



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

A Comprehensive Review: Enhancing The Solubility & Oral Bioavailability Through Solid Dispersion

Deepak D. Sabne*, Ashish Jain, Sofiya Moris

Department of Pharmaceutics, Shri D.D. Vispute College of Pharmacy and Research Centre, New Panvel

ARTICLE INFO

Received: 11 Aug 2024
Accepted: 15 Aug 2024
Published: 20 Aug 2024

Keywords:

Solid dispersion, Solvent evaporation, Spray drying, Differential Scanning Colorimetry, X-ray Diffraction.

DOI:

10.5281/zenodo.13346474

ABSTRACT

Approximately 40% of newly discovered chemical entities (NCEs) in the pharmaceutical industry today, identified through combinatorial chemistry and high-throughput screening, exhibit high lipophilicity or poor water solubility. Consequently, the prevalence of such compounds has risen significantly, posing a substantial challenge in formulation development due to their solubility behaviour. Solid dispersion technology has emerged as a promising approach to enhance the solubility and bioavailability of poorly water-soluble drugs. This review explores recent advancements in solid dispersion formulation, focusing on formulation strategies, characterization techniques, and applications in pharmaceutical drug delivery. Various methods for preparing solid dispersion are discussed, including melting method, solvent evaporation, spray drying, and hot melt extrusion methods. Characterization techniques such as Differential Scanning Colorimetry (DSC), X-Ray Diffraction(X-RD), and Scanning Electron Microscopy (SEM) are highlighted for evaluating the physical properties of solid dispersion. Additionally, this review discusses the impact of solid dispersion formulation on drug dissolution kinetics, stability, and in vivo performance.

INTRODUCTION

The absorption and therapeutic effectiveness of a drug are significantly influenced by its solubility, a crucial physicochemical factor. Poor aqueous solubility often leads to setbacks in the formulation development process. The primary reason for adequate drug bioavailability is its low dissolution rate and limited solubility in aqueous media. In contemporary pharmaceutical research,

numerous hydrophilic carriers have been explored and have demonstrated promising results enhancing solubility. Despite advancements in drug innovation, improving the solubility and dissolution of hydrophobic drug substances remain one of the most challenging tasks in drug development. To enhance the bioavailability of poorly water-soluble compounds, such as those classified under the Biopharmaceutical

***Corresponding Author:** Deepak D. Sabne

Address: Department of Pharmaceutics, Shri D.D. Vispute College of Pharmacy and Research Centre, New Panvel

Email ✉: deepaksabne596@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



Classification System as class II and IV drugs, polymer matrices of various origin can be employed [1]. Various solubility enhancement methods have been introduced to overcome this challenge. These techniques can be categorized into physical modifications, chemical modifications of the drug substance, and other innovative approaches. For a comprehensive understanding, these methods are listed in Table 1 [2-3]. According to the Biopharmaceutical Classification System (BCS), drugs characterized by low solubility in water and high permeability across membranes are classified as Class II drugs. Consequently, solid dispersion methods hold significant potential for enhancing the oral absorption and bioavailability of BCS Class II drugs [4].

SOLID DISPERSION:

In 1961, Sekiguchi and Obi were the first to propose using solid dispersions to enhance the dissolution and oral absorption of poorly water-soluble drugs. Their concept involved creating a eutectic mixture by combining a poorly water-soluble drug with a physiologically inert, easily soluble carrier (Chiou and Riegelman, 1969). Subsequently, in 1971, Chiou and Riegelman provided a definition for solid dispersion as the “the dispersal of one or more active ingredients within an inert carrier matrix in the solid-state, achieved through methods such as melting (fusion), solvent, or melting-solvent techniques” (Chiou and Riegelman, 1971). Additionally, solid dispersions were alternatively termed solid-state dispersion, as initially coined by Mayersohn and Gibaldi in 1966 [5].

ADVANTAGES:

Solid Dispersion (SD) has been widely utilized to enhance the water solubility of poorly water-soluble drug, offering several advantages:

- SD facilitates interactions between drugs and hydrophilic carriers, effectively reducing agglomeration and promoting release in a

supersaturation state, thereby facilitating rapid absorption and improved bioavailability (BA) [6].

- By enhancing drug wettability and increasing surface area, SD leads to improved aqueous solubility of drugs.
- SD can be formulated as solid oral dosage forms, which are more convenient for patients compared to other forms such as liquid products.
- SD presents advantages over salt formulations, co-crystallization, and other methods. While salt formulations utilize ionized active pharmaceutical ingredients (APIs) and offer versatility in design, they may face challenges such as limited ionized compatibility, phase dissociation, and stability issues.
- Salt formulations may also suffer from reduced solubility and dissolution rates, leading to decreased relative BA, particularly due to the common ion effect for HCl salts.
- Furthermore, strong acid salts isolated from alkyl alcohols may undergo greater regulatory scrutiny, and salts like Na and K may exhibit increased hygroscopicity. These disadvantages can be effectively addressed by SD formulations.
- Dissolution of drug is crucial for complete absorption and therapeutic efficacy, particularly in the case of anticancer drugs with poor aqueous solubility.
- SD addresses this limitation by inducing supersaturated drug dissolution, thereby enhancing in vivo adsorption and improving the therapeutic outcomes of anticancer drugs after oral administration.

DISADVANTAGES:

While solid dispersion (SD) stands as a promising technique for enhancing the solubility and bioavailability (BA) of hydrophobic drugs, it does come with certain drawbacks:



- Physical instability: SD formulations may exhibit changes in crystallinity and reduced dissolution rates over time.
- Aging effects: SDs are prone to alterations in their physical properties with aging, leading to decreased dissolution rates.
- Sensitivity to environmental factors: SDs are sensitive to temperature and humidity variations during storage, which can promote phase separation and crystallization. These changes occur due to increased molecular mobility, lowered glass transition temperature (T_g), or disruption of drug-carrier interactions, resulting in diminished solubility and dissolution rates of the drug.

For Patients undergoing cancer treatment, maintaining the stability of anticancer drugs is critical for ensuring treatment effectiveness. However, the instability of SD formulations during storage can compromise drug quality and therapeutics outcomes, potentially impacting patient health.

CLASSIFICATION:

Recent advancement in solid dispersion techniques have led to various classifications based on their characteristics and method of preparation:

1. First Generation Solid Dispersion:

The first generation of solid dispersion encompasses those formed using crystalline carriers [7], such as urea and sugars [8]. These solid dispersions yield thermodynamically stable crystalline structures, resulting in slow drug release. In contrast, amorphous solid dispersions (ASDs) exhibit faster dissolution rates compared to their crystalline counterparts. In a eutectic mixture, the melting point of the dispersion is lower than that of both the carrier and drug, while in a monotectic mixture, the melting points of the drug and carrier remain constant. Eutectic mixtures are preferred over monotectic ones because they facilitate simultaneous

crystallization of the drug and carrier during cooling. The specific composition in a eutectic mixture where the drug crystallizes out is termed the eutectic point, resulting in a mixture of fine crystals of both components. Smaller particle sizes increase the specific surface area, generally enhancing the dissolution rate and oral absorption of poorly water-soluble drugs. However, research into solid dispersions with precise eutectic compositions remain limited [9]. Solid solutions in solid dispersions are categorized based on the extent of miscibility between the two components or the crystalline structure. They are divided into continuous (or isomorphous, complete, unlimited) solid solutions and discontinuous (or restricted, partial, limited, complete) solid solutions. Additionally, they can be classified into two groups: substitutional solid solutions, where the solute molecule substitutes the solvent molecule in the crystal lattice of the solid solvent, and interstitial solid solutions, where the solute molecule occupies the interstitial space of the solvent lattice [10].

2. Second Generation Solid Dispersion:

Second-generation solid dispersions have proven more effective than their predecessor due to their enhanced thermodynamic stability [11]. Amorphous solid dispersion (ASDs) can be further classified based on the physical state of the drug into amorphous solid suspensions and amorphous solid solutions, also known as glass solutions. Amorphous solid suspension consists of distinct phases, while amorphous solid solutions exhibit a molecularly homogeneous blend of the drug and carriers, which can be synthetic or natural polymers [9]. Amorphous solid suspensions are suitable for drugs with limited carrier solubility or high melting points. In second-generation solid dispersions, the drug achieves a supersaturated state through forced solubilization in the carrier [11]. However, as the chain length or molecular weight of polymers increases, their aqueous



solubility decreases while viscosity increases. High viscosity polymers are advantageous for preventing drug recrystallization during manufacturing, storage, and dissolution, though they may also delay drug dissolution in aqueous media. A major challenge with second-generation solid dispersions is drug precipitation and recrystallization, which can significantly impact in vitro and in vivo drug release profiles [9].

3. Third Generation Solid Dispersion:

Third-generation solid dispersions employ carriers with surface activity or emulsifying properties to enhance the dissolution profile of drugs [11]. Utilizing these specialized carriers helps mitigate issues related to drug precipitation and recrystallization. Incorporating surfactants or emulsifiers not only improves drug dissolution but also enhances the physical and chemical stability of the solid dispersion. Examples of such carriers include inulin, Gelucire, poloxamer, among others [9]. The physical and chemical stability of solid dispersions is bolstered by preventing nucleation and agglomeration. The choice of surface-active agents or polymers depends on the drug's dissolution or stability profile. Surfactant are preferred when rapid dissolution is required, whereas polymers with higher glass transition temperatures (T_g) may be chosen to prevent recrystallization [9,12].

4. Fourth Generation Solid Dispersion:

These types of dispersion can be termed as Controlled Release Solid Dispersions (CRSD), designed specifically for poorly water-soluble drugs with short biological half-lives [9]. CRSD formulation utilize either water-soluble or water-insoluble carriers [8]. Aiming to achieve two primary objectives: enhancing solubility and providing extended release of the drug in a controlled manner [9]. Water-soluble carriers commonly employed in CRSD include ethyl cellulose, Eudragit RS, Eudragit RL, HPC, among others [8].

Binary solid dispersions can be classified into six distinct systems based on the physical state and molecular arrangement of the active pharmaceutical ingredient (API) and carrier. Meng et al. categorized solid dispersion into six groups — Class C-C, Class C-A, Class A-C, Class A-A, Class M-C, and Class M-A, according to the physical state and molecular arrangement of both the API and carrier. However, Further research is necessary to develop a clear classification system that effectively correlates with the performance of solid dispersion in terms of solubility and stability [13].

TYPES OF SOLID DISPERSIONS:

1. Eutectics
2. Amorphous solid solutions
3. Solid solution
 - a. Continuous solid solution
 - b. Discontinuous solid solution
 - c. Substitutional solid solution
 - d. Interstitial solid solution

1. Eutectic Mixtures:

A basic eutectic mixture comprises two compound that are fully miscible in the liquid phase but only to a very limited extent in the solid phase. It is created by rapidly solidifying a fused melt of two components that exhibit complete liquid miscibility but minimal solid-solid solution [14-15].

2. Amorphous precipitation in crystalline matrix:

This concept resembles simple eutectic mixtures, with the key distinction being that the drug precipitates out in an amorphous state.

3. Solid Solution:

Solid solutions resemble liquid solutions in that they consist of a single phase, regardless of the number of components present. In Solid solutions, the drug's particle size is minimized to molecular dimensions, and the dissolution rate is primarily governed by the carrier's dissolution rate. These solid solutions can be classified based on their



miscibility (discontinuous solid solutions versus continuous) or alternatively, based on how the solute molecules are distributed within the solvent (interstitial or amorphous, substitutional) [16].

a. Continuous Solid Solution:

Continuous solid solutions are characterized by the complete miscibility of their components in all proportions. This implies that the bonding strength between the two components surpasses the bonding strength between the molecules of each individual component. However, such solid solutions have not been documented in the pharmaceutical field as of now [16,17].

b. Discontinuous Solid Solutions:

Discontinuous solid solutions exhibit limited solubility of each component in the other. For practical reasons, Goldberg et al. proposed that the term “solid solution” should only be used when the mutual solubility of the two components exceeds 5% [16].

c. Substitutional Solid Solution:

Classic solid solutions possess a crystalline arrangement, where solute molecules can either replace solvent molecules. Substitution is viable when the size of the solute molecules deviates by approximately 15% or less from that of the solvent molecules [18].

d. Interstitial Solid Solution:

In interstitial solid solutions, they dissolved molecules fill the spaces between the solvent molecules within the crystal lattice. For interstitial crystalline solid solutions to form, the solute molecules must possess a molecular diameter that is less than or equal to 0.59 of the solvent molecule’s molecular diameter.

e. Glass Solution and Glass Suspension:

A “Glass solution” denotes a uniform, glassy system where the solute dissolves within the glassy solvent, while “Glass suspension” describes a blend where precipitated particles are held in suspension within a glassy solvent. Glassy states are identified by their transparency and

brittleness below the glass transition temperature, lacking sharp melting points and instead exhibiting progressive softening upon heating. In comparison to solid solution, glass solution has significantly lower lattice energy, reducing the barrier to rapid dissolution [10].

SELECTION CRITERIA FOR CARRIERS:

To be suitable for enhancing the dissolution rate of a drug, a carrier should fulfil the following criteria [2,25,26].

- Easily water-soluble, demonstrating intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Exhibits heat stability with a low melting point for methods involving melting.
- Solubility in various and can transition into a vitreous state upon solvent evaporation for methods involving solvents.
- Preferably increases the aqueous solubility of the drug.
- Chemically compatible with the drug and does not form strongly bonded complexes with it.

SELECTION OF SOLVENT:

The solvent chosen for formulating solid dispersions should adhere to the following criteria:

- Capable of dissolving both the drug and the carrier.
- Avoidance of toxic solvents such as chloroform and dichloromethane to prevent residual levels post-preparation [22].
- Ethanol can serve as an alternative due to its lower toxicity.
- Preference for water-based system.
- Use of surfactant to facilitate the formation of carrier-drug solutions, with caution due to their potential to reduce the glass transition temperature.

METHOD OF PREPARATION OF SOLID DISPERSION:

Numerous methods are employed for the preparation of solid dispersion, ranging from basic



manual procedures to sophisticated techniques necessitating specialized equipment to meet the demands of the modern pharmaceutical sector. Below, we briefly outline some of these diverse techniques.

1. Co-melting method.
2. Fusion method.
3. Solvent Evaporation method.
4. Kneading method.
5. Co-precipitation method.
6. Co-grinding method.
7. Gel entrapment technique.
8. Spray drying method.
9. Electrospinning method.
10. Freeze-drying method.
11. Supercritical fluid (SCF) method.
12. Direct capsule filling.

A. Co-melting Method:

This method involves creating a physical mixture of a drug and a water-soluble carrier, followed by direct heating until melting occurs. The molten mixture is then rapidly solidified in an ice bath while being vigorously stirred. The resulting solid mass is subsequently crushed, pulverized, and sieved. Alternatively, the homogeneous melt can be poured as a thin layer onto a ferrite or stainless-steel plate and cooled using flowing air or water on the opposite side of the plate. Additionally, supersaturation of a solute or drug in a system can be achieved by rapidly quenching the melt from a high temperature. This process effectively traps the solute molecule within the solvent matrix through instantaneous solidification. The quenching technique yields a finer dispersion of crystallites, especially for simple eutectic mixtures. The co-melting method offers economic advantages and is a solventless process. However, it may not be suitable for drugs or carriers that are unstable at fusion temperatures or prone to evaporation at higher temperatures. To address these issues, heating the physical mixture in a sealed container, melting under vacuum, or

conducting the process in the presence of an inert gas like nitrogen can be employed to prevent oxidative degradation of the drug or carrier [28].

B. Fusion Method:

This method modifies the co-melting technique. The carrier is placed in a porcelain dish and melted over a steam bath. The accurately weighed drug is gradually dispersed into the molten carrier using a glass rod. Once the drug is fully dispersed, the dish is removed from the steam bath and allowed to cool at room temperature until the mixture solidifies. The resulting solid dispersion is then pulverized and sieved. This approach is advantageous for reducing the thermal decomposition of drugs [29].

C. Solvent Evaporation Method:

The drug and carrier are both dissolved in an organic solvent. After they are fully dissolved, the solvent is evaporated. The resulting solid mass is then ground, sieved, and dried [30].

D. Kneading Method:

In this method, the carrier is mixed with water to form a paste. The drug is then added and the mixture is kneaded for a specific period. After kneading, the mixture is dried and sieved if necessary. This technique is suitable for thermolabile drugs but not for those sensitive to moisture [31].

E. Co-precipitation Method:

The specified quantity of drug is introduced into the carrier solution. The system is subjected to magnetic agitation while being shielded from light. The resulting precipitate is isolated via vacuum filtration and dried at ambient temperature [32].

F. Co-grinding Method:

The drug carrier is mixed together for a specified duration using a blender set at a specific speed. The resulting mixture is then transferred into the chamber of a vibrating ball mill. The powder mixture undergoes pulverization, after which the



product is collected and stored in a screw-capped glass vial at room temperature until needed [33].

G. Gel Entrapment Technique:

Hydroxypropyl methylcellulose (HPMC), employed as a carrier, is dissolved in an organic solvent until a clear and transparent gel is formed. Subsequently, the drug is dissolved in this gel through sonication for a brief period. The organic solvent is then removed under vacuum. The solid dispersions are further reduced in size using mortar and pestle, followed by sieving [34].

H. Spray Drying Method:

The drug is dissolved in an appropriate solvent, while the necessary quantity of carrier is dissolved in water. These solutions are then combined through sonication or another appropriate method yield to clear solution. Subsequently, the clear solution is subjected to spray drying using a spray dryer to generate solid dispersion in the form of fine, free-flowing particles [35].

I. Electrospinning Method:

Electrospinning involves the creation of solid fibres from a polymeric fluid stream solution or melt delivered through a small nozzle. This process utilizes a strong electrostatic field applied to a conductive capillary attached to a reservoir containing a polymer solution or melt, along with a conductive collection screen. When the electrostatic field applied to a conductive capillary attached to a reservoir containing a polymer solution or melt, along with a conductive collection screen. When the electrostatic field applied to a conductive collection screen. When the electrostatic field strength surpasses a critical value, charge species on the surface of a pendant drop destabilize its hemispherical shape into a conical form (known as the Taylor cone). Beyond this critical point, a charged polymer jet is expelled from the cone's apex and directed towards the collection screen by electrostatic force [36]. This technique shows promise for producing nanofibers and regulating the release of biomedicines. Due to

its simplicity and cost-effectiveness, electrospinning could be employed for future solid dispersion preparation [37].

J. Freeze-drying Method:

This method involves dissolving both the drug and carrier in a common solvent, which is then fully frozen by immersion in liquid nitrogen. Subsequently, the frozen solution undergoes lyophilization. Although it is recognized in literature as a promising and suitable technique for incorporating drug substance into stabilizing matrices, it is underutilized for solid dispersed preparation due to economic constraints. Freeze drying offers advantages such as minimal thermal stress on the drug during solid dispersion formation and reduced risk of phase separation [38].

K. Supercritical Fluid (SCF) Method:

Supercritical fluid methods, predominantly utilizing carbon dioxide (CO₂), employ it either as a solvent for both the drug and matrix or as an anti-solvent. This method involves dissolving the drug and carrier in a common solvent, which is then introduced into a particle formation vessel alongside supercritical CO₂ (heated beyond its critical temperature and pressure). Upon spraying the solution, the supercritical CO₂ rapidly extracts the solvent, leading to the precipitation of solid dispersion particles on the walls and bottom of the vessel. This technique offers benefits such as particle size reduction, decreased residual solvent content, and high yield [39].

L. Direct Capsule Filing:

The methods entail filing hard gelatine capsules directly with the liquid melt composed of both the drug and carrier. As this molten dispersion cools to room temperature, it solidifies to form a solid plug inside the capsule. This approach offers several advantages, including the prevention of grinding-induced alterations in the drug's crystallinity, decreased risks of cross-contamination and operator exposure in a dust-free



environment, as well as improved fill weight and content uniformity [40].

CHARACTERIZATION OF SOLID DISPERSION:

A. Detection of Crystallinity in Solid Dispersion:

Detection of crystallinity in solid dispersion is crucial as various molecular structures of the drug can exist within the matrix. Numerous efforts have been directed towards examining the molecular configuration in solid dispersions. Several techniques are currently available to measure the extent of crystalline material present in these dispersions.

1. Powder X-ray Diffraction:

This method can be utilized to qualitatively identify materials with long-range order. The presence of sharper diffraction peaks signifies a higher amount of crystalline material [41].

2. Infra-red Spectroscopy (IR):

This technique can identify variations in the energy distribution of interactions between the drug and the matrix. Sharp vibrational bands are indicative of crystallinity. Fourier Transform Infrared Spectroscopy has been employed to precisely detect crystallinity levels ranging from 1% to 99% in pure materials [18].

3. Isothermal Microcalorimetry:

This method measures the crystallization energy of amorphous material when it is heated above its glass transition temperature (T_g) [18].

4. Dissolution Calorimetry:

It measures the energy associated with dissolution, which depends on the sample's crystallinity. Typically, the dissolution of crystalline material is endothermic, while the dissolution of amorphous material is exothermic [42].

5. Differential Scanning Calorimetry (DSC):

Differential Scanning calorimetry (DSC) is a widely utilized technique that, measures heat flow into or out of a material as a function of time or

temperature. By quantifying the heat associated with the melting (fusion) of the material, DSC can be used to determine crystallinity. As the temperature of an amorphous solid rises, a change in heat capacity occurs without a formal phase change, leading to a glass transition. During this transition, the amorphous solid becomes less viscous, and at a certain temperature, the molecules may gain sufficient mobility to arrange themselves into a crystalline form, known as the crystallization temperature (T_c). This transition results in an exothermic peak in the DSC signal. Upon further heating, the sample eventually reaches its melting temperature (T_m), indicated by an endothermic peak in the DSC curve. To accurately characterize these thermal transitions, complementary, X-ray diffraction, or spectroscopic techniques are required [43,44].

6. Hot Stage Microscopy:

Hot stage microscopy, one of the oldest and simplest methods for studying phase transitions in crystals, involves altering the temperature of a substance while observing it under a microscope, often with crossed polarizers. This technique yields extensive information about melting, recrystallization behaviours, and solid-state transformations. It also enables the detection of solvates by observing the release of gas or liquid from a crystal. Furthermore, novel polymorphs can be created during this process, either through high-temperature transitions between forms or by crystallizing from the melt. Combining hot stage microscopy with vibrational spectroscopy or DSC enhances the method's capabilities even further [45,46].

7. Macroscopic Techniques:

Macroscopic techniques assess mechanical properties that distinguish between amorphous and crystalline materials, serving as indicators of crystallinity levels. Density measurements and dynamic mechanical analysis (DMA) evaluate the



modulus of elasticity and viscosity, which are influenced by the degree of crystallinity.

8. Nuclear Magnetic Resonance Spectroscopy (NMR):

Solid-state nuclear magnetic resonance (SS-NMR) spectroscopy is a valuable tool for investigating polymorphism by examining the atomic environments in the solid state. Non-equivalent nuclei exhibit resonance at distinct frequencies, and these shifts in chemical resonance often correspond to changes in conformation or chemical environment within the compound. Furthermore, SS-NMR spectroscopy enables the determination of the number of crystallographically inequivalent sites within a unit cell. In contrast to powder X-ray diffraction (PXRD), SS-NMR spectroscopy is particularly well-suited for studying amorphous forms of pharmaceuticals and solvates, which are typically challenging to detect due to their small size. Moreover, collecting spectra at various temperatures enhances the capability of SS-NMR spectroscopy in understanding polymorphic transformations and molecular motion within the solid state [47-49].

9. Water vapor Sorption:

Water vapor sorption can differentiate between amorphous and crystalline materials based on their varying hygroscopic properties. This method necessitates precise hygroscopicity data for both fully crystalline and fully amorphous samples. In certain studies, amorphous materials were plasticized by water sorption and subsequently crystallize during the experiment. However, crystallization may be accompanied by the expulsion of water, depending on the degree of hydration of the crystalline material [50].

APPLICATIONS OF SOLID DISPERSION IN PHARMACEUTICAL INDUSTRY:

- Enhances the oral bioavailability of poorly water-soluble drugs.

- Provides a solid state suitable for oral delivery.
- Maintains the chemical properties of the drug unchanged.
- Involves relatively simple processing techniques.
- Utilizes conventional equipment.
- Increases dissolution rates due to the metastable solid state.
- Achieves a homogeneous distribution of a small amount of drug in the solid state.
- Stabilizes unstable drugs.
- Allows for the incorporation of liquid (up to 10%) or gaseous compound into solid dosage forms.
- Enables the formulation of a fast-release primary dose within a sustained-release dosage form.
- Facilitates the creation of sustained-release regimens for soluble drugs by using poorly soluble or insoluble carriers.
- Reduces pre-systemic inactivation of drugs such as morphine and progesterone.

CONCLUSION:

As poorly water-soluble compounds become increasingly common in pharmaceutical markets, there is a growing effort to enhance the oral bioavailability of these drug candidates. Solid dispersions have emerged as one of the most promising strategies to address this issue. Over the past 20-30 years, the use of solid dispersions has proven to be an effective approach for improving the release rate and oral bioavailability of poorly water-soluble drugs. The availability of a diverse range of polymers, which are either poorly soluble or swell in aqueous conditions, indicates that solid dispersions hold significant potential for controlled-release dosage forms. The solubility issues of many drugs adversely affect their bioavailability, making solubility enhancement essential. Solid dispersion technology offers a



viable method for increasing the solubility of poorly soluble drugs. In recent years, the successful development of solid dispersion systems for preclinical, clinical, and commercial use has been made possible due to the availability of surface-active carriers and self-emulsifying carriers.

REFERENCES

1. Nikghalb, L.; Singh, G.; Singh, G.; Kahkeshan, K. Solid Dispersion: Methods and Polymers to Increase the Solubility of Poorly Soluble Drugs. *Journal of Applied Pharmaceutical Science* 2012, 2 (10), 170–175.
<https://doi.org/10.7324/JAPS.2012.21031>.
2. Patidar Kalpana; Soni Manish; Dinesh, S. K.; Surendra, J. K. Solid Dispersion: Approaches, Technology Involved, Unmet Need & Challenges. 2010, 349–357.
3. Biradar, S. V.; Patil, A. R.; Sudarsan, G. V.; Pokharkar, V. B. A Comparative Study of Approaches Used to Improve Solubility of Roxithromycin. *Powder Technology* 2006, 169 (1), 22–32.
<https://doi.org/10.1016/j.powtec.2006.07.016>
4. Gl, A. Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. *Pharm Res* 1995, 22, 11–23.
5. (Goldberg et al. 1965; Sekiguchi and Obi 1961; Chokshi et al. 2007) - Yahoo India Search Results. in.search.yahoo.com.
[https://in.search.yahoo.com/search?fr=mcafee&type=E211IN1274G0&p=\(Goldberg+et+al.+1965+1965%3B+Sekiguchi+and+Obi+1961%3B+Chokshi+et+al.+2007\)](https://in.search.yahoo.com/search?fr=mcafee&type=E211IN1274G0&p=(Goldberg+et+al.+1965+1965%3B+Sekiguchi+and+Obi+1961%3B+Chokshi+et+al.+2007)) (accessed 2024-05-12).
6. Dalbeth, N.; Merriman, T. R.; Stamp, L. K. Gout. *The Lancet* 2016, 388 (10055), 2039–2052.
[https://doi.org/10.1016/s0140-6736\(16\)00346-9](https://doi.org/10.1016/s0140-6736(16)00346-9).
7. Kim, K.-T.; Lee, J.-Y.; Lee, M.-Y.; Song, C.-K.; Choi, J.-H.; Kim, D.-D. Solid Dispersions as a Drug Delivery System. *Journal of Pharmaceutical Investigation* 2011, 41 (3), 125–142.
<https://doi.org/10.4333/kps.2011.41.3.125>.
8. Bindhani, S.; Mohapatra, S. RECENT APPROACHES of SOLID DISPERSION: A NEW CONCEPT toward ORAL BIOAVAILABILITY SABITRI BINDHANI*, SNEHAMAYEE MOHAPATRA. *Asian Journal of Pharmaceutical and Clinical Research* 2018, 11 (2), 72.
<https://doi.org/10.22159/ajpcr.2018.v11i2.23161>.
9. Vo, C. L.-N.; Park, C.; Lee, B.-J. Current Trends and Future Perspectives of Solid Dispersions Containing Poorly Water-Soluble Drugs. *European Journal of Pharmaceutics and Biopharmaceutics* 2013, 85 (3, Part B), 799–813.
<https://doi.org/10.1016/j.ejpb.2013.09.007>.
10. Chiou, W. L.; Riegelman, S. Pharmaceutical Applications of Solid Dispersion Systems. *Journal of Pharmaceutical Sciences* 1971, 60 (9), 1281–1302.
<https://doi.org/10.1002/jps.2600600902>.
11. Vasconcelos, T.; Sarmiento, B.; Costa, P. Solid Dispersions as Strategy to Improve Oral Bioavailability of Poor Water-Soluble Drugs. *Drug Discovery Today* 2007, 12 (23), 1068–1075.
<https://doi.org/10.1016/j.drudis.2007.09.005>.
12. Prasad, D.; Lande, J.; Chauhan, H.; Chauhan, H. Ternary Amorphous Solid Dispersions. *Journal of Developing Drugs* 2017, 06 (03).
<https://doi.org/10.4172/2329-6631.1000181>.
13. Meng, F.; Gala, U.; Chauhan, H. Classification of Solid Dispersions:



- Correlation to (I) Stability and Solubility (ii) Preparation and Characterization Techniques. *Drug Development and Industrial Pharmacy* 2015, 41 (9), 1401–1415. <https://doi.org/10.3109/03639045.2015.1018274>.
14. Sekiguchi, K.; Obi, N. Studies on Absorption of Eutectic Mixture. I. A Comparison of the Behavior of Eutectic Mixture of Sulfathiazole and that of Ordinary Sulfathiazole in Man. *CHEMICAL & PHARMACEUTICAL BULLETIN* 1961, 9 (11), 866–872. <https://doi.org/10.1248/cpb.9.866>.
15. Chiou, W. L.; Riegelman, S. Preparation and Dissolution Characteristics of Several Fast-Release Solid Dispersions of Griseofulvin. *Journal of Pharmaceutical Sciences* 1969, 58 (12), 1505–1510. <https://doi.org/10.1002/jps.2600581218>.
16. Singh, J.; Walia, M.; Harikumar, S. L. SOLUBILITY ENHANCEMENT by SOLID DISPERSION METHOD: A REVIEW. *Journal of Drug Delivery and Therapeutics* 2013, 3 (5). <https://doi.org/10.22270/jddt.v3i5.632>.
17. Shrestha, S.; Sudheer, P.; Sogali, B. S.; Soans, D. A Review: Solid Dispersion, a Technique of Solubility Enhancement. *Journal of Pharmaceutical Research* 2017, 16 (1), 25. <https://doi.org/10.18579/jpckc/2017/16/1/112470>.
18. DHILLON, V.; TYAGI, R. SOLID DISPERSION: A FRUITFUL APPROACH for IMPROVING the SOLUBILITY and DISSOLUTION RATE of POORLY SOLUBLE DRUGS. *Journal of Drug Delivery and Therapeutics* 2012, 2 (4). <https://doi.org/10.22270/jddt.v2i4.250>.
19. Ford, J. L. The Current Status of Solid Dispersions. *Pharmaceutica Acta Helveticae* 1986, 61 (3), 69–88.
20. Breitenbach, J. Melt Extrusion: From Process to Drug Delivery Technology. *European Journal of Pharmaceutics and Biopharmaceutics* 2002, 54 (2), 107–117. [https://doi.org/10.1016/S0939-6411\(02\)00061-9](https://doi.org/10.1016/S0939-6411(02)00061-9).
21. Mullins, J. D.; Macek, T. J. Some Pharmaceutical Properties of Novobiocin **Received August 21, 1959, from Merck Sharp and Dohme Research Laboratories, West Point, Pa. *Journal of the American Pharmaceutical Association* 1960, 49 (4), 245–248. <https://doi.org/10.1002/jps.3030490417>.
22. Goldberg, A. H.; Gibaldi, M.; Kanig, J. L. Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs via Solid Solutions and Eutectic Mixtures I. *Journal of Pharmaceutical Sciences* 1965, 54 (8), 1145–1148. <https://doi.org/10.1002/jps.2600540810>.
23. Marazban Sarkari; Judith Belle Brown; Chen, X.; Swinnea, S.; Williams, R. W.; Johnston, K. P. Enhanced Drug Dissolution Using Evaporative Precipitation into Aqueous Solution. *International Journal of Pharmaceutics* 2002, 243 (1-2), 17–31. [https://doi.org/10.1016/s0378-5173\(02\)00072-8](https://doi.org/10.1016/s0378-5173(02)00072-8).
24. Simonelli, A. P.; Mehta, S. C.; Higuchi, W. I. Dissolution Rates of High Energy Polyvinylpyrrolidone (PVP)-Sulfathiazole Coprecipitates. *Journal of Pharmaceutical Sciences* 1969, 58 (5), 538–549. <https://doi.org/10.1002/jps.2600580503>.
25. Dhirendra, K.; Lewis, S.; Udupa, N.; Atin, K. SOLID DISPERSIONS: A REVIEW. | *Pakistan Journal of Pharmaceutical Sciences* | EBSCOhost. openurl.ebsco.com. <https://openurl.ebsco.com/EPDB%3Agcd%3A12%3A706268/detailv2?sid=ebsco%3Apli>



- nk%3Ascholar&id=ebsco%3Agcd%3A39342845&crl=c (accessed 2024-05-17).
26. Solid Dispersions: A Review - ProQuest. www.proquest.com.
<https://www.proquest.com/openview/de59dc-d67aa9bab3bbac84dfbbd2c417/1?pq-origsite=gscholar&cbl=1936342>.
27. Kamalakkannan V, Puratchikody A, Masilamani K and Senthilnathan. Solubility enhancement of poorly-soluble drugs by solid dispersion technique – A review. *Journal of Pharmacy Research*, 2010, Vol. 3, p. 2314 - 2321.
28. Kalaiselvan, R.; Mohanta, G.; Manna, P.; Manavalan, R. Studies on Mechanism of Enhanced Dissolution of Albendazole Solid Dispersions with Crystalline Carriers. *Indian Journal of Pharmaceutical Sciences* 2006, 68 (5), 599. <https://doi.org/10.4103/0250-474x.29627>.
29. D. Jebasingh. PREPARATION and EVALUATION of PARACETAMOL by SOLID DISPERSION TECHNIQUE. 2011.
30. Dina, M. A. A.; Omaira, A. S.; Abd, E. A. A. E.; Demiana, I. N. Formulation and Evaluation of Binary and Ternary Solid Dispersions of Domperidone by Solvent Evaporation Method. *African Journal of Pharmacy and Pharmacology* 2014, 8 (3), 66–80. <https://doi.org/10.5897/ajpp2013.1401>.
31. Ghareeb, M. M.; Abdulrasool, A. A.; Hussein, A. A.; Noordin, M. I. Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188. *AAPS PharmSciTech* 2009, 10 (4), 1206–1215. <https://doi.org/10.1208/s12249-009-9316-0>.
32. Shah, N.; Iyer, R. M.; Mair, H.-J.; Choi, D.; Tian, H.; Diodone, R.; Fahrnich, K.; Pabst-Ravot, A.; Tang, K.; Scheubel, E.; Grippo, J. F.; Moreira, S. A.; Go, Z.; Mouskountakis, J.; Louie, T.; Ibrahim, P. N.; Sandhu, H.; Rubia, L.; Chokshi, H.; Singhal, D. Improved Human Bioavailability of Vemurafenib, a Practically Insoluble Drug, Using an Amorphous Polymer-Stabilized Solid Dispersion Prepared by a Solvent-Controlled Coprecipitation Process. *Journal of Pharmaceutical Sciences* 2013, 102 (3), 967–981. <https://doi.org/10.1002/jps.23425>.
33. Nokhodchi, A.; Talari, R.; Valizadeh, H.; Jalali, M. B. An Investigation on the Solid Dispersions of Chlordiazepoxide. *International journal of biomedical science: IJBS* 2007, 3 (3), 211–216.
34. Bhise, S. B.; Rajkumar, M. Effect of HPMC on Solubility and Dissolution of Carbamazepine Form III in Simulated Gastrointestinal Fluids. 2008, 2 (1), 38. <https://doi.org/10.22377/ajp.v2i1.170>.
35. Bakatselou, V.; Oppenheim, R. C.; Dressman, J. B. *Pharmaceutical Research* 1991, 08 (12), 1461–1469. <https://doi.org/10.1023/a:1015877929381>.
36. Hohman, M. M.; Shin, M.; Rutledge, G.; Brenner, M. P. Electrospinning and Electrically Forced Jets. II. Applications. *Physics of Fluids* 2001, 13 (8), 2221–2236. <https://doi.org/10.1063/1.1384013>.
37. Neamark, A.; Rujiravanit, R.; Supaphol, P. Electrospinning of Hexanoyl Chitosan. *Carbohydrate Polymers* 2006, 66 (3), 298–305. <https://doi.org/10.1016/j.carbpol.2006.03.015>.
38. van Drooge, D. J.; Hinrichs, W. L. J.; Visser, M. R.; Frijlink, H. W. Characterization of the Molecular Distribution of Drugs in Glassy Solid Dispersions at the Nano-Meter Scale, Using Differential Scanning Calorimetry and Gravimetric Water Vapour Sorption Techniques. *International Journal of Pharmaceutics* 2006, 310 (1-2), 220–229. <https://doi.org/10.1016/j.ijpharm.2005.12.007>

39. Majerik, V.; Charbit, G.; Badens, E.; Horváth, G.; Szokonya, L.; Bosc, N.; Teillaud, E. Bioavailability Enhancement of an Active Substance by Supercritical Antisolvent Precipitation. *The Journal of Supercritical Fluids* 2007, 40 (1), 101–110. <https://doi.org/10.1016/j.supflu.2006.03.027>.
40. Serajuddin, A. T. M.; Mufson, D.; Bernstein, D. F.; Sheen, P.-C.; Augustine, M. A. Effect of Vehicle Amphiphilicity on the Dissolution and Bioavailability of a Poorly Water-Soluble Drug from Solid Dispersions. *Journal of Pharmaceutical Sciences* 1988, 77 (5), 414–417. <https://doi.org/10.1002/jps.2600770512>.
41. Abdul-Fattah, A. M.; Bhargava, H. N. Preparation and in Vitro Evaluation of Solid Dispersions of Halofantrine. *International Journal of Pharmaceutics* 2002, 235 (1-2), 17–33. [https://doi.org/10.1016/s0378-5173\(01\)00941-3](https://doi.org/10.1016/s0378-5173(01)00941-3).
42. van Drooge, D. J.; Hinrichs, W. L. J.; Visser, M. R.; Frijlink, H. W. Characterization of the Molecular Distribution of Drugs in Glassy Solid Dispersions at the Nano-Meter Scale, Using Differential Scanning Calorimetry and Gravimetric Water Vapour Sorption Techniques. *International Journal of Pharmaceutics* 2006, 310 (1-2), 220–229. <https://doi.org/10.1016/j.ijpharm.2005.12.007>.
43. G.W.H. Höhne; Hemminger, W.; H.-J. Flammersheim. *Differential Scanning Calorimetry*; 2003. <https://doi.org/10.1007/978-3-662-06710-9>.
44. Ford, J. Thermal Analysis of Hydroxypropylmethylcellulose and Methylcellulose: Powders, Gels and Matrix Tablets. *International Journal of Pharmaceutics* 1999, 179 (2), 209–228. [https://doi.org/10.1016/s0378-5173\(98\)00339-1](https://doi.org/10.1016/s0378-5173(98)00339-1).
45. Kuhnert-Brandstätter, M. Thermomicroscopy in the Analysis of Pharmaceuticals. (No Title).
46. McCrone, W. C. *Fusion Methods in Chemical Microscopy*. (No Title).
47. Byrn, S. R. *Solid State Chemistry of Drugs*. (No Title).
48. Bugay, D. E. *Solid-State Nuclear Magnetic Resonance Spectroscopy: Theory and Pharmaceutical Applications*. *Pharmaceutical Research* 1993, 10 (3), 317–327. <https://doi.org/10.1023/a:1018967717781>.
49. Tishmack, P. A.; Bugay, D. E.; Byrn, S. R. Solid-State Nuclear Magnetic Resonance Spectroscopy-Pharmaceutical Applications. *Journal of Pharmaceutical Sciences* 2003, 92 (3), 441–474. <https://doi.org/10.1002/jps.10307>.
50. Buckton, G.; Darcy, P. The Use of Gravimetric Studies to Assess the Degree of Crystallinity of Predominantly Crystalline Powders. *International Journal of Pharmaceutics* 1995, 123 (2), 265–271. [https://doi.org/10.1016/0378-5173\(95\)00083-U](https://doi.org/10.1016/0378-5173(95)00083-U).

HOW TO CITE: Deepak D. Sabne , Ashish Jain, Sofiya Moris, A Comprehensive Review: Enhancing The Solubility & Oral Bioavailability Through Solid Dispersion, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 8, 3432-3436. <https://doi.org/10.5281/zenodo.13346474>



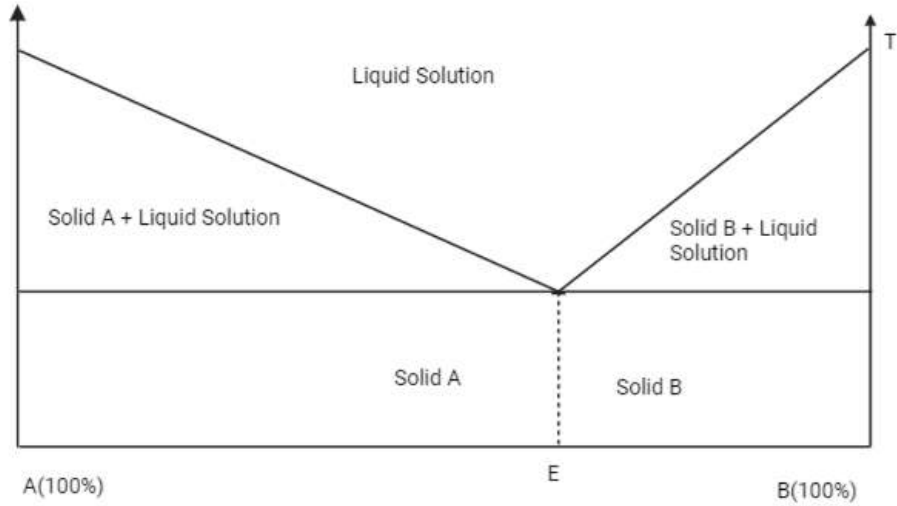


Figure No.01: Eutectic Mixtures

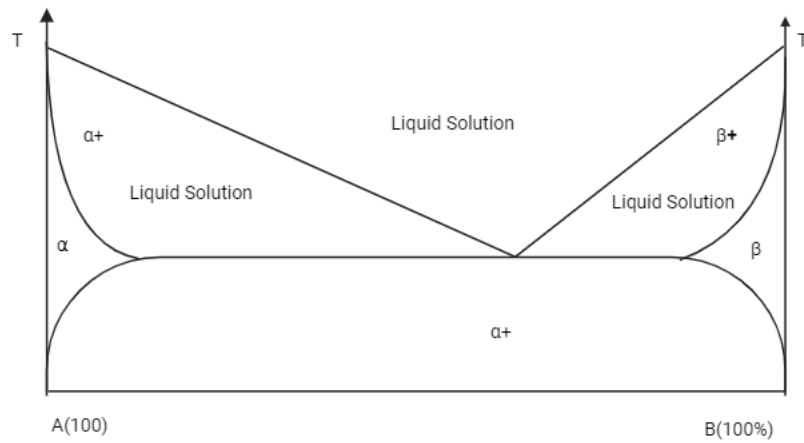


Figure No.02: Discontinuous solid solution.

Physical Modification	Chemical Modification	Miscellaneous Methods
a. Reduction Particle size b. Micronization c. Nanosuspension, d. Modification of the crystal habit e. Solid dispersions f. Eutectics mixtures g. Solid solutions h. Amorphous solid solutions i. Glass solutions and glass suspension j. Cryogenic techniques	a. Change of pH b. Use of buffer c. Derivatization d. Complexation e. Salt formation	a. Supercritical fluid process b. Use of adjuvant like surfactant, solubilizers, co-solvency, hydrotropy, and novel excipients.

Table No.01: Various Solubility Enhancement Techniques.

Class	Solubility	Permeability	Examples of drugs
Class I	High solubility	High permeability	Benazepril, Loxoprofen, Sumatriptan etc.
Class II	High solubility	Low permeability	Valsartan, Nimesulide, Loratadine, Glimepiride etc.
Class III	Low solubility	High permeability	Gabapentin, Atropine etc.
Class IV	Low solubility	Low permeability	Furosemide, Meloxicam etc.

Table No. 02: BCS Classification System.

Class	API	Carrier
C-C	Crystalline	Crystalline
C-A	Crystalline	Amorphous
A-C	Amorphous	Crystalline
A-A	Amorphous	Amorphous
M-C	Molecularly dispersed	Crystalline
M-A	Molecularly dispersed	Amorphous

Table No. 03: Classification According to Physical state and Molecular Arrangement of API and Carrier.

Solid Dispersion	Type	Matrix*	Drug*	Remarks	No. of phases	Reference
I	Eutectics	C	C	The first type of solid dispersions prepared	2	10
II	Amorphous Precipitations in crystalline matrix	C	A	Rarely encountered	2	20,21
III	Solid solutions					
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1	22
	Discontinuous solid solutions	C	M	Partially miscible,	2	14
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional.	1 or 2	23,24

				Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed		
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 0.59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous, Example: Drug in helical interstitial spaces of PEG.	2	10,15
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	10, 23
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	10, 23
VI	Glass solution	A	M	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many examples especially with PVP	1	24

Table No. 04: Classification of solid dispersion in six subjects.

*: A: matrix in the amorphous state, C: matrix in the crystalline state

**: A: drug dispersed as amorphous clusters in the matrix,

M: drug dispersed as crystalline particles in the matrix

Sr. No.	Material Used as Carrier	Examples.
1.	Sugars	Sorbitol, Maltose, Xylitol, Mannitol, Lactose, Galactose, Sucrose, Dextrose
2.	Polymeric materials	Polyethylene glycol (PEG), hydroxypropyl methyl cellulose, ethyl cellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan, povidone (PVP).
3.	Insoluble or enteric polymer	HPMC phthalate, Eudragit L100, Eudragit S100, Eudragit RL, Eudragit RS.
4.	Acids	Succinic acid & Citric acid
5.	Surfactants	Poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans, polyoxyethylene stearate, renex.
6.	Miscellaneous	Urea, Urethane, Hydroxy alkyl xanthine's, Pentaerythritol, Pentaerythrityl tetra-acetate.

Table No. 05: Materials used as carrier for solid dispersion [16,25].

Sr. No.	SOLVENT	MELTING POINT (°C)	BOILING POINT (°C)
1.	Water	0	100
2.	Methanol	-93.9	65
3.	Ethanol	-117	78.5
4.	Acetic acid	17	118
5.	1-propanol	-85	97.4
6.	2-propanol	-127	82.4
7.	Chloroform	-63	62
8.	DMSO	19	189

Table No. 06: List of Solvents Used in Solid Dispersion.

Sr. No.	SOLVENT	MELTING POINT (°C)	BOILING POINT (°C)
1.	Water	0	100
2.	Methanol	-93.9	65
3.	Ethanol	-117	78.5
4.	Acetic acid	17	118
5.	1-propanol	-85	97.4
6.	2-propanol	-127	82.4
7.	Chloroform	-63	62
8.	DMSO	19	189