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A Review on Solid Dispersion Techniques: A Exclusive Approach for Enhancing Drug Solubility and Bioavailability

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ABSTRACT
Insufficient aqueous solubility presents a major obstacle in drug development, resulting in diminished bioavailability and potential therapeutic failure. Solid dispersion techniques represent an efficient approach to improve the solubility and dissolution rates of drugs with poor water solubility. Different carriers like surfactants or co-solvents, polymers etc. are used to enhance the solubilization of poorly water-soluble drugs using different approaches. This article includes various methods of solid dispersion, such as fusion, solvent evaporation, hot-melt extrusion, and spray drying, while emphasizing their mechanism, advantages, disadvantages, challenges, pharmaceutical applications, marketed formulations and future perspectives in global market. Additionally, it discusses the influence of carrier selection, stability issues, and prospective research avenues.

Keywords: Solid dispersion, Solubility enhancement, Drug delivery, Bioavailability enhancement, pharmaceutical carriers.

INTRODUCTION

The pharmaceutical sector encounters major difficulties in creating drugs that have low water solubility. Around 40% of new chemical entities are affected by inadequate solubility, which restricts their bioavailability and therapeutic effectiveness.

A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limitedabsorption. Hence, two a reas of pharmaceutical research that focus on improving the oral
bioavailability of active agents include: enhancing solubility and dissolution rate of poorlywater soluble drug and enhancing permeability of poorly permeable drugs. Solid dispersion technology offers a novel method to enhance solubility by distributing drugs in hydrophilic carriers [1]. This paper examines the principles, classifications, preparation techniques, and obstacles associated with solid dispersion systems. Enhancing dissolution can primarily be achieved by increasing the surface area available for dissolution through the reduction of the solid compound's particle size and/or by optimizing the wetting properties of the compound's surface. This approach aims to reduce the thickness of the boundary layer, ensure sink conditions for dissolution, and, importantly, enhance the apparent solubility of the drug in physiologically

relevant environments. Among these strategies, modifying hydrodynamics presents challenges for in vivo applications, and maintaining sink conditions is contingent upon the permeability of the gastrointestinal mucosa to the compound, as well as the composition and volume of the luminal fluids. While some research has focused on improving permeability with suitable excipients, the outcomes thus far have not been particularly promising. In the Biopharmaceutical Classification System, drugs that exhibit low solubility in water and high permeability across membranes are classified as Class II drugs [2]. Consequently, solid dispersion technologies hold significant potential for enhancing the oral absorption and bioavailability of these drugs. The fundamental approach to improving the solubility of such drugs through solid dispersion involves the total elimination of the drug's crystalline structure, allowing for its molecular distribution within a hydrophilic polymeric carrier. When a solid dispersion comes into contact with aqueous media, the carrier dissolves, resulting in the release of the drug in the form of fine colloidal particles. This process enhances the surface area for dissolution, thereby improving the bioavailability of drugs that are poorly soluble in water [3]. The presence of the soluble hydrophilic carrier facilitates a higher dissolution rate by decreasing particle size and increasing porosity. Consequently, by optimizing the drug release characteristics of these compounds, it is feasible to enhance their bioavailability while minimizing side effects.

Solid dispersion

There are several methods for improving solubility. One of the finest methods for improving solubility is solid dispersion. The word "solid" A collection of solid products made up of at least two distinct components—typically a hydrophilic matrix and a hydrophobic drug—is referred to as a dispersion [4]. The matrix can be either crystalline or amorphous; generally amorphous is having good solubility than crystalline substance since no energy is required to break up the crystal lattice of a drug during dissolution process. Surrounding hydrophilic carriers may improve drug solubility and wettability as shown in fig. 1 [5].

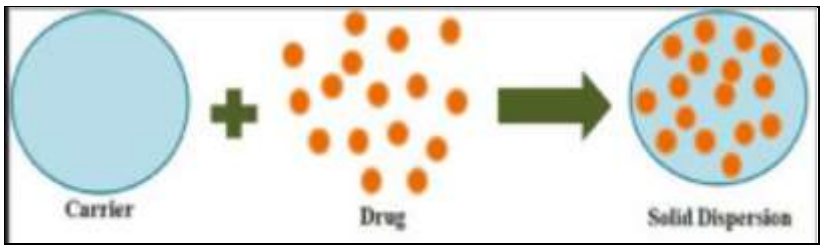

Fig. 1: Representation of solid dispersion

Classification

Solid dispersions are classified based on as follows [6]-

1. Molecular Arrangement

1.1 Eutectic Mixtures – Drug and carrier crystallize together at a specific composition.

These are made by quickly solidifying two components that have melted together to reveal full liquid miscibility and minimal solubility between solids. According to thermodynamics, such a system is a physically mixed mixture of its two crystalline constituents. Consequently, a eutectic's X-ray diffraction pattern is an additive composite of two elements. Examples include Griseofulvin and Tolbutamide with PEG 2000, Paracetamol-urea, and Chloramphenicol-urea.

2. Solid solutions on the miscibility

2.1 Continuous solid solutions: In this, the components are miscible in all proportions and the bonding strength between the components is stronger than the bonding between the individual component.

2.2 Discontinuous solid solutions: In this type the solubility of each of the component in the other component is limited in nature.

3. Distribution of the solvates in the solvent

3.1 Substitution crystalline solution: These are those solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.

3.2 Interstitial crystalline solid solution: These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice.

4. Amorphous Precipitations in a Crystalline Carrier

The difference between this group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter. For example, Sulfathiazole was precipitated in the amorphous form in crystalline urea.

5. Glass Solutions and Suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting point; instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions.

6. On the basis of recent advancement

6.1 First generation solid dispersion [7]

Crystalline carriers are used to create these solid dispersions.

The earliest crystalline carriers utilized to create solid dispersions were sugars and urea.

These have the drawbacks of not releasing the medication more quickly and being thermodynamically u nstable.

6.2 Second generation solid dispersion

In place of crystalline carriers, amorphous carriers are used to create these solid dispersions.

The polymeric carrier disperses the drug molecularly. It includes Synthetic polymers (povidone, polyethylene glycols and polymethacrylates) and Natural polymers (hydroxypropyl methylcellulose, ethyl cellulose, starch derivatives like cyclodextrin).

6.3 Third generation solid dispersion

A surfactant carrier or a combination of amorphous polymers and surfactants serve as carriers in these so lid dispersions.For medications with low solubility, these provide the maximum bioavailability.

Example- Inulin, poloxamer 407, and others [8].

6.4 Fourth generation solid dispersion

These are known as controlled release solid dispersions. It contains poorly water-soluble drug with a short biological half-life. The carrier used are either water soluble carrier or water insoluble carrier [9].

PREPARATION METHODS

Solid dispersions with the drug are prepared by various methods depends on physicochemical properties of drug-carrier interactions. Some of them are described as follows [10].

- **Fusion (Melt) Method**

The drug and a hydrophilic carrier (e.g., polyethylene glycol, mannitol, sorbitol) are melted together at high temperatures. The molten mixture is then rapidly cooled to form a solid mass. The solidified mass is pulverized into fine particles. The method is simple, solvent-free process, cost-effective and suitable for large-scale production. It has limitations of thermal degradation, risk for heat-sensitive drugs. Phase separation may occur if drug and carrier have different melting points. It is suitable for PEG-based dispersions of ibuprofen.

- **Solvent Evaporation Method**

The drug and carrier are dissolved in a common volatile solvent (e.g., ethanol, methanol, chloroform). The solvent is evaporated under controlled conditions, leaving behind a solid dispersion. The dried material is then ground into a fine powder. It avoids high-temperature processing, making it suitable for thermolabile drugs and produces fine and uniform particles.

Process limit to residual solvent toxicity concerns, time-consuming and expensive due to solvent recovery. Example: PVP-based dispersions of ketoconazole.

- **Hot-Melt Extrusion method**

A mixture of drug and polymer is heated and extruded through a nozzle at high pressure.

The extruded material is cooled, solidified, and milled into fine particles. It is a continuous, scalable process suitable for industrial production. No solvents required, reducing toxicity risks. It requires specialized equipment. High temperatures may degrade sensitive drugs.

Example: Solid dispersions of ritonavir with HPMC.

- **Spray Drying**

The drug and carrier are dissolved in a solvent and atomized into hot air. The solvent evaporates rapidly, leaving behind a fine, dry powder. Produces highly uniform and small particles and suitable for inhalable and oral formulations. It requires careful control of drying parameters and has high operational cost. Example: Spray-dried dispersions of curcumin with PVP.

- **Supercritical Fluid Method**

Supercritical CO_2 is used to dissolve and disperse the drug in the carrier. Upon depressurization, the drug precipitates as fine particles. This process is environmentally friendly, as no organic solvents are used. It produces ultra-fine drug particles with enhanced solubility. It is expensive and requires specialized equipment and has limited drug compatibility with supercritical CO_2.

- **Co-precipitation Method**

Drug and carrier are dissolved in a solvent, and then a non-solvent is added to precipitate the dispersion. The precipitate is collected, dried, and ground into a powder.

It is suitable for water-insoluble drugs. It is used to enhance drug-polymer interactions.

In this method solvent selection is critical due to risk of incomplete precipitation.

- **Lyophilization (Freeze-Drying) Method**

The drug and carrier are dissolved in water and frozen rapidly. The frozen solution is subjected to vacuum drying to remove ice by sublimation. It helps to preserves the drug stability. Avoids high temperatures, making it suitable for thermosensitive drugs. The method is expensive and time-consuming and not suitable for water-insoluble drugs.

- **Kneading method**

Drug and carrier weighed, they are mixed together, use motor & pestle to reduce the size of the both drug & carrier. Water methanol mixture 3:1 ratio was added to the above mixture. The solution was mixed well and slurry was collected by filtration and dried in hot air oven for 2hrs at 50C**.** Then dried mass was collected further dried in desiccated for 12hrs. Then the solid dispersion passed to sieve no:80 to obtained uniform particle size. Some of the solid dispersion methods are shown in Fig. 2.

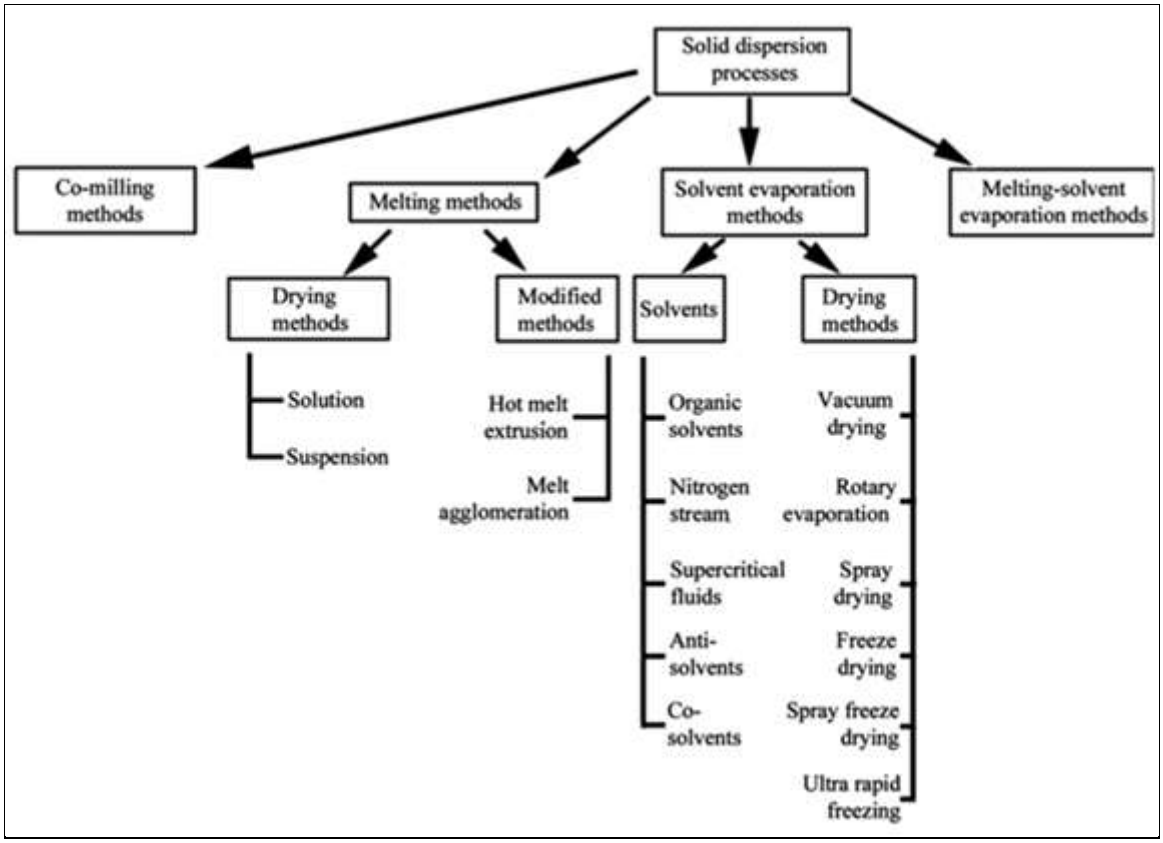

Fig.2: Some solid dispersion methods [11]

Selection of carriers in solid dispersion

Carriers play a crucial role in stabilizing solid dispersions by preventing processes like aggregation/crystallization of the dispersed drug. They providing physical support and hindering the movement of the dispersed phase and act as a matrix [12]. Some of the common carriers as shown in Table:1.

Table 1: Some of the common carriers for solid dispersion

Sr. No.	Common carriers	Examples
1	Hydrophilic Polymers	PEG, PVP, HPMC
2	Surfactants	Poloxamers, Tween 80
3	Sugars and Sugar Alcohols	Mannitol, Sorbitol
4	Cyclodextrins	Beta- Cyclodextrins, HP-B- Cyclodextrins

Pharmaceutical Advantages

- Enhancing drug bioavailability through modifications in water solubility can be accomplished using either chemical or formulation strategies.
- Chemical methods to boost bioavailability while preserving the active target include salt formation and the addition of polar or ionizable groups to the drug's core structure, leading to the creation of a pro-drug.
- Solid dispersions are considered a more effective method for increasing drug solubility compared to these techniques, as they are simpler to produce and more versatile in application.
- Particles in solid dispersions have been found to have a higher degree of porosity depends on the carrier properties
- Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate.
- The increased porosity of solid dispersion particles also hastens the drug release profile.

Disadvantages

- Some solid dispersions are showing their instability.
- Chances of showing changes in crystallinity and a decrease in dissolution rate on ageing.
- By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place.
- Chances of the reduction of drug solubility.
- Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures.
- Sometimes it is difficult to handle because of tackiness [13].

Mechanism of Solubility Enhancement in Solid Dispersions

Solid dispersion enhances drug solubility through following methods-

- **Particle Size Reduction (micronization/ nanonization).** In solid dispersions, the drug is molecularly dispersed in a carrier matrix. This reduces particle size to the molecular or amorphous level. Increases the surface area, resulting in quicker dissolution.
- **Amorphization of the Drug:** Drugs in solid dispersions often exist in an amorphous rather than crystalline state. Amorphous forms have higher energy and greater solubility compared to crystalline forms.
- **Improved Wettability:** Hydrophilic carriers (e.g., PVP, PEG, HPMC) improve the wettability of the drug particles. It helps to enhance water penetration, leading to faster drug dissolution.
- **Solubilization Effect of Carriers:** Some carriers act as surfactants or co-solvents (e.g., Poloxamers, Soluplus), which can solubilize drug molecules. Enhances apparent solubility and maintains drug in solution longer.
- **Reduction in Drug Aggregation:** The solid dispersion system inhibits drug particle aggregation or recrystallization. It maintains the drug in a dispersed, solubilized state.
- **Increased Thermodynamic Activity:** The drug in amorphous form has higher chemical potential. Leads to a higher driving force for dissolution.

  Fig. 3 shows schematic representation of Solid Dispersions A, B, C mechanism [14].

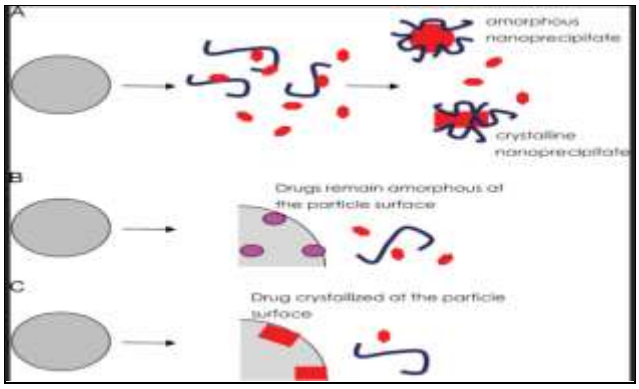

Fig. 3: Schematic representation of Mechanism of Solid Dispersions

Evaluation of physicochemical properties

- **Phase Solubility Study**: The process is conducted with the presence of a polymer (carrier) utilizing the shaking flask technique, primarily following the guidelines established by Higuchi and Connors. In this approach, the drug is introduced into a 25 ml solution containing varying concentrations of polymer at 1%, 2%, 3%, 4%, and 5%. The mixture is then subjected to an orbital flask shaker for a duration of 48 h at a temperature of 37 ℃±0.5℃. Subsequently, the sample is filtered and analysed using a UV spectrophotometer to ascertain the drug concentration [15].
- **Saturation Solubility Study**: Drug and solid dispersion samples are introduced in excess into 25 ml of distilled water until reaching supersaturation. The mixture is then subjected to shaking in an orbital flask for 48 h at a temperature of 37℃ ± 0.5 ℃. Following this period, the solution is filtered using Whatman filter paper, and the concentration of the drug is subsequently analysed using a UV spectrophotometer [16].
- **Drug content:** A specific amount of solid dispersion is dissolved in a solvent and subsequently analysed using a UV spectrophotometer to determine the drug content. The percentage of drug loading and the percentage of entrapment efficiency are calculated using the following formula:
  % Drug loading = (Weight of drug in solid dispersion powder) / (Weight of solid dispersion powder) × 100.

Characterization methods

- **Fourier Transform Infrared Spectroscopy**: It is primarily employed to assess the compatibility between drugs and polymers, serving as a key method for examining the interactions that occur in the solid state between these two components.
- **Differential Scanning Calorimetry (DSC)**: is a robust analytical technique utilized to investigate the amorphous content of materials. It is capable of identifying both endothermic and exothermic peaks, and it also helps determine whether a drug has been successfully incorporated into a polymer carrier by analysing changes in melting points.
- **Powder X-ray Diffraction:** is particularly effective in distinguishing between amorphous and crystalline solid dispersions, with sharper peaks indicating a higher degree of crystallinity.
- **Scanning Electron Microscopy:** is employed to analyse the morphology of particles, providing detailed insights into their structural characteristics.
  Some others characteristics and adopted methods are shown in Table 2 [17].

Table 2: Characteristics of solid dispersion and their adopted methods

Sr. No.	characteristics	Methods Adopted
1	Surface microscopy	polarized light optical microscopy, Solid state nuclear magnetic resonance spectroscopy
2	Structure elucidation	Solid state NMR, Fourier transform infrared spectroscopy
3	Drug carrier interactions	DSC, Fourier transform infrared spectroscopy, NMR
4	Physical state examination	DSC, Powder X-ray diffraction, Hot stage & Humidity stage microscopy
5	Stability	DSC, NMR spectroscopy, Fourier transform infrared spectroscopy
6	Dissolution rate	Dissolution studies, dynamic solubility studies

Pharmaceutical applications

The pharmaceutical applications of Solid dispersions technique are as follows [18]-

- It is used to obtain a homogeneous distribution of a small amount of drug in solid state.
- Helps to enhance the drug absorption.
- Stabilization of unstable drugs from decomposition by processes of photo oxidation hydrolysis, oxidation, racemization, etc.
- For dispensing of liquid or gaseous matter and conversion of liquid/solid to formulation.
- For formulation of a sustained release dosage form by dispersing the drug in carrier-mediated delivery.
- To reduce side effects via binding ability of drugs by making its inclusion complex.
- To mask unpleasant taste and smell for some drugs.

Current overview on Marketed formulations

Solid dispersed dosage forms are available in the market. Some of them are listed in Table 3 [19].

Table 3: Some examples of Solid dispersions in Market:

Products	Drugs	Polymers	Company
Afeditab®	Nifedipine	Poloxamer or PVP	Elan Corp, Ireland
Cesamet®	Nabilone	PVP	Lilly, USA
Cesamet®	Nabilone	PVP	Valeant Pharmaceuticals, Canada
Certican®	Everolimus	HPMC	Novartis, Switzweland
Gris-PEG®	Griseofulvin	PEG	Novartis, Switzweland
Gris-PEG®	Griseofulvin	PVP	VIP Pharma, Denmark
Fenoglide®	Fenofibrate	PEG	LifeCycle Pharma, Denmark
Nivadil®	Nivaldipine	HPC/HPMC	Fujisawa Pharmaceuticals Co., Lt
Nimotop®	Nimodipine	PEG	Bayer
Torcetrapib®	Torcetrapib	HPMC AS	Pfizer, USA
Ibuprofen®	Ibuprofen	Various	Soliqs, Germany

Incivek®	Telaprevir	HPMC AS	Vertex
Sporanox®	Itraconazole	HPMC	Janssen Pharmaceutica, Belgium
Onmel®	Itraconazole	HPMC	Stiefel
Prograf®	Tacrolimus	HPMC	Fujisawa Pharmaceuticals Co., Lt
Cymbalta®	Duloxetine	HPMC AS	Lilly, USA
Noxafil®	Posaconazole	HPMC AS	Merck
LCP-Tacro®	Tacrolimus	HPMC	LifeCycle Pharma, Denmark
Intelence®	Etravirine	HPMC	Tibotec, Yardley, PA
Incivo®	Etravirine	HPMC	Janssen Pharmaceutica, Belgium
Rezulin®	Troglitazone	PVP	Pfizer, USA
Isoptin SRE-240®	Verapamil	Various	Soliqs, Germany
Isoptin SR-E®	Verapamil	HPC/HPMC	Abbott Laboratories, USA
Crestor®	Rosuvastatin	HPMC	AstraZeneca

The marketed size in 2023, for oral solid dosage pharmaceutical formulation Market was valued at USD 727.77 Bn and expected the total revenue to grow at 7.1% by 2024 to 2030, around USD 1176.32 Bn. For revenue point of view, in 2023, North America led the global Oral Solid Dosage Pharmaceutical Formulation market and this trend is continued over the forecast timeframe having a CAGR of 6.7%. Oral solid dosage form market from 2023-2030 has been graphically represented in Fig. 4 [20].

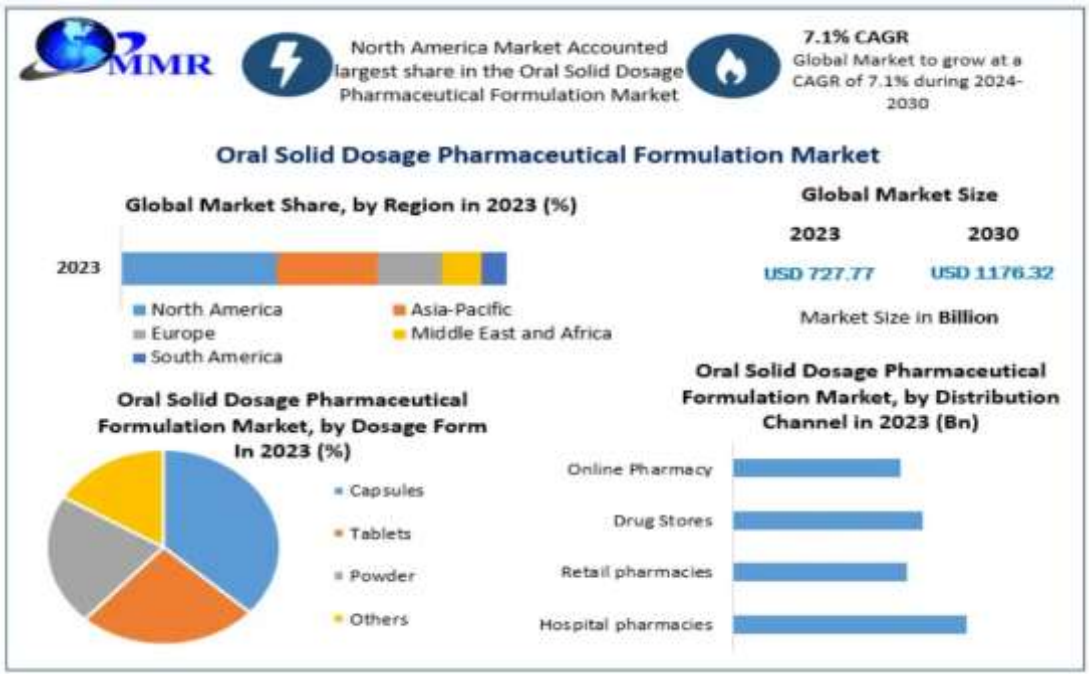

Fig. 4 Oral solid dosage form global market growth from 2023-2030.

CHALLENGES IN SOLID DISPERSION TECHNOLOGY

- **Physical Stability:** There is a potential risk of phase separation or recrystallization occurring.
- **Chemical Stability:** Interactions between the drug and polymer may lead to degradation.
- **Scale-up Challenges:** Transitioning from laboratory-scale production to industrial-scale manufacturing presents difficulties [21].

PERSPECTIVES AND RESEARCH DIRECTIONS

The application of nanotechnology aims to improve the solubility of pharmaceuticals. The creation of intelligent polymers provides the ability to regulate the release of medications effectively. Progress in 3D printing technology facilitates the customization of drug formulations tailored to individual needs. The utilization of artificial intelligence in formulation design enhances the optimization of dispersion methods.

CONCLUSION

Solid dispersion represents a valuable approach for improving the solubility and bioavailability of pharmaceuticals. Despite existing challenges, ongoing progress in formulation science and processing technologies is steadily enhancing the practicality of drug delivery systems that utilize solid dispersion. Future investigations should prioritize the enhancement of stability and scalability to facilitate the introduction of additional solid dispersion-based formulations into the marketplace.

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