference
1961	Sekiguchi and Obi	Studied absorption behavior of eutectic mixture of sulphathiazole and compared with ordinary sulphathiazole. It was assumed that this new type of formulation could be utilized for better therapeutic effect.	13
1963	Levy	Demonstrated a simple and precise method for the preparation of SD and solid solution. It was concluded that that solid solution may enhance the drug dissolution.	55
1965	Tachibani and Nakamura	Described the preparation of an aqueous colloidal dispersion of carotene by solvent evaporation method with polyvinyl pyrrolidone (PVP) as hydrophilic carrier. Analytical data showed that carotene is molecularly dispersed in SD improved solubility.	56
1966	Mayersohn and Gibaldi	Studied a method for the preparation of Griseofulvin SD with marked increment in solubility.	57
1979	Reigelman and Chiou	Reported that the absorption in body fluids of poorly soluble drugs can be enhanced by forming a glassy solid matrix of a carrier and the drug.	58
1989	Baudier *et al.*	Reported the invention related to a novel galenic form of verapamil with excellent bioavailability.	59
1994	Nakano *et al.*	Described a novel thermal-mechano-chemical process for preparation of S	48
1995	Nakamichi *et al.*	Reported the solvent free and temperature independent approach for the formulation of SD using the twin screw extruder. The resulting SD was found to be superior in terms of its performance and stability.	60
1997	Fort *et al.*	They introduced one of the pharmaceutical SD compositions comprising of an HIV protease inhibitor as drug and peg as carrier system. The SD claimed to effectively cure HIV; as it was able to enhance the solubility and hence the bioavailability of drug.	61
2000	Terracol and Duclos	Described a simple solvent evaporation method for the production of SD, comprising of at least one therapeutic agent. It was found that the SD enhances the solubility of drug in aqueous media.	62
2007	Bedrosian	Reported a method for oral administration of mTOR inhibitors especially in case of oral cancer patient SD Technique.	63
2008	Patel and Pillai	Expressed the composition and therapeutic use of water dispersible molecular SD constituting of sparingly water soluble drug or any salt in particulatable lipidic matrix.	64
2009	Besse *et al.*	Demonstrated a method of preparation of disintegrant free orodispersible tablet containing SD.	65
2011	Baert *et al.*	Reported a method of preparation of reconstituted powder for oral administration of Etravirine for safe and effective management of HIV via SD technology.	66
2011	Kiser and Gupta	Reported a tactful employment of SD technique for the preparation of intravaginal ring containing a homogenously distributed drug.	67
2011	Tiwari *et al.*	Reported a method of preparation of solid dosage form comprising of SD, containing an anti-HIV drug with hydrophilic polymer of low glass transition temperature approx 50 °C.	68
2012	Dixit *et al.*	Reviewed the SD a strategy for improving the solubility of poorly soluble drugs.	32
2012	Kaur *et al.*	Reviewed SD and its possible approaches for improvement of drug solubility.	14
2013	Bhatnagar *et al.*	Explored the possibility of SD in pharmaceutical drug development from basics to clinical applications.	19
2013	Singh *et al.*	Reviewed the various preparation techniques for SD, characterization and compiled some of the recent technology transfers.	17
2014	Kommavarapu *et al.*	Gave an overview of SD for solubility and bioavailability enhancement of poorly aqueous soluble drugs.	3

Table 6: Marketed products of SD

Product name	Drug name	Company name
Grispeg	Griseofulvin	Pendinal pharm inc
Cesamet	Nabilone	Eli lilly
Sproranox	Itraconazole	Janssen
Rezulin	Troglitazone	Pfizer
Hepcure	Hepatitis type b	Cjjeiljedang
Keletra	Lopinavir	Abbott

Characterization of SD

The physical nature of SD can be characterized by various methods. Single method is not sufficient to furnish the complete information rather a combination of two or more techniques is needed [32, 47].

- Thermal analysis
- X-ray diffraction method
- Spectroscopic method
- Modulated temperature differential scanning calorimetric
- Environmental scanning electron microscopy
- Dissolution testing
- Dissolution rate method
- Microscopic method
- Thermodynamic method [4]

Thermal analysis techniques

The thermal analysis comprises a group of techniques in which a physical property of a substance is measured as a function of temperature while the substance is subjected to a controlled temperature programmed [48]. In differential thermal analysis (DTA), the temperature difference existing between a sample and an inert reference material is measured. [1, 33].

X-ray crystallography

This method can be used to determine the arrangement of atoms within a crystal. In this method X-ray beam hit a crystal and diffracts into many directions. A crystallographer can produce a three-dimensional picture of the density of electrons within the crystal from the angles and intensities of these diffracted beams. The mean positions of the atoms in the crystal can be determined from this electron density [34, 49].

Spectroscopy

It is the study of the interaction between radiation and matter as a function of wavelength (λ). Conventionally, spectroscopy referred to as the use of visible light dispersed according to its wavelength, e. g. by a prism [50]. Later on the concept was further extended to comprise the measurement of a quantity as a function of either wavelength or frequency [35, 51].

Environmental scanning electron microscopy

The morphology of the spray-dried ternary SD can be characterized with a Philips XL30 ESEM FEG environmental scanning electron microscope operating at 25 kV accelerating voltage and a vacuum[52]. The samples were sprayed on double-sided carbon tape that was mounted on conventional SEM stubs [36, 37, 53].

Applications of sd in pharmaceutical field

Apart from absorption enhancement, the SDcould have numerous other pharmaceutical applications, which need to be explored [32]. Currently, they have been applied successfully to develop orodispersible tablets, mouth dissolving tablets, enhancement of dissolution rate, mucoadhesive drug delivery, dry powder for reconstitution, controlled drug delivery (table 4)[19, 54].

Marketed products

Application of SD is not restricted only to laboratory scale, but it has been applied successfully on a commercial scale. Various products available at commercial scale are listed below table 6 [69, 27].

CONCLUSION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Successful development of SD system for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface active carriers and self-emulsifying carriers. These significantly help to improve the bioavailability and bioequivalence. Finally it is asserted that if the manufacturing of SD are properly controlled and validated then it can be suitably propelled on commercial scale and various cost-effective dosage form can be launched.

Future prospects

The most frequent concerns with SD have been the ability to scale-up the manufacturing method, the physical stability of the dispersion, and the amount of carrier needed to facilitate the required increase in the release rate. When a high carrier/drug ratio must be used, the amount of dispersion required to administer the usual dose of the drug may be too high to produce a tablet or capsule that can be easily swallowed. The higher the unit dose of the drug, the more likely this problem is to occur. Another aspect that must be considered is the correlation between *in vitro* and *in vivo* results. Dispersions with a rapid *in vitro* release rate may fail to improve the oral bioavailability if the *in vitro* test conditions do not adequately simulate the gastrointestinal conditions, or if there is some specific interaction between the carrier and a component of the GI. Several products containing SD are already on the market and the number is expected to increase dramatically in the next years.

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