SOLID DISPERSION-BASED SUSTAINED RELEASE SYSTEMS FOR POORLY WATER-SOLUBLE ANTIBIOTICS

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ABSTRACT

Poor aqueous solubility remains one of the most significant challenges in the oral delivery of many antibiotics, often resulting in poor dissolution, limited absorption, and consequently reduced bioavailability and therapeutic inefficiency. Solid dispersion (SD) technology has emerged as a promising and widely investigated approach to address solubility-related challenges. In this technique, the poorly soluble drug is dispersed within a hydrophilic polymer matrix, often in an amorphous or molecularly dispersed form, resulting in enhanced wettability, reduced particle size, and improved dissolution rate. The use of carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC) has shown significant improvements in drug solubility and bioavailability. However, while SD systems are effective in enhancing dissolution, they may sometimes lead to rapid drug release, which is not always desirable, especially for antibiotics This review focuses on the design and development of SD-based sustained release systems for poorly water-soluble antibiotics. It discusses various preparation methods such as hot-melt extrusion, solvent evaporation, and spray drying, along with the role of different polymers in modulating drug release behavior. The mechanisms governing drug release, including diffusion, erosion, and polymer relaxation, are also examined. Furthermore, recent advancements, challenges related to stability and scalability, regulatory considerations, and future perspectives in this field are critically highlighted. Overall, this integrated approach represents a promising direction in improving the efficacy and safety of antibiotic therapy.

Keywords: Solid dispersion, sustained release, poorly water-soluble drugs, antibiotics, polymers, drug delivery

INTRODUCTION

The increasing prevalence of poorly water-soluble drug candidates has posed a persistent challenge to pharmaceutical scientists, particularly in the development of oral dosage forms. According to the Biopharmaceutics Classification System (BCS), Class II and Class IV drugs are characterized by low aqueous solubility, resulting in dissolution-limited absorption and suboptimal bioavailability.[1] A substantial number of clinically important antibiotics fall into these categories, thereby compromising their therapeutic effectiveness when administered via conventional formulations. Over the past few decades, solid dispersion technology has emerged as a robust and versatile approach to enhance drug solubility by improving wettability, reducing particle size, and inducing amorphization. In parallel, sustained release systems have gained considerable attention for their ability to provide controlled drug delivery, minimize plasma concentration fluctuations, and enhance patient compliance. The integration of these two strategies is increasingly being recognized as a promising approach to overcome both solubility and pharmacokinetic limitations, thereby optimizing antibiotic therapy.[2]

Challenges of Poorly Water-Soluble Drugs

The increasing prevalence of poorly water-soluble drug candidates has posed a persistent challenge to pharmaceutical scientists, particularly in the development of oral dosage forms. A large proportion of newly discovered and existing drugs exhibit limited aqueous solubility, which significantly affects their dissolution rate in gastrointestinal fluids. Since dissolution is a prerequisite for drug absorption, poor solubility often results in incomplete or variable bioavailability. This limitation ultimately reduces therapeutic efficacy and may lead to inconsistent clinical outcomes, making formulation development more complex and demanding.[3]

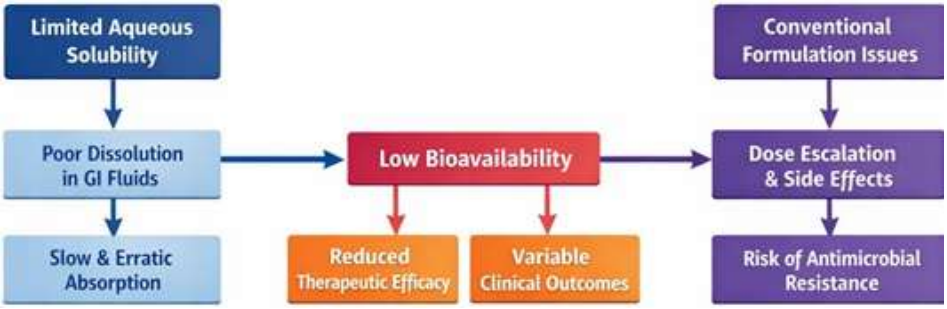
Biopharmaceutics Classification System (BCS) Perspective

According to the Biopharmaceutics Classification System, drugs are categorized based on their solubility and permeability characteristics. Class II and Class IV drugs are particularly problematic due to their low aqueous solubility.4 These drugs exhibit dissolution-limited absorption, where the rate of drug dissolution becomes the controlling factor for systemic availability. A significant number of clinically important antibiotics fall into these categories, which compromises their therapeutic effectiveness when administered through conventional dosage forms. This challenge necessitates the development of advanced formulation strategies to improve their solubility and

absorption.[5]

Role of Solid Dispersion Technology

Over the past few decades, solid dispersion technology has emerged as a robust and versatile approach to enhance drug solubility. In this technique, the poorly soluble drug is dispersed within a hydrophilic polymer matrix, often in an amorphous or molecularly dispersed state. This transformation leads to improved wettability, reduced particle size, and increased surface area, all of which contribute to enhanced dissolution rates. Furthermore, the amorphous form of the drug possesses higher free energy compared to its crystalline counterpart, resulting in improved apparent solubility and bioavailability.[6]



Importance of Sustained Release Systems

Sustained release systems have gained considerable attention due to their ability to provide controlled drug delivery over an extended period. These systems are designed to release the drug at a predetermined rate, maintaining consistent plasma drug concentrations and minimizing fluctuations associated with conventional dosage forms. This not only improves therapeutic efficacy but also reduces dosing frequency, thereby enhancing patient compliance.[7] In the case of antibiotics, sustained release formulations are particularly beneficial as they help maintain therapeutic levels for longer durations, which is essential for effective infection control and prevention of resistance.[8]

Integration of Solid Dispersion and Sustained Release Approaches

The integration of solid dispersion technology with sustained release systems is increasingly recognized as a promising strategy to address both solubility and pharmacokinetic challenges. By combining enhanced solubility with controlled drug release, this approach ensures improved dissolution along with prolonged therapeutic action.[9] Such integrated systems are particularly advantageous for poorly water-soluble antibiotics, as they enhance drug bioavailability while maintaining optimal plasma concentrations. This dual approach represents a significant advancement in pharmaceutical formulation, offering improved therapeutic outcomes and better patient adherence.[10]

POORLY WATER-SOLUBLE ANTIBIOTICS

A wide range of clinically important antibiotics, including cefiximetrihydrate, ciprofloxacin, clarithromycin, and azithromycin, are characterized by poor aqueous solubility, which significantly limits their dissolution rate and subsequent oral absorption. Since drug dissolution is a prerequisite for absorption across the gastrointestinal tract, inadequate solubility often results in incomplete and erratic bioavailability. This issue is particularly critical for antibiotics, where maintaining effective plasma concentrations is essential for achieving optimal therapeutic outcomes and preventing the development of resistance. Poor solubility leads to dissolution-limited absorption, thereby reducing the fraction of drug that reaches systemic circulation in an active form.[11]

The consequences of poor aqueous solubility extend beyond reduced bioavailability. These drugs often exhibit delayed onset of action due to slower dissolution rates, which can compromise their effectiveness in treating acute infections.[12] Additionally, variability in absorption may lead to unpredictable pharmacokinetic profiles, making it difficult to achieve consistent therapeutic levels in patients. In clinical settings, such variability can result in subtherapeutic drug concentrations, increasing the risk of treatment failure. To compensate for low bioavailability, higher doses are frequently administered, which may enhance drug exposure but simultaneously increases the risk of adverse effects, toxicity, and patient non-compliance.

Moreover, the use of higher doses or improper drug release profiles can contribute to the growing global concern of antimicrobial resistance. When drug concentrations fall below the minimum inhibitory concentration (MIC), pathogens may survive and adapt, leading to resistant strains. This issue underscores the importance of designing drug delivery systems that not only improve solubility but also ensure sustained and controlled drug release over time. Therefore, addressing solubility challenges is not only a pharmacokinetic concern but also a critical factor in ensuring the long-term effectiveness of antibiotic therapy.[13]

To overcome these limitations, advanced formulation strategies have been developed, among which solid dispersion

technology has gained considerable attention. Solid dispersion involves dispersing the poorly soluble drug in a hydrophilic carrier matrix, often in an amorphous or molecularly dispersed state. This transformation significantly enhances the drug's wettability, reduces particle size, and increases surface area, thereby improving dissolution rate and solubility. As a result, a higher fraction of the drug becomes available for absorption, leading to improved bioavailability.[14]

In parallel, sustained release systems are designed to control the release of the drug over an extended period, maintaining consistent plasma drug concentrations and reducing fluctuations associated with conventional dosage forms. These systems are particularly beneficial for antibiotics, as they ensure prolonged exposure of the drug to the target site, enhancing therapeutic efficacy while minimizing dosing frequency. The integration of solid dispersion with sustained release systems represents a synergistic approach that addresses both solubility and release-related challenges simultaneously.[15]

In such combined systems, the solid dispersion component enhances initial drug dissolution, while the sustained release matrix modulates the rate of drug release over time. This dual mechanism not only improves the pharmacokinetic profile of poorly water-soluble antibiotics but also enhances their pharmacodynamic performance.[16] Consequently, solid dispersion-based sustained release systems have emerged as a promising and rational strategy for improving the therapeutic effectiveness of poorly soluble antibiotics, ensuring better patient compliance, and reducing the risk of antimicrobial resistance.[17]

SOLID DISPERSION TECHNOLOGY

Solid dispersion technology has emerged as one of the most effective and widely explored approaches for improving the solubility and dissolution behavior of poorly water-soluble drugs. Solid dispersions are defined as molecular mixtures in which one or more active pharmaceutical ingredients are uniformly dispersed within an inert hydrophilic carrier matrix in the solid state. This approach significantly enhances drug dissolution and bioavailability by altering the physical state and surface properties of the drug. The underlying principle of solid dispersion involves the transformation of crystalline drug particles into an amorphous or molecularly dispersed form, which possesses higher free energy and, consequently, greater solubility compared to its crystalline counterpart.[18]

Based on the physicochemical nature of the drug-carrier system and their interactions, solid dispersions can be broadly classified into eutectic mixtures, solid solutions, glass solutions, and amorphous precipitations. In eutectic systems, the drug and carrier crystallize simultaneously but remain in intimate contact, resulting in improved dissolution. Solid solutions involve the complete miscibility of drug and carrier at the molecular level, offering uniform distribution and enhanced stability.[19] Among all types, amorphous solid dispersions are considered particularly advantageous due to their high internal energy and lack of long-range molecular order, which facilitate rapid drug dissolution and improved bioavailability. However, the amorphous state is thermodynamically unstable and tends to revert to the more stable crystalline form over time, posing significant formulation challenges.[20]

The effectiveness of solid dispersion systems is primarily attributed to several key mechanisms, including enhanced wettability, reduced particle size, and increased surface area available for dissolution. Hydrophilic carriers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and hydroxypropyl methylcellulose (HPMC) improve the wetting properties of the drug, thereby facilitating faster interaction with dissolution media. Additionally, the dispersion of drug molecules at a molecular or colloidal level eliminates the need for particle size reduction during dissolution, leading to rapid drug release. The combined effect of these factors results in a substantial increase in dissolution rate and, ultimately, improved oral bioavailability.[21]

A variety of preparation techniques have been developed to produce solid dispersions with desired physicochemical properties. The fusion or melting method is one of the simplest approaches, where the drug and carrier are melted together and subsequently solidified. While this method is solvent-free and easy to scale up, it may not be suitable for thermolabile drugs. The solvent evaporation method involves dissolving both drug and carrier in a common solvent followed by solvent removal, making it suitable for heat-sensitive compounds, although residual solvent issues may arise.[22] Advanced techniques such as hot-melt extrusion and spray drying have gained significant attention due to their scalability and ability to produce uniform and stable dispersions. Hot-melt extrusion is particularly advantageous for continuous manufacturing, whereas spray drying enables the formation of fine particles with high surface area. Lyophilization, or freeze-drying, is another technique used for sensitive drugs, although it is relatively expensive and time-consuming.[23]

Despite the numerous advantages associated with solid dispersion technology, several challenges must be addressed to ensure successful formulation development. One of the most critical issues is physical instability, particularly the tendency of amorphous drugs to undergo recrystallization during storage, which can significantly reduce solubility and dissolution performance. Moisture uptake and temperature fluctuations can further accelerate this process. Additionally, the selection of suitable carriers and optimization of drug-polymer interactions are essential to maintain stability and performance.[24] Scale-up and manufacturing reproducibility also present practical challenges that must be carefully managed. Therefore, a comprehensive understanding of material properties, processing conditions, and stability considerations is essential for the successful development of

solid dispersion systems.[25]

SUSTAINED RELEASE SYSTEMS

Sustained release systems are specifically engineered to deliver drugs at a controlled rate over an extended period, thereby maintaining consistent therapeutic levels and reducing dosing frequency. These systems offer significant clinical advantages, including improved patient adherence, reduced side effects, and enhanced therapeutic outcomes. Drug release from SR systems is governed by various mechanisms, such as diffusion through polymer matrices, dissolution of drug particles, osmotic pressure-driven release, and polymer erosion. Matrix-based systems, particularly those utilizing hydrophilic polymers like hydroxypropyl methylcellulose, are widely employed due to their simplicity and effectiveness. The performance of SR systems is highly dependent on the physicochemical properties of the drug, polymer characteristics, and formulation parameters. Therefore, a systematic approach is required to optimize these factors and achieve the desired release profile.[26]

INTEGRATION OF SOLID DISPERSION WITH SUSTAINED RELEASE SYSTEMS

The integration of solid dispersion with sustained release systems represents a strategically advantageous approach that combines rapid drug dissolution with prolonged drug release. In such hybrid systems, the solid dispersion component enhances drug solubility and dissolution rate, while the sustained release matrix modulates drug release kinetics. This dual functionality enables the formulation to overcome the limitations of both poor solubility and short biological half-life.[27] The incorporation of SD into matrix tablets, capsules, or multiparticulate systems has been widely explored, with promising results in terms of improved bioavailability and extended drug action. The choice of polymers plays a critical role in determining system performance, as hydrophilic carriers facilitate drug dissolution, whereas hydrophobic polymers control release rate. Recent studies have demonstrated that polymer blending and advanced processing techniques can further enhance the stability and performance of these systems, making them highly suitable for antibiotic delivery.[28]

EVALUATION PARAMETERS

The comprehensive evaluation of SD-based SR systems is essential to ensure their quality, performance, and stability. Analytical techniques such as differential scanning calorimetry and X-ray diffraction are employed to assess the physical state and crystallinity of the drug, while Fourier transform infrared spectroscopy is used to investigate drug-polymer interactions. In vitro dissolution studies play a crucial role in determining drug release profiles and predicting in vivo performance.[29] Additionally, particle size analysis and drug content uniformity tests provide insights into formulation consistency and quality. Advanced characterization techniques are increasingly being utilized to gain a deeper understanding of the structural and functional attributes of these systems, thereby facilitating rational formulation design.[30]

Importance of Evaluation

The comprehensive evaluation of solid dispersion (SD)-based sustained release (SR) systems is essential to ensure their quality, performance, and long-term stability. Since these systems involve complex drug-polymer interactions and modified drug release mechanisms, systematic characterization is necessary to confirm that the formulation meets desired therapeutic objectives. Proper evaluation also helps in optimizing formulation variables and ensuring batch-to-batch reproducibility.[31]

Thermal and Crystallinity Analysis

Analytical techniques such as differential scanning calorimetry (DSC) and X-ray diffraction (XRD) are widely employed to assess the physical state and crystallinity of the drug within the formulation. DSC provides information about melting behavior, glass transition temperature, and possible drug-polymer miscibility, while XRD helps in distinguishing between crystalline and amorphous forms of the drug. These techniques are critical in confirming the successful formation of solid dispersions and detecting any recrystallization during storage.[32]

Drug-Polymer Interaction Studies

Fourier transform infrared spectroscopy (FTIR) is commonly used to investigate drug-polymer interactions at the molecular level. FTIR analysis helps in identifying potential chemical interactions such as hydrogen bonding, which play a significant role in stabilizing the amorphous form of the drug and controlling its release behavior. Understanding these interactions is crucial for designing stable and effective SD-based SR systems.[33]

In Vitro Dissolution Studies

In vitro dissolution studies play a pivotal role in evaluating the drug release profile of SD-based sustained release formulations. These studies simulate physiological conditions and provide insight into the rate and mechanism of drug release over time. The obtained data are often fitted into kinetic models to understand release mechanisms and predict in vivo performance. Consistent and controlled drug release is a key requirement for the success of sustained release systems.[34]

Particle Size and Content Uniformity

Particle size analysis is an important parameter that influences drug dissolution and release characteristics. Smaller and uniformly distributed particles enhance surface area and improve dissolution efficiency. In addition, drug content uniformity tests are conducted to ensure consistent distribution of the drug within the formulation, which is essential for dose accuracy and therapeutic efficacy.[35]

Advanced Characterization Techniques

Advanced characterization techniques are increasingly being utilized to gain deeper insights into the structural and functional attributes of SD-based SR systems. Methods such as scanning electron microscopy (SEM), atomic force microscopy (AFM), and solid-state nuclear magnetic resonance (ssNMR) provide detailed information about surface morphology, molecular arrangement, and internal structure. These sophisticated tools facilitate rational formulation design by enabling a better understanding of the relationship between formulation variables and drug release behavior.[36]

APPLICATIONS IN ANTIBIOTICS

The application of solid dispersion-based sustained release systems in antibiotic delivery has shown considerable promise in improving therapeutic outcomes. For instance, cefiximetrihydrate formulations developed using SD techniques have demonstrated enhanced dissolution rates and sustained plasma drug levels.[37] Similarly, ciprofloxacin and azithromycin formulations have exhibited improved bioavailability and prolonged release profiles when incorporated into polymer-based SD systems. These findings highlight the potential of such hybrid systems to address the challenges associated with poorly water-soluble antibiotics, thereby enhancing their clinical effectiveness and reducing dosing frequency.[38]

DRUG RELEASE KINETICS

Understanding drug release kinetics is essential for the rational design of sustained release systems. Various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations, are commonly used to describe drug release behavior.[39] In most SD-based SR systems, drug release follows non-Fickian or anomalous transport, indicating a combination of diffusion and polymer erosion mechanisms. This complex release behavior underscores the importance of optimizing formulation variables to achieve the desired therapeutic profile. Advanced modeling approaches are increasingly being employed to predict and control drug release kinetics in such systems.[40]

CHALLENGES

Despite significant advancements, several challenges hinder the widespread application of SD-based SR systems. Physical instability, particularly drug recrystallization, remains a major concern that can adversely affect solubility and dissolution. Moisture sensitivity and environmental factors further complicate stability issues. Additionally, large-scale manufacturing and process reproducibility pose significant challenges, particularly for techniques such as spray drying and hot-melt extrusion. The selection of compatible polymers and optimization of formulation parameters are critical to overcoming these limitations. Addressing these challenges requires a multidisciplinary approach involving material science, process engineering, and analytical characterization.

REGULATORY CONSIDERATIONS

The development of SD-based SR systems must comply with stringent regulatory requirements to ensure product safety, efficacy, and quality. Regulatory agencies advocate the implementation of the Quality by Design (QbD) approach, which emphasizes systematic formulation development, risk assessment, and process optimization. Key considerations include identification of critical quality attributes, validation of manufacturing processes, and establishment of in vitro-in vivo correlation. Comprehensive stability studies and robust documentation are essential for regulatory approval. The adoption of advanced analytical tools and predictive models is expected to streamline the regulatory process and facilitate the development of complex drug delivery systems.

FUTURE PERSPECTIVES

The future of solid dispersion-based sustained release systems is promising, with ongoing research focusing on the development of novel polymers, advanced manufacturing techniques, and predictive modeling approaches. The integration of nanotechnology and artificial intelligence into formulation design is expected to further enhance system performance and efficiency. Continuous manufacturing processes such as hot-melt extrusion and 3D printing offer significant advantages in terms of scalability and reproducibility. These technological advancements are likely to address existing challenges and pave the way for the commercialization of innovative drug delivery systems for poorly water-soluble antibiotics.

CONCLUSION

In conclusion, solid dispersion-based sustained release systems offer a comprehensive and effective solution for improving the delivery of poorly water-soluble antibiotics. By addressing both solubility and release-related challenges, these systems significantly enhance bioavailability, therapeutic efficacy, and patient compliance. Although certain challenges remain, ongoing advancements in formulation science and technology are expected to overcome these limitations and facilitate the development of commercially viable products. The continued exploration of this integrated approach holds great potential for advancing pharmaceutical drug delivery systems.

REFERENCES

1. Chiou, W. L., &Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences, 60(9), 1281-1302.
2. Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixtures. Chemical and Pharmaceutical Bulletin, 9, 866-872.
3. Leuner, C., &Dressman, J. (2000). Improving drug solubility using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics, 50, 47-60.
4. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability.

Drug Discovery Today, 12, 1068-1075.

5. Craig, D. Q. M. (2002). Mechanisms of drug release from solid dispersions. International Journal of Pharmaceutics, 231, 131-144.
6. Hancock, B. C., & Parks, M. (2000). What is the solubility advantage for amorphous pharmaceuticals? Pharmaceutical Research, 17, 397-404.
7. Baghel, S., Cathcart, H., & O'Reilly, N. (2016). Polymeric amorphous solid dispersions review. Advanced Drug Delivery Reviews, 100, 116-125.
8. Repka, M. A., et al. (2012). Melt extrusion: Process to product. Expert Opinion on Drug Delivery, 9, 105-125.
9. Paudel, A., et al. (2013). Manufacturing of solid dispersions by spray drying. International Journal of Pharmaceutics, 453, 253-284.
10. Ford, J. L. (1999). HPMC matrix tablets for controlled release. Journal of Pharmaceutical Sciences, 88, 332-336.
11. Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs. Journal of Pharmaceutical Sciences, 88, 1058-1066.
12. Dhirendra, K., et al. (2009). Solid dispersions: A review. Pakistan Journal of Pharmaceutical Sciences, 22, 234-246.
13. Chauhan, B., &Shimpi, S. (2015). Preparation and characterization of solid dispersions. Pharmaceutics, 7, 100-124.
14. Vo, C. L., et al. (2013). Amorphous solid dispersions review. European Journal of Pharmaceutics, 85, 799-813.
15. Crowley, M. M., et al. (2007). Pharmaceutical applications of hot-melt extrusion. Drug Development and Industrial Pharmacy, 33, 909-926.
16. Shah, S., et al. (2014). Melt extrusion with poorly soluble drugs. Journal of Pharmaceutical Sciences, 103, 3239-3250.
17. Kalepu, S., &Nekkanti, V. (2015). Insoluble drug delivery strategies. ActaPharmaceuticaSinica B, 5, 442-453.
18. Savjani, K. T., et al. (2012). Techniques to enhance solubility. ISRN Pharmaceutics, 2012, 195727.
19. Lipinski, C. A. (2000). Drug-like properties. Journal of Pharmacological and Toxicological Methods, 44, 235-249.
20. Amidon, G. L., et al. (1995). BCS classification system. Pharmaceutical Research, 12, 413-420.
21. Dressman, J., &Reppas, C. (2000). In vitro-in vivo correlations. European Journal of Pharmaceutical Sciences, 11, S73-S80.
22. Colombo, P. (1993). Swellable matrix systems. Pharmaceutical Science & Technology Today, 6, 198-204.
23. Siepmann, J., &Peppas, N. (2001). Modeling drug release. International Journal of Pharmaceutics, 224, 23-36.
24. Ritger, P., &Peppas, N. (1987). Diffusion-controlled release. Journal of Controlled Release, 5, 23-36.
25. Higuchi, T. (1963). Mechanism of sustained release. Journal of Pharmaceutical Sciences, 52, 1145-1149.
26. Korsmeyer, R. W., et al. (1983). Mechanism of drug release. International Journal of Pharmaceutics, 15, 25-35.
27. Dash, S., et al. (2010). Kinetic modeling of drug release. ActaPoloniaePharmaceutica, 67, 217-223.
28. Patel, M. R., et al. (2019). Solid dispersion review. Drug Development Research, 80, 859-870.
29. Shamma, R. N., &Basha, M. (2013). Solubility enhancement. Pharmaceutics, 5, 644-671.
30. Sharma, D., et al. (2016). Solubility enhancement techniques. Journal of Advanced Pharmacy Education, 6, 1-9.
31. Kumar, S., et al. (2011). Solid dispersion techniques review. International Journal of Pharmaceutical Sciences Review, 9, 41-49.
32. Kapoor, B., et al. (2012). Solubility enhancement methods. International Journal of Pharmaceutical Sciences, 4, 1-14.
33. Chen, Y., et al. (2020). Amorphous dispersions advances. Pharmaceutics, 12, 1-25.
34. Ueda, K., et al. (2020). Stability of solid dispersions. Journal of Pharmaceutical Sciences, 109, 123-136.
35. Li, J., et al. (2021). Polymer selection in SD. Pharmaceutics, 13, 1-18.
36. Huang, Y., et al. (2022). Spray drying applications. International Journal of Pharmaceutics, 620, 121706.
37. Chen, L., et al. (2024). Polymer matrix SD systems. Pharmaceutical Research, 41, 1-12.
38. Moseson, D. E., et al. (2024). ASD trends. International Journal of Pharmaceutics X, 6, 100-120.
39. Haq, S. A., et al. (2024). Sustained SD formulations. International Journal of Pharmaceutics.
40. Su, D., et al. (2024). pH-sensitive SD systems. Frontiers in Pharmaceutical Sciences.