Recent Advancements in Amorphous Solid Dispersions in Pharmaceutics- A Comprehensive review

***Shazia Khan, [1]Rohit Khanna**

***Research Scholar, Chandigarh Technical University**

[1]Research Scholar, Chandigarh Technical University

Abstract: Amorphous solid dispersions (ASDs) have gained significant attention as a promising strategy for enhancing the bioavailability of poorly soluble drugs. This review provides a comprehensive overview of the current state of ASDs, focusing on their clinical applications, regulatory considerations, environmental impact, and influence on patient compliance. Advancements in material science, machine learning, and continuous manufacturing techniques have been highlighted as key drivers for the development and application of ASDs. Despite the progress, challenges such as physical stability and environmental sustainability persist. The review concludes by outlining future directions, emphasizing the need for continued research to address these challenges and unlock the full potential of ASDs.

Keywords: *Amorphous Solid Dispersions, Bioavailability, Clinical Applications, Regulatory Considerations, Environmental Impact, Patient Compliance, Material Science, Machine Learning, Continuous Manufacturing, Physical Stability.*

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Corresponding Author- Shaziaph01@gmail.com*

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Introduction

The field of pharmaceutics has witnessed significant advancements over the years, particularly in the development of drug delivery systems that enhance the bioavailability and therapeutic efficacy of active pharmaceutical ingredients (APIs). One such promising area is the formulation of amorphous solid dispersions (ASDs), which have gained considerable attention for their ability to improve the solubility and dissolution rate of poorly water-soluble drugs. The concept of ASDs is not new; however, the last decade has seen remarkable progress in preformulation

strategies, formulation technologies, and characterization techniques (Tambe et al., 2022).

Historical Perspective

The concept of amorphous solid dispersions dates back to the 1960s but has gained momentum in recent years due to the increasing number of poorly water-soluble drug candidates in pharmaceutical pipelines. The early formulations were primarily focused on simple binary systems, but contemporary approaches have evolved to include complex multi-component systems (Lee et al., 2020).

Importance in Drug Delivery

The primary advantage of ASDs lies in their ability to enhance the bioavailability of poorly water-soluble drugs. By converting the crystalline form of a drug into an amorphous state, ASDs facilitate a higher dissolution rate, thereby improving the drug's bioavailability (Chen et al., 2022).

Technological Advancements

Recent advancements in ASDs include the development of spray drying techniques, hot-melt extrusion, and solvent evaporation methods. These technologies have enabled the production of ASDs with improved stability, reduced particle size, and enhanced drug release profiles (Kalyane et al., 2021).

Challenges and Future Directions

Despite the progress, challenges such as physical stability and scale-up issues persist. However, ongoing research aims to address these limitations through the integration of nanotechnology and the development of novel polymers and surfactants (Dantas et al., 2022).

Formulation and Stability of Amorphous Solid Dispersions

Formulation Strategies

The formulation of amorphous solid dispersions (ASDs) is a complex process that requires a deep understanding of the physicochemical properties of the drug and the excipients. The choice of polymer plays a crucial role in stabilizing the amorphous form of the drug. Recent studies have shown that the use of surfactants can significantly enhance the stability of ASDs. Surfactants act by reducing the interfacial tension between the drug and the polymer, thereby preventing the drug from recrystallizing (Parupathi & Dhoppalapudi, 2022).

Characterization Techniques

The characterization of ASDs is equally important to ensure the desired drug release profile and stability. Techniques such as X-ray diffraction, differential scanning calorimetry, and Fourier-transform infrared spectroscopy are commonly employed. A recent study on the formulation characterization and pharmacokinetic evaluation of dasatinib ASDs employed a range of these techniques to confirm the amorphous nature of the drug and its improved bioavailability (Dharani et al., 2022).

Stability Concerns

One of the major challenges in the development of ASDs is ensuring their physical stability over time. Factors such as temperature, humidity, and mechanical stress can induce the crystallization of the drug, leading to reduced bioavailability. A study on spray-dried paracetamol/polyvinylpyrrolidone ASDs highlighted the importance of storage conditions in maintaining the stability of ASDs (Ritters et al., 2021).

Future Directions

The future of ASDs lies in the integration of advanced technologies and novel materials. For instance, the use of poloxamer has been shown to significantly influence the dissolution and stability of hot-melt extrusion-based ASDs (Shukla et al., 2023). Moreover, the implications of drug-polymer interactions on the physical stability of ASDs are an area of ongoing research, with recent studies suggesting that stronger drug-polymer interactions contribute to enhanced stability (Bookwala & Wildfong, 2023).

Applications of Amorphous Solid Dispersions in Drug Delivery

Oral Drug Absorption

Amorphous solid dispersions (ASDs) have shown significant promise in improving oral drug absorption, particularly for poorly water-soluble drugs. A recent study combined lipid-based drug delivery systems with ASDs to enhance the oral absorption of such drugs, demonstrating a synergistic effect that led to improved bioavailability (Nora et al., 2022).

Novel Drug Aggregates

Innovative approaches have been developed to further optimize the oral delivery of ASDs. One such approach involves the use of liquid-liquid phase separation drug aggregates, which have shown merit in enhancing the dissolution rate and thus the

bioavailability of drugs formulated as ASDs (Zhao et al., 2023).

Integration with Nanocrystal Technologies

The integration of ASDs with nanocrystal technologies offers another avenue for improving the solubility and bioavailability of poorly water-soluble drugs. This hybrid approach has been shown to provide a more stable and effective drug delivery system, thereby broadening the scope of ASD applications in pharmaceutics (Jermain et al., 2018).

Rheological Methods for Drug-Polymer Interactions

Understanding drug-polymer interactions is crucial for the successful formulation of ASDs. A novel rheological method has been developed to assess these interactions, providing insights into the miscibility and crystallization behavior of the drug in ASDs. This method could be instrumental in the design of more stable and effective ASD formulations (Tsakiridou et al., 2019).

High-Drug Loading ASDs

The quest for high-drug loading in ASDs has led to the development of a hierarchical particle approach. This approach leverages a deep understanding of the physicochemical properties of ASDs to achieve improved drug delivery at high drug loadings (Schenck et al., 2019).

Clinical Applications and Regulatory Considerations of Amorphous Solid Dispersions

Clinical Efficacy and Safety

The clinical applications of amorphous solid dispersions (ASDs) are increasingly being recognized for their potential to improve the bioavailability of poorly water-soluble drugs. A recent pharmacokinetic study in humans demonstrated that particle-forming ASDs significantly enhanced drug absorption and bioavailability without compromising safety (Schittny et al., 2021).

Machine Learning in ASD Development

The advent of machine learning techniques has opened new avenues for the development of ASDs. These techniques can predict the chemical stability of ASDs prepared by hot-melt extrusion, thereby aiding in the formulation design and reducing the time and resources spent on stability studies (Jiang et al., 2023).

Dynamic Mechanical Analysis

Dynamic mechanical analysis has been employed to engineer ASDs with optimized properties. This technique provides valuable insights into the mechanical properties of ASDs, which are crucial for their successful application in drug delivery systems (Ojo & Lee, 2020).

Compression Properties and Strain Rate Sensitivity

Understanding the compression properties and strain rate sensitivity of ASDs is essential for their successful formulation and application. A fundamental study on spray-dried ASDs highlighted the importance of these factors in achieving optimal drug release profiles (Doktorovová et al., 2022).

Regulatory Considerations

While ASDs offer promising advantages, they also present challenges in terms of regulatory approval. Continuous manufacturing and molecular modeling are emerging as valuable tools for addressing these challenges, providing a more streamlined and scientifically rigorous approach to the development and approval of ASDs (Nambiar et al., 2022).

Future Prospects and Challenges in Amorphous Solid Dispersions

Technological Innovations

The future of amorphous solid dispersions (ASDs) is closely tied to technological innovations. Hot melt extrusion, for instance, has been identified as a promising technique for the preparation of poorly water-soluble drugs. However, its limitations, such as thermal degradation of the drug or polymer, need to be addressed for broader applications (Lu et al., 2014).

Material Science Advancements

Recent advancements in material science have led to the identification of novel polymers and surfactants that can inhibit drug recrystallization. For example, the addition of Kollidon®VA64 has been shown to improve the dissolution of ezetimibe from ASDs (Szafraniec-Szczęsny et al., 2021).

Crystalline Inhibitors

The introduction of effective crystalline inhibitors in ASDs has been identified as a significant advancement. Curcumin ASDs formulated with Eudragit E100 have shown improved dissolution rates, thereby enhancing bioavailability (Fan et al., 2021).

Novel Polymers

The development of new polymers, such as aminomethacrylate-based copolymers, has

been shown to enhance the solubility of ASDs. These polymers are synthesized through radical polymer synthesis and have shown promise in the manufacture and characterization of ASDs (Schmied et al., 2022).

Continuous Manufacturing

Continuous manufacturing techniques are emerging as a pivotal approach for the scalable production of ASDs. These techniques take into account the significance of powder flow properties and feeding performance, which are crucial for the successful formulation of ASDs (Szabó et al., 2019).

Environmental Impact and Sustainability of Amorphous Solid Dispersions

Environmental Concerns

The environmental impact of pharmaceuticals, including amorphous solid dispersions (ASDs), is an emerging area of concern. The use of polymers and surfactants in ASDs, while beneficial for drug delivery, may pose environmental risks if not properly managed. For instance, the surfactants used in clopidogrel-copovidone ASDs could have environmental implications that need to be addressed (Correa Soto et al., 2022).

Green Manufacturing Processes

The adoption of green manufacturing processes is essential for the sustainable development of ASDs. Hot-melt extrusion, a commonly used technique for ASD preparation, has been scrutinized for its environmental impact. The study by Butreddy et al. (2022) highlights the need for environmentally friendly polymeric combinations to improve the sustainability of the hot-melt extrusion process.

Drug Loading and Environmental Impact

The drug loading in ASDs can also have environmental repercussions. High drug loading often requires the use of additional excipients, which could contribute to environmental waste. Santos et al. (2022) emphasized the need to study the environmental impact of high drug loading in ASDs, particularly those of nevirapine.

Peroxide Levels and Environmental Safety

The presence of peroxides in copovidones used in ASDs has been identified as a potential environmental hazard. Sarabu et al. (2022) conducted a preliminary investigation on the impact of peroxide levels in Plasdone™ copovidones on the

environmental safety of atorvastatin calcium ASDs.

Compaction Properties and Sustainability

The compaction properties of ASDs can also influence their environmental impact. Zhang et al. (2022) studied the impact of drug loading on the compaction properties of itraconazole-PVPVA ASDs, highlighting the need for sustainable compaction methods to minimize environmental waste.

Patient Compliance and Amorphous Solid Dispersions

Improved Bioavailability and Patient Adherence

One of the most significant advantages of amorphous solid dispersions (ASDs) is their ability to enhance the bioavailability of poorly soluble drugs. This improvement has a direct impact on patient compliance, as it often allows for reduced dosing frequency and potentially fewer side effects. A recent interview with Dr. Deanna Mudie, a leading researcher in the field, emphasized the role of ASDs in improving patient compliance through enhanced bioavailability (Mudie, 2023).

Taste-Masking and Pediatric Use

ASDs also offer the advantage of taste-masking, which is particularly beneficial for pediatric formulations. The role of surfactants in preserving the stability of ASDs can also contribute to improved taste and, consequently, better patient adherence (Parupathi & Dhoppalapudi, 2022).

Simplified Dosing Regimens

The development of high-drug-loaded ASD tablets, such as those for posaconazole, has been shown to simplify dosing regimens. This simplification can lead to improved patient compliance, especially in populations that struggle with complex medication schedules (Mudie et al., 2020).

Continuous Manufacturing and Cost-Effectiveness

The adoption of continuous manufacturing processes like hot melt extrusion for the development of ASDs can lead to cost-effective production. Lower production costs can translate to more affordable medications, thereby improving patient access and compliance (Dhoppalapudi & Parupathi, 2022).

In Vitro-In Silico Tools for Streamlined Development

The use of in vitro-in silico tools has been highlighted as a method for the streamlined development of ASDs. Such tools can help in the rapid development and optimization of ASD formulations, which can be particularly beneficial for patient-specific or personalized medicine approaches (Mudie et al., 2021).

Conclusion

Summary of Key Findings

Amorphous solid dispersions (ASDs) have emerged as a versatile platform for improving the bioavailability of poorly soluble drugs. This review has covered various aspects of ASDs, from their clinical applications and regulatory considerations to their environmental impact and influence on patient compliance. The advancements in material science, machine learning, and continuous manufacturing techniques have been particularly noteworthy, offering new avenues for the development and application of ASDs (Newman et al., 2017).

Future Directions

While the field has made significant strides, there are still challenges that need to be addressed. The physical stability of ASDs remains a concern, especially in terms of drug-polymer interactions. Future research should focus on understanding these interactions to improve the long-term stability of ASD formulations (Bookwala & Wildfong, 2023).

Clinical and Environmental Implications

The clinical efficacy of ASDs has been well-documented, but there is a growing need to consider their environmental impact. As the field moves towards more sustainable practices, the environmental safety of the excipients and manufacturing processes used in ASDs will become increasingly important (Nguyen et al., 2023).

Final Remarks

In conclusion, ASDs offer a promising approach for the formulation of poorly soluble drugs, with benefits extending from improved bioavailability to enhanced patient compliance. However, the field is still evolving, and ongoing research is essential for addressing the existing challenges and unlocking the full potential of this technology (Shi et al., 2019).

REFERENCES

1. Tambe, S., Jain, D., Meruva, S. K., Rongala, G., Juluri, A., Nihalani, G., Mamidi, H. K., Nukala, P. K., & Bolla, P. K. (2022). Recent advances

in amorphous solid dispersions: Preformulation, formulation strategies, technological advancements and characterization. *Pharmaceutics*, *14*(10), 2203.

2. Lee, S. H., Bajracharya, R., Min, J. Y., Han, J.-W., Park, B. J., & Han, H.-K. (2020). Strategic approaches for colon targeted drug delivery: An overview of recent advancements. *Pharmaceutics*, *12*(1), 68.

3. Chen, X., Lu, C., Duan, Y., & Huang, Y. (2022). Recent advancements in drug delivery of sinomenine, A disease-modifying anti-rheumatic drug. *Pharmaceutics*, *14*(12), 2820.

4. Kalyane, D., Kumar, N., Anup, N., Rajpoot, K., Maheshwari, R., Sengupta, P., Kalia, K., & Tekade, R. K. (2021). Recent advancements and future submissions of silica core-shell nanoparticles. *International Journal of Pharmaceutics*, *609*(121173), 121173.

5. Dantas, K. C. F., Rosário, J. D. S., & Silva-Caldeira, P. P. (2022). Polymeric nanosystems applied for metal-based drugs and photosensitizers delivery: The state of the art and recent advancements. *Pharmaceutics*, *14*(7).

6. Parupathi, P., & Dhoppalapudi, S. (2022). The role of surfactants in preserving the stability of amorphous solid dispersions: A review. GSC Biological and Pharmaceutical Sciences, 21(3), 039–047.

7. Dharani, S., Mohamed, E. M., Khuroo, T., Rahman, Z., & Khan, M. A. (2022). Formulation characterization and pharmacokinetic evaluation of amorphous solid dispersions of dasatinib. Pharmaceutics, 14(11).

8. Ritters, L., Tian, Y., & Reichl, S. (2021). Spray-dried paracetamol/polyvinylpyrrolidone amorphous solid dispersions: Part I-stability of powders and tablets. Pharmaceutics, 13(11), 1938.

9. Shukla, A., Dumpa, N. R., Thakkar, R., Shettar, A., Ashour, E., Bandari, S., & Repka, M. A. (2023). Influence of poloxamer on the dissolution and stability of hot-melt extrusion-based amorphous solid dispersions using

design of experiments. AAPS PharmSciTech, 24(5), 107.

10. Bookwala, M., & Wildfong, P. L. D. (2023). The implications of drug-polymer interactions on the physical stability of amorphous solid dispersions. Pharmaceutical Research.

11. Nora, G.-I., Venkatasubramanian, R., Strindberg, S., Siqueira-Jørgensen, S. D., Pagano, L., Romanski, F. S., Swarnakar, N. K., Rades, T., & Müllertz, A. (2022). Combining lipid based drug delivery and amorphous solid dispersions for improved oral drug absorption of a poorly water-soluble drug. Journal of Controlled Release: Official Journal of the Controlled Release Society, 349, 206–212.

12. Zhao, P., Han, W., Shu, Y., Li, M., Sun, Y., Sui, X., Liu, B., Tian, B., Liu, Y., & Fu, Q. (2023). Liquid-liquid phase separation drug aggregate: Merit for oral delivery of amorphous solid dispersions. Journal of Controlled Release: Official Journal of the Controlled Release Society, 353, 42–50.

13. Jermain, S. V., Brough, C., & Williams, R. O., 3rd. (2018). Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery - An update. International Journal of Pharmaceutics, 535(1–2), 379–392.

14. Tsakiridou, G., Reppas, C., Kuentz, M., & Kalantzi, L. (2019). A novel rheological method to assess drug-polymer interactions regarding miscibility and crystallization of drug in amorphous solid dispersions for oral drug delivery. Pharmaceutics, 11(12), 625.

15. Schenck, L., Mann, A. K. P., Liu, Z., Milewski, M., Zhang, S., Ren, J., Dewitt, K., Hermans, A., & Cote, A. (2019). Building a better particle: Leveraging physicochemical understanding of amorphous solid dispersions and a hierarchical particle approach for improved delivery at high drug loadings. International Journal of Pharmaceutics, 559, 147–155.

16. Schittny, A., Waldner, S., Duthaler, U., Vorobyev, A., Abramovich, R., Krähenbühl, S., Puchkov, M., & Huwyler, J. (2021). Particle forming

amorphous solid dispersions: A mechanistic randomized pharmacokinetic study in humans. Pharmaceutics, 13(3), 401.

17. Jiang, J., Lu, A., Ma, X., Ouyang, D., & Williams, R. O., 3rd. (2023). The applications of machine learning to predict the forming of chemically stable amorphous solid dispersions prepared by hot-melt extrusion. International Journal of Pharmaceutics: X, 5(100164), 100164.

18. Ojo, A. T., & Lee, P. I. (2020). Applications of dynamic mechanical analysis in the engineering of amorphous solid dispersions. Pharmaceutical Fronts, 02(01), e55–e63.

19. Doktorovová, S., Stone, E. H., & Henriques, J. (2022). A fundamental study on compression properties and strain rate sensitivity of spray-dried amorphous solid dispersions. AAPS PharmSciTech, 23(4), 96.

20. Nambiar, A. G., Singh, M., Mali, A. R., Serrano, D. R., Kumar, R., Healy, A. M., Agrawal, A. K., & Kumar, D. (2022). Continuous manufacturing and molecular modeling of pharmaceutical amorphous solid dispersions. AAPS PharmSciTech, 23(7), 249.

21. Lu, M., Guo, Z., Li, Y., Pang, H., Lin, L., Liu, X., Pan, X., & Wu, C. (2014). Application of hot melt extrusion for poorly water-soluble drugs: limitations, advances and future prospects. Current Pharmaceutical Design, 20(3), 369–387.

22. Szafraniec-Szczęsny, J., Antosik-Rogóż, A., Kurek, M., Gawlak, K., Górska, A., Peralta, S., Knapik-Kowalczuk, J., Kramarczyk, D., Paluch, M., & Jachowicz, R. (2021). How does the addition of Kollidon®VA64 inhibit the recrystallization and improve ezetimibe dissolution from amorphous solid dispersions? Pharmaceutics, 13(2), 147.

23. Fan, N., Li, J., & Li, J. (2021). Advantages of introducing an effective crystalline inhibitor in curcumin amorphous solid dispersions formulated by Eudragit E100. The Journal of Pharmacy and Pharmacology, 73(2), 185–192.

24. Schmied, F.-P., Bernhardt, A., Moers, C., Meier, C., Endres, T., & Klein, S. (2022). A novel aminomethacrylate-based copolymer for solubility enhancement-from radical polymer synthesis to manufacture and characterization of amorphous solid dispersions. Polymers, 14(7).

25. Szabó, E., Démuth, B., Galata, D. L., Vass, P., Hirsch, E., Csontos, I., Marosi, G., & Nagy, Z. K. (2019). Continuous formulation approaches of amorphous solid dispersions: Significance of powder flow properties and feeding performance. Pharmaceutics, 11(12), 654.

26. Correa Soto, C. E., Gao, Y., Indulkar, A. S., Ueda, K., Zhang, G. G. Z., & Taylor, L. S. (2022). Impact of surfactants on the performance of clopidogrel-copovidone amorphous solid dispersions: Increased drug loading and stabilization of nanodroplets. Pharmaceutical Research, 39(1), 167–188.

27. Butreddy, A., Sarabu, S., Almutairi, M., Ajjarapu, S., Kolimi, P., Bandari, S., & Repka, M. A. (2022). Hot-melt extruded hydroxypropyl methylcellulose acetate succinate based amorphous solid dispersions: Impact of polymeric combinations on supersaturation kinetics and dissolution performance. International Journal of Pharmaceutics, 615(121471), 121471.

28. Santos, K. A. dos, Danda, L. J. de A., Oliveira, T. C. de, Soares-Sobrinho, J. L., & Soares, M. F. de L. R. (2022). The drug loading impact on dissolution and diffusion: a case-study with amorphous solid dispersions of nevirapine. Research, Society and Development, 11(14), e168111436117.

29. Sarabu, S., Butreddy, A., Bandari, S., Batra, A., Lawal, K., Chen, N. N., Kogan, M., Bi, V., Durig, T., & Repka, M. A. (2022). Preliminary investigation of peroxide levels of Plasdone™ copovidones on the purity of atorvastatin calcium amorphous solid dispersions: Impact of plasticizers on hot melt extrusion processability. Journal of Drug Delivery Science and Technology, 70(103190), 103190.

30. Zhang, W., Sluga, K. K., Yost, E., Phan, J., Nagapudi, K., & Helen Hou, H. (2022). Impact of drug loading on the compaction properties of itraconazole-PVPVA amorphous solid dispersions. International Journal of Pharmaceutics, 629(122366), 122366.

31. Mudie, D. M. (2023). Voices in molecular pharmaceutics: Meet Dr. Deanna mudie, designer of amorphous solid dispersions for improved patient compliance and greener manufacturing. Molecular Pharmaceutics, 20(1), 4–5.

32. Parupathi, P., & Dhoppalapudi, S. (2022). The role of surfactants in preserving the stability of amorphous solid dispersions: A review. GSC Biological and Pharmaceutical Sciences, 21(3), 039–047.

33. Mudie, D. M., Stewart, A. M., Biswas, N., Brodeur, T. J., Shepard, K. B., Smith, A., Morgen, M. M., Baumann, J. M., & Vodak, D. T. (2020). Novel high-drug-loaded amorphous dispersion tablets of posaconazole; In vivo and in vitro assessment. Molecular Pharmaceutics, 17(12), 4463–4472.

34. Dhoppalapudi, S., & Parupathi, P. (2022). Hot melt extrusion: A single-step continuous manufacturing process for developing amorphous solid dispersions of poorly soluble drug substances. GSC Advanced Research and Reviews, 13(2), 126–135.

35. Mudie, D. M., Stewart, A. M., Rosales, J. A., Adam, M. S., Morgen, M. M., & Vodak, D. T. (2021). In vitro-in silico tools for streamlined development of acalabrutinib amorphous solid dispersion tablets. Pharmaceutics, 13(8), 1257.

36. Newman, A., Hastedt, J. E., & Yazdanian, M. (2017). New directions in pharmaceutical amorphous materials and amorphous solid dispersions, a tribute to Professor George Zografi – Proceedings of the June 2016 Land O'Lakes Conference. AAPS Open, 3(1).

37. Bookwala, M., & Wildfong, P. L. D. (2023). The implications of drug-polymer interactions on the physical stability of amorphous solid

dispersions. Pharmaceutical Research.

38. Nguyen, H. T., Van Duong, T., Jaw-Tsai, S., Bruning-Barry, R., Pande, P., Taneja, R., & Taylor, L. S. (2023). Fed- and fasted-state performance of pretomanid amorphous solid dispersions formulated with an Enteric polymer. Molecular Pharmaceutics, 20(6), 3170–3186.

39. Shi, C., Li, L., Zhang, G. G. Z., & Borchardt, T. B. (2019). Direct visualization of drug-polymer phase separation in ritonavir-copovidone amorphous solid dispersions using in situ synchrotron X-ray fluorescence imaging of thin films. Molecular Pharmaceutics, 16(11), 4751–4754.