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OVERVIEW OF SOLID DISPERSION: METHODS OF PREPARATIONAND PHARMACEUTICAL APPLICATIONS

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ABSTRACT

Solid dispersion is a versatile and widely employed technique in the field of pharmaceuticals to enhance the solubility and bioavailability of poorly water-soluble drugs. This review article explores the various methods of preparing solid dispersions, the factors influencing their formation, and their applications in pharmaceutical formulations. The goal of this review is to provide a comprehensive understanding of solid dispersion technology, highlighting its importance in drug delivery systems.

Keywords *– Solid dispersion, Pharmaceutical Applications, Drug delivery Systems, Solubility, Technologies*

1. INTRODUCTION

The oral route of medicine administration is the most common and preferred form of delivery due to its simplicity and convenience of oral administration. From the patient's perspective, ingesting medicine is a convenient and accustomed way to take medicines. Oral drug delivery is more efficient in terms of patient compliance compared to alternate modes of administration, such as parenteral. Oral drug delivery presents multiple options of formulation design around strategies whereby drug is tailored to be released either immediate release, extended release, delayed-release, targeted release, etc. When taken orally, an active drug must dissolve in the stomach and/or intestinal fluids before it can cross the GI tract's membranes and enter the bloodstream. Low medication bioavailability is caused by low drug absorption from the gastrointestinal (GI) tract, which is significantly influenced by the drug's molecule's water solubility and membrane permeability.

The development of novel pharmaceuticals often faces challenges associated with the poor solubility of active pharmaceutical ingredients (APIs) [1]. Low solubility can limit drug absorption and bioavailability, consequently reducing therapeutic efficacy. Pharmaceutical scientists have two approaches to improve oral bioavailability of pharmacologically active agents: (i) improving the solubility and dissolution rate of poorly water-soluble medications, and (ii) improving the permeability of poorly permeable drugs. Solid dispersion has emerged as an effective strategy to address this issue by improving the dissolution rate and overall bioavailability of poorly water-soluble drugs.

According to Chiou and Riegelman, solid dispersion systems are “the solid-state dispersion of one or more active substances in an inert carrier or matrix generated by the fusion, solvent evaporation, or melting-solvent process.” Matrix is hydrophilic, whereas the medication is hydrophobic. Simple eutectic mixtures, solid solutions, glass solutions, and glass suspensions, amorphous precipitation in a crystalline carrier, compound, or complicated forms are solid dispersion types. Based on this, there is significant role of a hydrophilic carriers in formation of solid dispersions which are the applied towards improving solubility and hence bioavailability of

BCS class-II and BCS class-IV drugs (BCS: Biopharmaceutical Classification System). Improving solubility and bioavailability is also area of focus for emerging anti-cancer drugs. Table 1 below defines solubility class of drug as per USP and Figure 1 below summarizes classification of drug based on Biopharmaceutical Classification System. Important to note, while referring to low or high soluble drug in context to BCS class which is more relevant physiologically. Per BCS, a drug substance is considered as highly soluble if its highest single therapeutic dose is completely soluble in 250 milliliter (mL) or less of aqueous media over the pH range of 1.2– 6.8 at 37±1°C [14].

This article describes methods of preparation, factors influencing and pharmaceutical applications of solid dispersions.

Table 1: Solubility Classification per USP

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
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
Practically insoluble, or Insoluble	10,000 and over

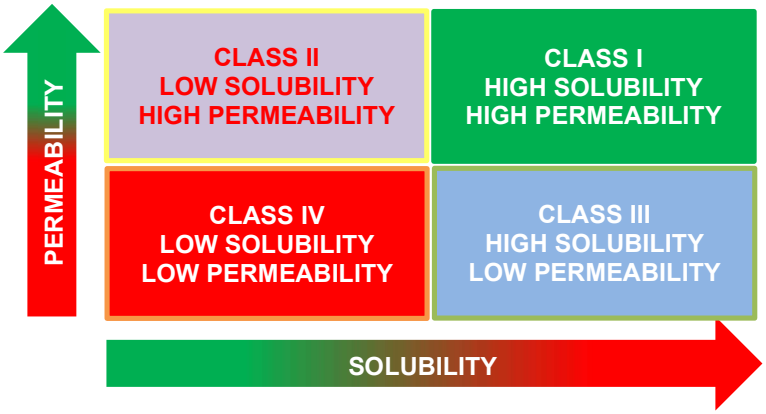

Figure 1: BCS classification system

2. METHODS OF PREPARATION

2.1. Melting Method

The melting method involves the fusion of the drug and a suitable carrier, followed by cooling to form a solid dispersion [2]. Common carriers include polymers like PEG (polyethylene glycol), PVP (polyvinylpyrrolidone), and HPMC (hydroxypropyl methylcellulose). This method is particularly useful for drugs that are stable at elevated temperatures.

2.2. Solvent Evaporation Method

In the solvent evaporation method, a drug and carrier are dissolved in a common solvent [3]. The solvent is then evaporated, leaving behind a solid dispersion. This method is versatile and can be applied to a wide range of drugs and carriers. It is advantageous for temperature-sensitive drugs.

2.3. Spray Drying

Spray drying involves the atomization of a drug-carrier solution into fine droplets, which are then dried to form solid particles [4]. It is a scalable and continuous process suitable for industrial applications. A spray dried dispersion is a dispersion of a drug in a polymer matrix, created by dissolving drug and polymer in a solvent and then spray drying the solution. Spray drying can yield amorphous or crystalline solid dispersions depending on process parameters. The main advantages of Spray Drying technology are consistent particle size distribution, high drug load, enables taste masking, stability, etc.

2.4. Hot-Melt Extrusion

Hot-melt extrusion (HME) is a continuous process where the drug and polymer are combined and heated to a molten state, followed by extrusion through a die to form solid dispersions [5]. HME offers precise control over drug dispersion, can accommodate a variety of polymers and drugs and high drug loads. Nowadays, HME, is preferred option and is also explored as an option of modification of existing therapy such that to benefit patients. HME as a process reduces number of manufacturing processes significantly.

2.5. Freeze-Drying (Lyophilization)

Freeze-drying involves freezing a drug-carrier solution and then subjecting it to a vacuum to remove the solvent by sublimation [6]. This process is commonly used for labile drugs and biopharmaceuticals and was proposed as alternate to solvent evaporation technique.

2.6. Coprecipitation Method

The carrier is dissolved in water, while the medication is dissolved in an organic solvent. To the organic drug solution is added, the aqueous carrier solution. Solvents are ejected, dispersion is crushed, sieved, and dried using a pestle and mortar. See Figure 2

Table 2: Marketed preparations by solid dispersion [15]

Product name	Drug name	Carrier used	Method used	Company name
Grispeg®	Griseofulvin	PEG	Melt process, the exact process is unknown	Pendinal pharm inc.
Cesamet®	Nabilone	PVP	Process is unknown	Eli lilly
Sproranox®	Itraconazole	Hypromellose, HMPC, PEG 20000	Spray layering	Janssen
Rezulin®	Troglitazone	PVP	Melt-extrusion	Pfizer
Hepcure®	Hepatitis type b	Amorphous adefovir dipivoxil in solid dispersion	Amorphous adefovir in solid dispersion	CJ CheilJedang

Keletra®	Lopinavir	PVPV	Melt-extrusion	Abbott
Afeditab®	Nifedipine	Poloxamer or PVP	Melt/absorb on the carrier	Elan corp, Ireland
Certican®	Everolimus	HPMC	Melt or spray drying	Novartis, Switzerland
Fenoglide®	Fenofibrate	PEG	Unknown process	Life cycle pharma, Denmark
Nivadil®	Nivaldipine	HPC/HPMC	Solvent method	Fujisawa pharmaceuticals co., ltd
Nimotop®	Nimodipine	PEG	Unknown process	Bayer
Torcetrapib®	Torcetrapib	HPMC		Pfizer, USA
Ibuprofen®	Ibuprofen	PEG, HPMC, and PVP	Melt-extrusion	Soliqs, Germany
Incivek®	Telaprevir	HPMC as	Spray drying	Vertex
Prograf®	Tacrolimus	HPMC	Wet granulation	Fujisawa pharmaceuticals co., ltd
Cymbalta®	Duloxetine	HPMC AS	Unknown process	Lilly, USA
Noxafil®	Posaconazole	HPMC AS	Melt extrusion	Merck
Intelence®	Etravirine	HPMC	Spray drying	Tibotec, Yardley, PA
Isoptin SRE-240®	Verapamil	Various	Melt-extrusion	Soliqs, Germany
Isoptin SR-E®	Verapamil	HPC/HPMC HPC/HPMC Abbott	Spray drying	Abbott Laboratories, USA,
Crestor®	Rosuvastatin	HPMC	Solvent evaporation	AstraZeneca
Zelboraf®	Vemurafenib	HPMC as	Coprecipitation	Roche

Zortress®	Everolimus	HPMC	Spray drying	Novartis, Switzerland
Kalydeco®	Ivacaftor	HPMC as	New solvate of ivacaftor, processes, exact process unknown	Vertex

HPMC: hydroxypropylmethylcellulose; HPC: hydroxypropylcellulose; HMPC AS: hydroxypropylmethylcellulose acetylsuccinate; PEG: polyethyleneglycol; PVP: polyvinylpyrrolidone.

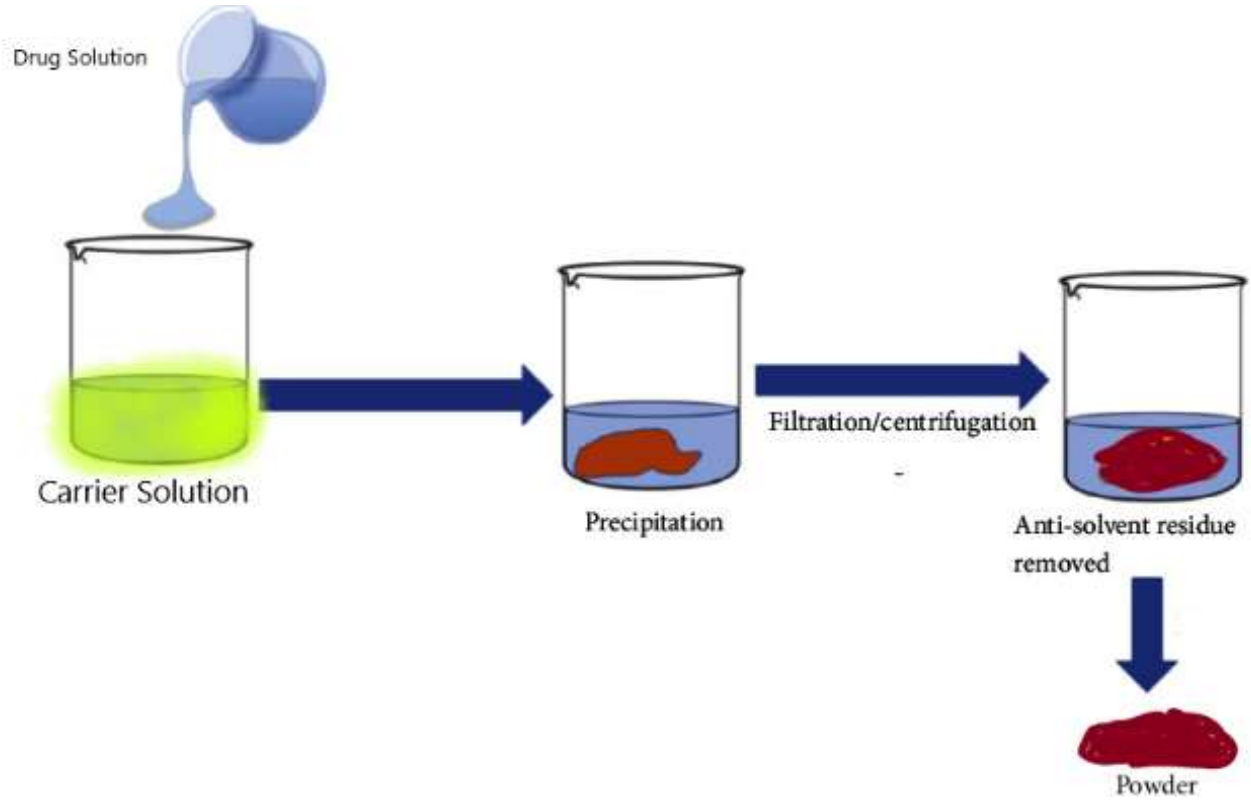

Figure 2: coprecipitation process

3. FACTORS INFLUENCING SOLID DISPERSION FORMATION

In brief, several factors influence the formation of solid dispersions, include drug-carrier compatibility, drug-carrier ratio, preparation method, and the presence of stabilizers or surfactants [7]. Careful consideration of these factors is crucial to obtain a stable and effective solid dispersion.

4. PHARMACEUTICAL APPLICATIONS

4.1. Improved Bioavailability

Solid dispersions significantly enhance the dissolution rate of poorly water-soluble drugs, leading to improved bioavailability [8]. This is particularly valuable for drugs with a narrow therapeutic window.

4.2. Controlled Release

Solid dispersions can be tailored to provide controlled release of the drug [9]. This is beneficial for achieving prolonged therapeutic effects and reducing side effects.

4.3. Combination Products

Solid dispersions enable the co-delivery of multiple drugs in a single dosage form [10]. This simplifies complex dosing regimens and improves patient compliance.

4.4. Pediatric Formulations

Solid dispersions can be used to formulate pediatric dosage forms of poorly soluble drugs [11]. This facilitates drug administration to children.

4.5. Nutraceuticals

Solid dispersion technology has also found applications in nutraceutical formulations [12]. It enhances the solubility and bioavailability of bioactive compounds in dietary supplements.

4.6 Taste Making: techniques like spray drying molecularly trap bitter drug substances in a carrier thereby taste mask drugs.

5. ADVANTAGES OF SOLID DISPERSIONS (SD)

SD is used for enhancing solubility and bioavailability of BCS class II and IV drug with advantages as listed below:

- By drugs interaction with hydrophilic carrier, decreases agglomeration and enhances release in a supersaturation state, resulting in rapid absorption.
- Most of anti-cancer drugs possess poor aqueous solubility resulting low bioavailability, this limitation of solubility and dissolution is improved by SD, leading to enhanced in-vivo absorption.
- SD improves drug wettability, facilitating good interaction with physiological fluids and miscibility in them
- disadvantages of salt formulation can be resolved when the formulation is produced using an SD.
- SD can be formulated into solid oral dosage form, convenient for patients compared to other dosage forms.

6. DRAWBACKS OF SOLID DISPERSIONS

There are several drawbacks that limit the use of solid dispersion in the drug formulation process, including [13] the following:

- Demanding and costly techniques of preparation
- Physicochemical properties and reproducibility
- Difficulty in merging dosage forms into the formulation
- Scaling up of the manufacturing process
- Stability of medications and solvent

7. CONCLUSION

Solid dispersion is a versatile approach to address the solubility challenges of poorly water-soluble drugs in pharmaceutical formulations. Various methods of preparation offer flexibility and scalability, making this technology a valuable tool in drug development. With its potential to improve bioavailability, controlled release, and combination product formulations, solid dispersion continues to play a pivotal role in the pharmaceutical industry. With increased focus on solving the poor bioavailability

of new chemical entities, solid dispersion is getting more attention for exploration. Ongoing research focuses to materialize techniques of solid dispersion preparation into drug delivery systems so as to make it as viable option and benefiting patients.

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