

Surface Solid Dispersion Review

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ABSTRACT: Oral route is mostly preferred route for administering drugs to patient. But due to the poor solubility many drug has limited used in oral administration. Enhancement of water solubility of poor water soluble drug is a main target in a pharmaceutical field. Surface solid dispersion is an effective method to enhance the solubility of poorly water soluble drugs, however due to ease of method of formation of surface solid dispersion, it is a novel method that is cost effective, in which surface area for absorption of drug can be increased which increases dissolution of drug. The review article focuses on the methods of preparation, advantages, disadvantages and characterization of the surface solid dispersions.

Keywords: surface solid dispersion, poorly water soluble drug, solvent evaporation, dissolution enhancement, amorphous form

Definition: Preparation of Surface Solid Dispersion (SSD) is a technique that provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate.

I. INTRODUCTION

The substance ability to dissolve in a specific solvent is known as solubility. It is a measure of the concentration of dissolved solute in a saturated solution at a particular temperature. In terms of quality, it denotes the spontaneous interaction of two or more components to produce a single, distinct phase homogeneous dispersion of molecules [1]. Since the dissolution rate is the mechanism that limits the rate with which a drug is absorbed from a solid dosage form, the pharmaceutical industry has long struggled with the poor solubility characteristics of relatively insoluble compounds. While summarizing the physicochemical elements influencing the dissolution rate in this instance, the Noyes-Whitney and formulas for Nernst. Surface area directly affects the dissolution rate, which can be raised by aiming to reduce the drug's particle

size [2]. Numerous methods, involving salt formation, turning drugs into prodrugs, and micronization, were used to increase the solubility of poorly soluble drugs besides this, complexation, micelle formation, and nanonization emulsions, solid-lipid nanoparticles, and solid-liquid dispersions. A typical way to improve a drug's aqueous solubility is solid dispersion, in which one more active ingredient(s) is distributed evenly in a water-soluble inert carrier matrix [1]. Drug amorphization promotes wettability which is the principal mechanism in which there is decrease in particle size which can greatly facilitate disintegration. Despite the fact that solid dispersions have a range of benefits, the water soluble carriers employed in their production result in a soft, sticky mass that is challenging to handle. Particularly in tablet compression [3]. Another method for dispersion of one or more active substances on a water-insoluble-hydrophilic carrier of exceptionally large surface area to achieve increased dissolution rates and bioavailability of insoluble drugs is Surface Solid Dispersion (SSD). SSD uses a carrier which spreads when it comes into touch with water, enabling the drug's quick release right away. [5]. Moreover, at high concentrations of such carriers might reduce solvation due to the high viscosity surface boundary [4]. Surface solid dispersion technology is likely to significantly increase the solubility and bioavailability of poorly water soluble drugs. This when combined with product development, technique Orodispersible tablets are anticipated to improve the drug's ability to dissolve [6].

History:

To enhance the dissolution and, consequently, oral absorption and bioavailability of poorly water soluble drugs, several approaches have been developed. Solid dispersion is one method that has showed promise in increasing a drug's solubility, wettability, rate of drug dissolution, and ultimately its bioavailability. However, there are few solid dispersion products on the market. Some of the drawbacks of the traditional solid dispersions can be overcome by the surface solid dispersions. Hydrophilic, water-

insoluble, porous materials are the carriers employed in surface solid dispersion. As carriers for surface solid dispersion, a variety of frequently used tablet excipients including microcrystalline cellulose, silicon dioxide, sodium starch glycolate, potato starch, croscarmellose, and crospovidone have been utilised. Drug release from the carrier material is influenced by its hydrophilicity, particle size, porosity, and surface area. The release rate is improved by the drug's surface area available for surface adsorption. A lesser amount of the carrier can result in a higher rate of dissolution for those carriers, such silicon dioxide, that have a larger surface area. In order to boost the solubility, dissolution, and subsequently the bioavailability of many virtually insoluble or poorly water soluble medications, surface solid dispersion technique has been widely used. [7]

Mechanism of Enhanced Dissolution in surface Solid Dispersion:[8]

A number of factors may influence or increase the dissolution rate for surface solid dispersion. These factors include the following;

1. Reduced Particle size or Reduced Agglomeration:

Both are connected to a decrease in particle size and an increase in the drug's accessible surface area. It's been expected that size reduction is caused by a eutectic or solid solution formation. Additionally, it has been proposed that presenting the particles in the dissolution media as physically distinct entities may lessen aggregation. Many of the carriers used for solid dispersion may have some wetting capabilities, which could reduce agglomeration and enhance surface area through improved wetting.

2.Increased solubility or Dissolution rate of the drug:

Using several carriers may result in increased solubility of drug. As a result, the carrier controlled the release of drug and is independent of drug. Second, some systems exhibit release behaviour that is influenced by the properties of the drug rather than polymer.

3. from crystalline to amorphous state transformation/ Formation of high Energy State:

Amorphous drugs can be comparable to cooled liquids because of their higher energy state, minimal stability, and amorphous nature. A

molecule have been released from a crystal by more energy. They have greater aqueous solubility than crystalline forms because less energy is needed for non-crystalline (amorphous) solids. For instance, novobiocin is 10 times more soluble in amorphous form than in crystalline form.

4.Wetting:

A strong affinity between a liquid and solid causes the liquid to create a film across the solid surface. The liquid has difficulty displacing the air and there exist an angle of contact between the liquid and the solid. There is an angle of contact when the liquid and the solid come into touch when the air is released. This contact angle is consequence of an equilibrium involving three interfacial tensions

Techniques for Surface Solid Dispersions:

Various methods used for preparation of surface solid dispersion system. These methods are given below.

- Solvent evaporation (co-evaporation)
- melt method
- co-grinding
- Kneading Method

Advantages of surface Solid Dispersion: [8]

- Reduction in particle size.
- Improved wettability.
- Improved porosity of drug.
- To transform the crystalline structure of drug in to amorphous form.
- To improve solubility of a poorly water-soluble drug.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.
- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs.
- To formulate a faster release priming dose in a sustained release dosage form.
- They can be used as an alternate to parenteral therapy for immediate action.
- Solid dispersions improve the onset of action for drugs such as NSAIDs where immediate action is crucial in relieving acute pain and inflammation.
- Bioavailability of anticancer drugs has been improved by incorporating them in solid dispersions.

Limitations of surface solid dispersion: [9]

Problems limiting the commercial application of surface solid dispersion involve

- its method of preparation
- reproducibility of its physicochemical properties
- its formulation into dosage forms
- the scale up of manufacturing processes
- the physical and chemical stability of drug and vehicle

Applications of The Surface Solid Dispersion:[10,11]

- The surface solid dispersion systems can increase the bioavailable oral dosage forms for anti-cancer medications, which can be used instead of traditional injections to increase patient compliance and comfort.
- Surface solid dispersions have the great benefit of modulating the release of drugs that are poorly water soluble into highly soluble forms for optimal site absorption.
- Additionally, it was discovered that the surface solid dispersion systems decreased the impact of food on drug absorption, making drug therapy more convenient with doing away with the requirement that some medications be taken with food.
- For medications like NSAIDS [non-steroidal anti-inflammatory medicines], where early action is critical in reducing acute pain and inflammation, it has been shown that surface solid dispersion formulations can hasten the onset of effect.
- The surface solid dispersion systems enhanced absorption efficiency was shown to allow for a reduction in the amount of the active agent per dose, which lowers the cost of these therapeutic regimens.
- The use of unpleasant solvents and local anaesthesia are two issues that can be avoided by using surface solid dispersion. Dry powder formulation for inhalation is being developed

to enhance immunosuppressive treatment for lung transplant patients.

Carrier and Solvent selection:[12]

The chemistry of the drug should be taken into consideration when choosing a carrier and solvent. The drug's solubility in the carrier should be optimised.

➤ **Carrier selection**

1st Generation: Crystalline carriers; Urea, sugar and organic acid

2nd Generation: Amorphous carriers; PEG, PVA, Povidone and Cellulose derivatives

3rd Generation: Surface active self-emulsifying carriers; Poloxamer 407, tween 80, Gelucire 44/14, compritol 888 ATO +/- polymer

➤ **Ideal properties of a carrier for surface solid dispersions**

1. High water solubility, promotes wettability and increases dissolution
2. High glass transition point (T_g) and improve stability
3. Minimal water uptake (reduces T_g)
4. Soluble in common solvent with drug (solvent evaporation technique)
5. Relatively low melting point (melting process)
6. Capable of forming a solid solution with the drug
7. Good compressibility index and flow index
8. Ability to protect drug from moisture

➤ **solvent selection**

- i) Dissolve both drug and carrier
- ii) Toxic solvents to be avoided due to the risk of residual levels after preparation. e.g. chloroform and dichloromethane
- iii) Ethanol is a less toxic alternative
- iv) Water based systems preferable
- v) Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point.

Examples of different polymers used in surface solid dispersions:

drug	polymer	method of preparation	Results observed	reference
Ebastine	Croscarmellosesodium, Avicel®pH101, Avicel®pH102, Sodium Starch Glycolate (SSG)	Solvent Evaporation Method	(EBS: CCS 1:15) showed high percentage yield (98.5%), high drug content (98.39%) and 8.2fold increase	1

			in solubility compared to solubility of pure drug with improved dissolution rate	
Felodipine	Porous Silicon Dioxide kg 100, Sodium Chloride	Physical Mixture, Solvent Deposition	the dissolution rate of felodipine from solvent deposit as well as vacuum-prepared surface solid dispersions increased markedly as compared to the dissolution rate of felodipine alone, and also increased in comparison to the dissolution rate of ambient-temperature-prep& physical mixture	2
Meloxicam	Crospovidone	Co-grinding and Solvent Evaporation Method	Tablet formulation F3 made with SSD3 with a disintegration time of 11 secs, by wetting time= 6 sec, high water absorption of 78% by wt and cumulative drug release of 97% proved to be superior than the tablet made with SD3	3
Nifedipine	Sodium Starch Glycolate (SSG) and Croscarmellose sodium (CCS)	Co-precipitation technique	Tablets prepared from SD of nifedipine with Poloxamer and PEG 6000 were found to have better drug release profile than the marketed products.	4
Glimepiride	Crospovidone, Pregelatinised Starch, Croscarmellose Sodium and Avicel pH 101	Solvent Evaporation Method.	The surface solid dispersion on crospovidone with drug to carrier ratio of 1:19 showed highest dissolution rate with the dissolution efficiency of 81.89%	7

			in comparison to pure drug (22.88%) and physical mixture (35.96%)	
Clopidogrelbisulfate	PEG 4000, PEG 6000, Poloxamer 188	Solvent Evaporation and Hot melt Method.	The Clopidogrelbisulfate containing an optimized formulation of surface solid dispersion showed 85.69% drug release in 30 min.	13
Piroxicam	Microcrystalline Cellulose (Avicel pH101) and Potato Starch	Coevaporation Method.	The dissolution rate of the drug in potato starch based surface solid dispersion was significantly higher than that in the microcrystalline cellulose based SSD.	14
Irbesartan	Crospovidone (CP), Sodium Starch Glycolate (SSG), Potato Starch (PS), Croscarmellose (CC), Microcrystalline Cellulose (MC)	Solvent Coevaporation Method.	The in vitro dissolution studies of surface solid dispersion of crospovidone with drug to carrier ratio of 1:10 showed highest dissolution rate with the dissolution efficiency of 98.18% (10 min)	15
Meclizine hydrochloride	Gelucire 50/13 and Gelucire 44/14, Polyethylene Glycol 8000	Melt Method	The presence of Gelucire 44/14 in the formulation showed significant enhancement in solubility (152 folds) and dissolution rate (7.23 folds).	16
Telmisartan	Avicel pH101, Alginate Acid, Aerosil 200, PEG 4000, PEG 6000, poloxamer 407, Poloxamer 188,	Solvent Evaporation Method	The hydrophilic polymers, such as Avicel PH101, Alginate acid, and Aerosil200 were found to be effective in increasing the aqueous solubility and dissolution rate of Telmisartan in surface solid dispersions when compared to the pure	17,18

Ketoprofen	Aerosil 200	Solvent Evaporation Method	drug Surface adsorption on inert carriers such as aerosil 200 was very successful tool for enhancement the dissolution rate of ketoprofen.	19
Simvastatin	1. polyethylene glycol 6000, Pluronic f68, Myrj 52 and Polyvinyl Pyrrolidone K-30 2. Sodium Starch Glycolate (SSG) and Croscarmellose sodium (CCS)	Solvent Deposition Technique, Coevaporation and Cogrounding	1. PVP K-30 showing better dissolution parameters that was comparable to that of marketed product. 2. Bioavailability is improved due to enhancement in rate and extent of drug release when drug was administered as an SSD using CCS as a carrier.	6,20
Carvedilol	Avicel pH 101, Pluronic f68	Solvent Evaporation Method	Water insoluble, hydrophilic carrier accompanied by Pluronic F68, as a wetting agent, largely improved drug dissolution that was comparable to the marketed product of CRV	21
Olmesartan Medoxomil	Avicel pH 102, Ac-di-Sol, Kyron t-314, crospovidone, Lycatab, Starlac,	Solvent evaporation method	SSD18 consisting of drug: SSG at 1:9 ratio and SSD20 consisting of drug: Kyron T-314 at 1:5 ratio showed the highest enhancement in the dissolution rate and efficiency of olmesartan medoxomil compared to the plain drug and the physical mixtures.	22

Evaluation of physicochemical properties of surface solid dispersion: (1,3,17,18)

• **Drug content**

Equivalent weight of SSD containing specific amount of Drug were weighed accurately and

dissolved in organic solvent. The solution was filtered and drug content was analysed.

• **Saturation solubility studies**

Pure drug and SSDs in excess quantity were placed in flasks containing distilled water. The samples

were placed in an Incubator shaker at 37°C and 40-50 rpm for 12-48 hr. The solutions were analyzed by UV-spectrophotometer.

• **In vitro dissolution studies**

Dissolution studies were carried out in triplicate in USP Apparatus 2. SSDs equivalent to dose of drug were added to 900 ml of phosphate buffer of desired pH by setting rpm. Aliquots of 5/10ml were withdrawn at specified time intervals and analyzed at spectroscopic wavelengths of drug.

• **Percentage practical yield**

It is calculated to know about percent yield or efficiency of any method and thus its help in selection of appropriate method of formulation. The final weights of prepared solid surface dispersion were taken and percentage crystal yield was calculated with following equation.

$$(\% \text{ yield}) = \text{Practical yield} / \text{Theoretical yield} \times 100$$

• **Percentage Drug Content**

Equivalent weight of prepared microcrystals containing specific amount of drug were taken and transfer into 100 ml standard flask and volume was made up of 200 ml with organic solvent (i.e., methanol or ethanol). The resulting solution were filtered through a membrane filter and suitably diluted. The absorbance of the solution was measured.

$$\frac{\text{Drug Content (\%)}}{\text{experimental drug content}} = \frac{\text{drug content}}{\text{theoretical drug content}} \times 100$$

• **Powder properties**

The SSDs were subjected to a range of powder properties determination. Angle of repose was determined using cylinder method.²⁰ Apparent bulk density (ρ_b) was determined by pouring weighed amount of powder into a 50 cc graduated cylinder. The bulk volume (V_b) was noted and divided by the powder weight to get the bulk density. The tapped density was determined by subjecting the powder to 50 tapping at height of 1 inch. The tapped volume (V_t) was divided by weight of the powder to get tapped density (ρ_t).

$$\text{Compressibility Index} = \frac{V_b - V_t}{V_b} \times 100$$

Next, Hausner ratio which is an indirect index of ease of powder flow was calculated by dividing tapped density by bulk density.

• **Determination of hydration capacity**

According to the solubility study, one gram of the best carriers' formulas was placed separately in 10 ml pre-weighed centrifuge tube. Sufficient distilled water was added to make up the volume to 10 ml and the suspension was shaken manually. The suspension was allowed to stand for 10 min and then by centrifugation for 15 min at 1000 rpm. Then after, the supernatant was decanted. Then a tube was reweighed, and hydration capacity was calculated by using the following equation

$$\text{Hydration capacity (\%)} = \frac{\text{Weight of tubewith sediment} - \text{weight of empty tube}}{\text{weight of sample on dry basis}} \times 100$$

Characterization of Surface solid dispersion : (solid dispersion review)

Sr. no	Characterization	Method	Significance
1.	Drug-carrier Miscibility	<ul style="list-style-type: none"> DSC pXRD 	To find out the complex formation between drug and carrier.
2.	Drug-carrier interactions	<ul style="list-style-type: none"> FT-IR spectroscopy 	To find out the interaction between drug and carrier and formation of inclusion complex
3.	Physical structure	<ul style="list-style-type: none"> SEM Surface area analysis 	To find out the particle size and shape
4.	Amorphous content	<ul style="list-style-type: none"> DSC pXRD 	To find out the amorphous from drug.
5.	Stability	<ul style="list-style-type: none"> DSC Humidity studies 	To find out the degree of crystallinity
6.	Dissolution enhancement	<ul style="list-style-type: none"> Dissolution Saturated 	To find out the rate and extent of dissolution

		solubility studies <ul style="list-style-type: none"> ● Intrinsic dissolution ● Dynamic solubility ● Dissolution in bio-relevant media 	
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FTIR:

FT-IR mostly used for to characterize drug- polymer (carrier) compatibility study. Its main application is to study the solid state interaction between drug and polymer.

Pure drug and KBr powder was dried in hot air oven for half an hour at 50 °C, ensuring the removal of moisture. Then the drug was mixed with KBr in the ratio of 9:1 and triturated, afterwards it was exposed to infrared rays[3].

The FTIR spectra of pure drug, the best carrier, physical mixture PM and the selected SSD formulation were recorded in KBr medium pellets using FTIR spectrophotometer. The scan was performed in the range of 200-4000 cm⁻¹ [1,4,6,15,20]

Each formula (5 mg) was mixed with about 100-400 mg. potassium bromide and compressed into discs under pressure of 10,000 to 15,000 pounds per square inch. The IR spectra were recorded using Infra-red Spectrophotometer.[7,17,18,22]

DSC:

It is a powerful technique used to study amorphous content. It also detect endothermic and exothermic peak. It also studies whether the drug was incorporated into the polymer (carrier) or not on the basis of melting point.

DSC analysis of the free drug, drug with carrier and the drug with carrier and additives were carried out using DSC .The pan was placed in the DSC instrument and scanned between 30 and 300/C at a rate of 10°C/min. Accurately weighed about 2-5 mg of sample was placed in an open, flat bottom, hermetically sealed aluminium pans over a temperature range of 20°C–300°C at a constant rate of 10°C/min under a stream of nitrogen. Dry nitrogen was used as a carrier gas to eliminate the oxidative and pyrolytic effects with a flow rate of 10 -50 ml/min. The melting and transition point measurements were performed using the software provided with the device.[3,4,9,10,15,17,18,22]

Powder X-ray diffraction (PXRD) analysis

It is mostly useful for to characterize whether the surface solid dispersion is amorphous or crystalline. Sharper peak indicate more crystallinity.

The X-ray diffractograms of the drug, the best carrier, PM and optimized SSD formulation were obtained by using X-ray diffractometer (Shimadzu, Japan) (19) X- ray diffraction of drug, physical mixture and SSD prepared using dichloromethane and methanol as solvents were obtained on a D-5000 Siemens X-ray diffractometer, using Cu Ka radiation (wave length=1.5406Å). The data were recorded over a scanning 2θ range of 20 to 650 at step time of 0.045 steps/0.5 sec.[glimipiride]

P-XRD patterns of the samples were recorded, using X-ray diffractometer, (Rigaku MiniFlex) Advance with Cu-Kα (Ni-filter), radiation (1 ¼ 1.5418 Å). The experiments were carried out at room temperature under the following conditions: voltage 20 kV, current 20 mA, 2θ angle range 3e60 with scanning speed 5/min.[irbesartan]

The PXRD spectra of samples were recorded using a high-power powder x-ray diffractometer (Ru-200B, Pune, India) with Cu as target filter having a voltage/current of 40 KV/40 mA at a scan speed of 4°/min. The samples were analyzed at a 2θ angle range of 2–45°. Step time was 0.5 sec, and acquisition time was 1 h.[simvastatin]

Powder X-ray diffractograms of pure materials and all binary systems (physical mixture and adsorbate) were performed by using Philips Analytical XRD (PW 3710). The samples were irradiated with monochromatized Cu Ka radiation and analyzed between 2θ angles of 10 and 80°. The voltage, current, and time per step used were 30 Kv, 20 mA, and 0.5 s, respectively.[ketoprofen].

The scanning speed was 5° to 8°/min over a 2θ range of 0–80°.[1,6,20,21]

X-ray diffraction [piroxicam]

X-ray diffraction patterns of the samples were recorded, using X-ray diffractometer, Semens-D500, Germany with Cu-Kα (Ni-filter),

radiation ($\lambda = 1.5418 \text{ \AA}$). The experiments were carried out at room temperature under the following conditions: voltage 20 kV, current 20 mA, 2θ angle range 10-60 with scanning speed, $5^\circ/\text{minute}$. [piroxicam]

XRD spectra of samples were recorded using a high-power powder x-ray diffractometer. [telmisartan]

SCANNING ELECTRON MICROSCOPY (SEM)

SEM is useful in ascertaining the morphology, particle size of solid particles and sometimes polymorphism of drug. The fine dispersion of drug particles in the carrier matrix may be visualized. The application of the electron microscope technique, however usually limited to chemicals with high resolution [8]

The surface morphology of samples was determined by using an analytical SEM (Hitachi S-34000N, Japan). The samples were lightly sprinkled on a double-sided adhesive tape stuck to an aluminium stub. The stubs were then coated with gold/platinum to a thickness of about 10 \AA under an argon atmosphere using a gold sputter module in a high vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the SEM chamber and observed at a specific voltage [6,7,15,20,21]

DTA

In differential thermal analysis, the difference in temperature between the sample and a thermally inert reference material is measured as a function of temperature. With a corresponding deviation of sample temperature from that of the reference any transition that the sample undergoes results in liberation or absorption of energy by the sample. Whether the transition temperature is exothermic or endothermic is shown by plot of the differential temperature versus the programmed temperature. In constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution obtained is the main advantage of this technique. A sample size of less than 1 mg can be used [8]

Challenging futures in surface solid dispersion:

Surface Solid dispersion formulations are recently becoming more and more attractive in drug delivery for overcoming poor solubility and bioavailability issues of new drug candidates, but their commercial application is limited. Various methods have been tried recently to overcome the

limitation and make the preparation practically feasible. Various issues that impeded the commercial development of surface solid dispersions include (a) inability to scale benchtop formulations to manufacturing-sized batches, (b) difficulty to control physicochemical properties, (c) physical and chemical instability of the drug and/or the formulation itself.

II. CONCLUSION

Drugs with low water solubility can dissolve more quickly when they are dispersed in surface solid dispersions, however the stability of these systems must be taken into account and the carriers must be chosen for each medication individually. The type of glass amorphous system created depends on the processing parameters and can be optimised in solutions made of solvent systems made up of mixtures of solvents. Both in the lab and during scale-up, the numerous technologies presented have shown promise. Utilizing innovations like surface-active carriers, certain products have been marketed. Thus, in the near future, it is anticipated that these technologies will serve as a foundation for the commercialization of numerous drugs that poorly water soluble and completely water insoluble. Surface solid dispersion technology holds out the tremendous promise of accelerating the drug release profile of weakly water soluble medicines, despite challenges like scale-up and manufacturing expense must be overcome.

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