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AN OVERVIEW: FORMULATION ASPECT OF SOLID DISPERSION AND ITS PHARMACEUTICAL APPLICATION

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Abstract:

Most common problem with conventional dosage form is solubility, so the new approach in the formulation is solid dispersion. Solubility affects the dissolution and hence the bioavailability of a drug. This review emphasizes methods for improving solubility, carrier selection, classification, advantages, disadvantages, application, characterization, and scope of solid dispersion in formulations other than a tablet. Also involves recent research in solid dispersion formulation with drugs, methods of preparation as well as polymer. Methods of preparation for solid dispersion are highlighted in this article, methods like kneading, solvent evaporation, and fusion can be performed on a lab scale. Solid dispersion enhances the solvation property of the drug by decreasing its particle size and improving wettability. This article introduces the basic concept of solid dispersion along with different types of carriers which can be useful for the formulation of a more stable solid dispersion product. Hence this study involves detailed insight into aspects of solid dispersion and its pertinence in different formulations.

Keywords: *Solubility, Solid Dispersion, Dissolution, Bioavailability, Carriers, Wettability.*

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INTRODUCTION

The term "solubility" is both a qualitative and quantitative phrase. Solubility refers to the amount of solute which can get dissolved in a given amount of solvent. [1] It has an impact on drug absorption and therapeutic effectiveness. [2] According to the BCS system, class II drugs have low water solubility, making formulation development problematic [2]. To improve dissolution rate and thus bioavailability, these drugs' solubility must be altered.

Drugs with low water solubility account for at least 40% of the novel chemical compounds studied. In general, numerous formulation technologies such as particle size reduction, salt formation, precipitation inhibitors, metastable forms, solid dispersion, complexation, and lipid technologies can help to improve BCS Class II drug absorption. One of the recent approaches, Solid dispersion, has been widely and successfully used to increase the solubility, dissolution rates, and, as a result, the bioavailability of poorly soluble drugs. [3] Researchers in the field of pharmaceutical technology are currently working on improving the solubility of insoluble drugs. In 1961, Sekiguchi and Obi suggested solid dispersions for the first time.[4] [5]

According to the US Food and Drug Administration, a drug is highly soluble if it dissolves in 250 mL of aqueous media over a pH range of 1-7.5 at 37.5 ^{0}C, and it is highly permeable if the absorption of an orally administered dose in humans is greater than 90% when measured using a mass balance or compared to an intravenous reference dose. [4] Furthermore, while making solid dispersions, process parameters and formulation composition can be controlled to produce powders with good mechanical qualities. In the solid-state, solid dispersions are characterized as molecular or intimate mixtures of drugs in hydrophilic carriers.[6] Solid dispersions are one of the most often used ways of increasing the solubility and dissolution rates of drugs that are poorly water-soluble. SDs are API polymer systems in which the API is dispersed molecularly in a polymeric matrix.[7]

In SD, particle size reduction enhances medication aqueous solubility by increasing porosity, wettability, and polymorphism alterations. Solvent evaporation, melting, and solvent wetting techniques are some methods in the manufacture of solid dispersion. [8] Solid dispersions are two-component systems that can significantly improve drug wettability and bioavailability by reducing the effective drug particle size to the smallest possible size, increasing the drug surface area, reducing its crystallinity, and increasing wettability by surrounding hydrophilic carriers due to their unique morphology.[9]

Table no. 1 :- There are several methods for improving the solubility of poorly soluble drugs. The following are some strategies for increasing solubility: [1],[10][11]

❖ Physical Modification	
I. Particle size reduction	1. Micro ionization 2. Nano ionization
II. Modification of crystal habit	1. Polymorphs 2. Pseudo polymorphs
III. Drug dispersion in carrier	1. Eutectic mixtures 2. Solid dispersion 3. Solid solution
IV. Inclusion complexation	
V. Chemical modification	1. Change in pH of the system 2. Salt formation
VI. Formulation based approaches	1. Co-crystallization 2. Co-solvency 3. Hydrotrophy 4. Addition of solubilizer 5. Ultra-rapid freezing 6. Porous microparticle technology

❖ Chemical modification	I. pH adjustment II. Salt formation III. Co-crystallization IV. Co-solvency

Table no. 2 :- Carriers used in solid dispersion [1][12]

Category	Acids	Sugars	Polymers	Insoluble/Enteric polymer	Surfactants	Miscellaneous
Carrier	Citric acid, succinic acid, etc	Dextrose, sucrose, galactose, sorbitol, maltose, etc	PVP, PEG, HPMC, hydroxyl ethyl cellulose, cyclodextrins, pectin, galactomannan, etc.	HPMC phthalate, Eudragit L100, Eudragit E100, Eudragit RL, Eudragit RS, etc.	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, Tweens, spans, etc.	Pentaerythritol, pentaerythritol tetraacetate, urea, urethane, hydroxy alkyl xanthins, etc
examples	Primidone solid dispersion using citric acid	Clotrimazole solid dispersion using sugars	Efavirenz solid dispersion pvpk 30	Diclofenac sodium solid dispersion eudragit RS and eudragit RL	Aripiprazole SD using Poloxamer 188	Ursodeoxycholic acid SD using pentaerythritol
Reference	[28]	[20]	[21]	[30]	[31]	[32]

Classification of solid dispersion [1][2][13][14][15]

I. 1st Generation: Crystalline carriers
E.g. Urea, sugar, and organic acid
II. 2nd Generation: Amorphous carriers
E.g. PEG, PVA, Povidone, and Cellulose derivatives
III. 3rd Generation: Surface active, self-emulsifying carriers
E.g. Poloxamer 407, tween 80.
IV. 4th Generation: Amorphous carriers being also complexing agents or amorphous carriers controlling drug release

On the basis of the interaction between drug and carrier, Choiu and Riegelman have classified solid dispersion into six groups which are as follows.[16]

1] Simple eutectic mixtures
2] Solid solutions
3]Glass solutions
4] Glass suspension
5]Amorphous precipitations of a drug in a crystalline carrier,
6]Compound or complex formations between the drug and the carrier and any combinations of these.

Ideal carrier characteristics for solid dispersion [17][18]

1. It is freely water-soluble and has inherent quick dissolution qualities.
2. Non-toxic to drug molecules and pharmacologically inert
3. The melting process requires a thermally stable material with a low melting point.
4. Soluble in a wide range of solvents and, in the solvent technique, pass through a glassy state upon evaporation of the solvent.
5. Ideally capable of increasing the drug's water solubility.
6. Chemically compatible with the drug and not forming a tightly bound compound with it.

Solvent selection [19]

(1) It should dissolve the drug as well as the carrier
(2) Toxic solvents should be avoided since residual levels may occur after preparation. for example, chloroform and dichloromethane
(3) Ethanol is a safer alternative
(4) Preference for water-based systems
(5) Surfactants can be used to make carrier drug solutions, but they should be used with caution because they can lower the glass transition point.

Methods of preparation of solid dispersion

A) Kneading Method
The carrier is penetrated with water and turned into a paste in this manner. The drug is subsequently added and kneaded for a specific

amount of time. The kneaded material is then dried and if required, pass through a sieve.[2]

B) Solvent Evaporation
This approach involves dissolving the physical mixture of drug and carrier in a common solvent, which is then evaporated until a clear, solvent-free film is left. After that, the film is dried to a consistent weight. The creation of a solution comprising both matrix material and the drug is the first step in the solvent technique. The second phase is the elimination of solvent. The production of a solid dispersion as a result of the solvent(s). It is preferable to mix at the molecular level because this leads to better results to get the best dissolving properties. The solvent method's key advantage is that thermal degradation of medications or carriers can be avoided because of the low temperatures required for organic solvent evaporation [21]

C) Fusion method
The drug and the carriers were thoroughly mixed in the fusion method, then melted on a heating mantle at a constant temperature with continuous stirring, the residue was poured on a porcelain dish that had previously been cooled in an ice bath for solidification, dried in a desiccator, pulverized, and passed through sieve number.[4]

D) Melting method
It includes dissolving the drug in a suitable liquid solvent and then directly incorporating the solution into the melt of polyethylene glycol, which is then evaporated until a clear, solvent-free film is left. The film is then dried until it reaches a consistent weight. Liquid compounds in the range of 5–10% (w/w) can be added to polyethylene glycol 6000 without significantly reducing its solid properties. It's possible that the chosen solvent or dissolved medication will not mix with the polyethylene glycol melt. The drug's polymorphic form, which precipitates as a solid dispersion, may also be affected by the liquid solvent utilized. The advantages of both the fusion and solvent evaporation procedures are combined in this technique. It's a good option in a practical sense.[26][27]

E) Spray drying
The drug is dissolved in a suitable solvent, and the carrier is dissolved in water in the desired amount. After that, the solutions are combined using sonication or another suitable process to create a clear solution. After that, a spray dryer is used to dry it.[2]

F) Freeze-drying
Heat and mass are transferred to and from the product under preparation during freeze-drying. This method was offered as a viable alternative to solvent evaporation. Lyophilization is a molecular mixing procedure in which the medicine and carrier are mixed together in the same solvent, frozen, then sublimed to produce a powder. Molecular dispersion that has been lyophilized.[27]

G) Hot melt extrusion
This method produces solid dispersion by hot-stage extrusion with a co-rotating twin-screw extruder, which is made up of active ingredients and a carrier. In the dispersions, the drug concentration is always 40% (w/w). In the pharmaceutical sector, the melt extrusion process is used to make a variety of dosage forms.[2]

H) Electrospinning
It is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone) [27]

I) Super Critical Fluid (SCF) Technology:
Carbon dioxide (CO2) is commonly employed in supercritical fluid technologies as either a drug and matrix solvent or as an anti-solvent [13]. When supercritical CO2 is utilized as a solvent, the matrix and drug are dissolved and sprayed through a nozzle into a lower-pressure expansion tank, where particles are created almost instantly. The mixture cools quickly due to adiabatic expansion. This method does not necessitate the use of organic materials. Because CO2 is an environmentally friendly solvent, this approach is referred described as "solvent-free." The Rapid Expansion of

Supercritical Solution is a technique (RESS).[27]

J) Co-precipitation
It is a well-known method for improving bioavailability by enhancing the dissolution of poorly water-soluble drugs. Under continual stirring, nonsolvent is added drop by drop to the drug and carrier solution in this approach. The drug and carrier are co-precipitated to produce microparticles during the nonsolvent addition. The resulting microparticle dispersion is filtered and dried. To achieve a clear solution, the needed amount of polymer and drug were mixed together, and then the solvent was added. The solution was dried under a vacuum at ambient temperature before being placed in a 370°C incubator for 12 hours. Finally, it was passed through sieve no. 41. [27]

Advantage [1] [20][21]
Solid dispersion was commonly used to improve the dissolvability of poorly water-soluble medicines in water, with the following benefits:

1. One of the most significant benefits of SD is that medications that interact with hydrophilic carriers can be detected.
2. In a supersaturated state, minimize agglomeration and release, resulting in fast absorption and release.BA has improved [22].
3. SD can improve drug wettability and surface area, resulting in improved aqueous absorption. Drug solubility is the ability of a substance to dissolve in water.[1]
4. SD can be manufactured as a solid oral dose form, which is more patient-friendly than other options for example liquid products.
5. In addition, SD outperformed salt formulation, co-crystallization, and other methods. Salt formulations, for example, use of ionized active medicinal substances (APIs) (cationic or anionic form) is frequently employed in the pharmaceutical industry due to their antimicrobial properties.

Disadvantages [1]
1. On storage, possibility of change of amorphous state into crystalline
2. Due to moisture, storage stability of SD is also main problem as it absorbs moisture
3. Poor scale up in manufacturing process

Application [19]
Apart from improving absorption, the solid dispersion approach may have a variety of medicinal uses that should be investigated further.

It's possible that a technique like this will be used:

1. To achieve a uniform dispersion of a little amount of medication in solid form.
2. To keep the medication from becoming unstable.
3. To make poorly soluble substances more soluble as a result, drugs increase the rate of dissolution, bioavailability and absorption
4. To protect unstable medications against hydrolysis, oxidation, and recrimination, they must be stabilized. Decomposition methods include isomerization, photo oxidation, and others.
5. To lessen the adverse effects of certain medications
6. The masking of a drug's undesirable taste and odor.
7. Drug release from ointment, creams, and gels is improved.
8. To avoid incompatibilities that aren't desirable.
9. To administer liquid or gaseous drugs in a solid dose (up to 10%).

Table no. 3 :- Here are some examples of solid dispersion along with drug, polymer and methods used.

S.N.	Drug	Polymer	Method	Reference
1.	Cefixime	B-CD	Kneading method	33
2.	Sulfamethoxazole	Mannitol	Melting/melt solvent method	42
3.	Quercetin	HPMC acetate succinate and L –Lysin	Solvent evaporation	43
4.	Carvedilol	Kollidon VA 64, HPMCAS, Klucel ™ EXF	Hot-melt extrusion	44
5.	Meloxicam	Poloxamer	Kneading method	41
6.	Ibuprofen	Kollidon	SCF	40

7.	Quercetin	Plasdone K90 K30 Eudragit	Solvent evaporation	35
8.	Carvedilol	PVPK30	Solvent Evaporation	34
9.	Quercetin	HPMC acetate succinate	Co precipitation	36
10.	Vemurafenib	HPMCAS	Solvent controlled co-precipitation	39
11.	Efavirenz	PVPK30	Conventional and kneading method	37
12.	Ritonavir	Copovidone	Hot melt extrusion	38
13.	Lapatinib ditosylate	Soluplus and poloxamer188	Solvent rotary evaporation and Hot melt extrusion	45
14.	Mega sterol acetate	Co povidone	Solvent evaporation and Fluidized bed coating	46
15.	Curcumin	PEG 600 and HPMC		47
16.	Glyburide	PEG 4000, PEG 6000	Melt method and solvent method	48
17.	Luteolin	PVP 40	Solvent evaporation	49
18.	Linarin	PVPK30	Solvent method	50
19.	Cannabidiol	Kollidon® VA 64, Parteck® MXP and Eudragit®	Hot-melt extrusion	51
20.	Mefenamic acid	Soluplus	Hot-melt extrusion	52
21.	Methotrexate	Pluronic F127	Fusion method	53
22.	Diclofenac sodium	Eudragit RS and Eudragit RL	Coevaporation	30
23.	Aripiprazole	Poloxamer 188	Hot melt extrusion	31
24.	Ursodeoxycholic	Pentaerythritol	Solvent evaporation method	32

Characterization of solid dispersion [20]

- Drug -carrier miscibility
  - a. Hot stage microscopy.
  - b. Differential scanning calorimetry
  - c. Powder X-ray diffraction
- Drug carrier interaction
  - a. FTIR Spectroscopy
  - b. Raman spectroscopy
- Physical structure
  - a. SEM (scanning electron microscopy)
  - b. Surface area analysis
  - c. Surface properties
- Dissolution enhancement
  - a. Dissolution
  - b. Dissolution in biorelevant media
  - c. Supersaturated solution study
- Amorphous content
  - a. Hot stage microscopy
  - b. DSC

Incorporation of solid dispersion into the topical formulation.

- In order to accept several chemicals with distinct, if not incompatible, physicochemical features, an efficient topical formulation must create a stable chemical environment in a suitable dispensing container. To accomplish proper skin absorption, a topical formulation must interact with the skin environment after application, which might alter the rate of component release. Excipients have additional physical effects on the skin, such as drying, occluding, or hydrating it.[23]
- Patil and mohite prepared SD to increase the drug's therapeutic efficiency by boosting skin permeability via a solid dispersion contained in the gel. The aqueous solubility of drugs

determines how well they penetrate the skin from a gel. A solid dispersion integrated gel will be developed to increase drug solubility and dissolving properties. and authors concluded improvement in dissolution as well as diffusion property of gel [24]

- It also proved that SD incorporated gel formulation shows good physicochemical properties, better drug release, and reasonable stability so it can be considered the use of the proper technique in SD can be applied for commercial and mass production.[25]

CONCLUSION:

Solid dispersions have shown to be a very profitable technique for enhancing the release rate also the bioavailability of hydrophobic medications during the last few decades. The expanding number of poorly soluble drug candidates, as well as significant developments in solid dispersion manufacturing techniques over the previous few years, point to solid dispersions playing an increasingly important role in pharmaceutical development. Another advantage of solid dispersions over other techniques is that many of the carriers that can be utilised are already widely used as excipients in the pharmaceutical industry, eliminating the need for toxicity studies. Drug solubility and dissolution were improved by increasing drug wettability and surface area. Understanding the qualities of the carrier and medication, as well as selecting an appropriate technique, are critical for the formulation's success.

Abbreviation:

1. SD	Solid dispersion
2. API	Active pharmaceutical ingredient
3. DSC	Differential scanning calorimetry
4. SEM	Scanning electron microscopy
5. FTIR	Fourier-transform infrared spectroscopy
6. BCS	Biopharmaceutics Classification System
7. US	United states
8. W/W	Weight/weight

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