Indonesian Journal of Pharmaceutical Science and Technology
Journal Homepage : http://jurnal.unpad.ac.id/ijpst/
Review Article

Drug Solubility Enhancement Strategies Using Amorphous Solid Dispersion: Examination on Type and The Amount of the Polymer

Muhammad Seftian[1], Marlyn D. Laksitorini[2], Teuku N. S. Sulaiman[2*]

[1]Master in Pharmaceutical Science, Faculty of Pharmacy, Universitas Gadjah Mada, Jl. Sekip Utara, Sleman, Yogyakarta 5528, Indonesia.

[2] Department of Pharmaceutics, Universitas Gadjah Mada, Jl. Sekip Utara, Sleman, Yogyakarta 5528, Indonesia.

Submitted 18 April 2023; Revised 07 November 2023; Accepted 17 November 2023; Published 07 June 2024

*Corresponding author: tn_saifullah@ugm.ac.id

Abstract

Solubility significantly impacts the biopharmaceutical process of drugs, dictating dissolution rates and oral bioavailability. Low solubility necessitates higher drug loads to compensate. Solid dispersion offers a solution for enhancing solubility, where polymers play a crucial role. This review investigates the influence of polymer type and quantity on solid dispersions, drawing from 45 diverse references across various journal databases namely Scopus, ScienceDirect, and Google Scholar. Amorphous solid dispersion (ASD) emerges as a contemporary method for boosting drug solubility by dispersing it in a carrier, typically a hydrophilic polymer. This approach alters the thermodynamic equilibrium of the drug in solution, enhancing solubility and dissolution rates. Its amorphous structure, characterized by a random molecular arrangement, increases thermodynamic activity, resulting in higher solubility and dissolution rates. Polymers, the primary component alongside the active substance in ASD, dictate its success. Polymer selection, along with additives and their proportions, is crucial. Surfactants are often incorporated into a ternary system to synergistically enhance dissolution rates, maintaining drug supersaturation via mechanisms like reducing molecular mobility and providing a plasticizing effect.

Keywords: Amorphous solid dispersion, Dissolution, Polymers, Surfactants

Strategi Peningkatan Kelarutan Obat Menggunakan Amorphous Solid Dispersion: Kajian pada Jenis dan Jumlah Polimer

Abstrak

Kelarutan secara signifikan berdampak pada proses biofarmasetika obat, menentukan laju disolusi dan ketersediaan hayati obat. Dispersi padat menawarkan solusi untuk meningkatkan kelarutan, dimana polimer memainkan peran penting. Artikel ini mengkaji pengaruh jenis dan jumlah polimer pada sistem dispersi padat, yang diambil dari 45 referensi yang beragam di berbagai database jurnal yaitu Scopus, ScienceDirect, dan Google Scholar. Amorphous solid dispersion (ASD) muncul sebagai teknologi terkini untuk meningkatkan kelarutan obat dengan mendispersikannya dalam pembawa, biasanya polimer hidrofilik. Pendekatan ini mengubah kesetimbangan termodinamika obat dalam larutan, meningkatkan kelarutan dan laju disolusi. Struktur amorfnya, yang memiliki susunan molekul acak, meningkatkan aktivitas termodinamika, menghasilkan kelarutan dan laju disolusi yang lebih tinggi. Polimer, komponen utama bersama zat aktif dalam ASD, menentukan keberhasilan pengembangan sistem ASD. Pemilihan polimer, bersama dengan aditif dan proporsinya, sangat penting. Surfaktan sering kali digabungkan ke dalam sistem terner untuk secara sinergis meningkatkan laju pelarutan, mempertahankan supersaturasi obat melalui mekanisme seperti mengurangi mobilitas molekuler dan memberikan efek plastisisasi.

Kata Kunci: *Amorphous solid dispersion*, Disolusi, Polimer, Surfaktan

1. Introduction

Solubility is one of the critical factors affecting the biopharmaceutical process of drugs. Nowadays, drug discovery and development are primarily concerned with solubility problems due to nearly 90% of new active ingredients being poorly water-soluble. Solubility is a significant challenge for research and drug development as it potentially limits drug dissolution. Thus, the dose strength consumed does not dissolve completely in a physiological amount of gastrointestinal fluid and limits the ready-to-absorbed free drug concentration in the gastrointestinal tract. Drugs are classified into four categories based on their solubility and permeability called biopharmaceutical classification systems (BSC) (Table 1).[1]

A drug is considered highly soluble if the highest clinical dose can be dissolved in 250mL of media in the pH range of 1 – 7.5 at 37oC. Low solubility retards the dissolution rate and limits its oral bioavailability. Thus, leading to a high dose burden required.[2,3] Some strategies have been developed to improve drug solubility, such as nanotechnology,[4] co-solvents,[5] modification of salt structures,[6] encapsulation with cyclodextrin and its derivatives,[7] and amorphous solid dispersion (ASD).[8]

Amorphous solid dispersion (ASD) is a recent approach to increase drug solubility by dispersing the drug in a carrier-commonly a hydrophilic polymer. Previous studies showed that ASD could increase the solubility and bioavailability of drugs. Tadalafil solid dispersion formulated with PVP-VA enhanced drug solubility compared to its pure form.[9] Other studies have succeeded in increasing valsartan dissolution rate and bioavailability relative to its pure form.[10] ASD formulations enhance drug solubility by increasing drug supersaturation degree. The system maintains drug supersaturation in the solution state through two main mechanisms, reducing molecular mobility and anti-plasticizing effect. Several reviews on ASD formulations have been published.[11,12] However, a review regarding the effect of polymer selection and drug-polymer ratio on the physical characteristics and drug release profile of ASD has not been done. Previous studies have demonstrated a positive correlation between the quantity of polymer and the enhancement of solubility in SD systems.[13,14] Nonetheless, additional research has highlighted that after a certain point, an increase in the amount of polymer hinders drug release.[9,15] This article is aimed to describe how the polymer type and drug-polymer ratio would affect the characteristics and dissolution behavior of ASD.

2. Method

The process of preparing the review was carried out based on the workflow shown in the figure 1.

3. Result and Discussion

3.1. Crystalline vs Amorphous

The drug-dissolving process is an "act of battling" the interaction energy to crack the crystal lattice. The crystalline form of a drug has a compact crystal structure with a neat and dense molecular arrangement. This structure provides a high barrier in the dissolution process. The higher the energy to be overcome, the lower the dissolution rate of a drug. One strategy that can be done to reduce the barrier is to modify the crystal form to become amorphous. The amorphous form has a more random crystal molecular arrangement than the crystalline and has a tenuous structure leading to higher thermodynamic activity.

Table 1. Drugs Classification Based on The Biopharmaceutical Classification System (BCS)[1]

BCS Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

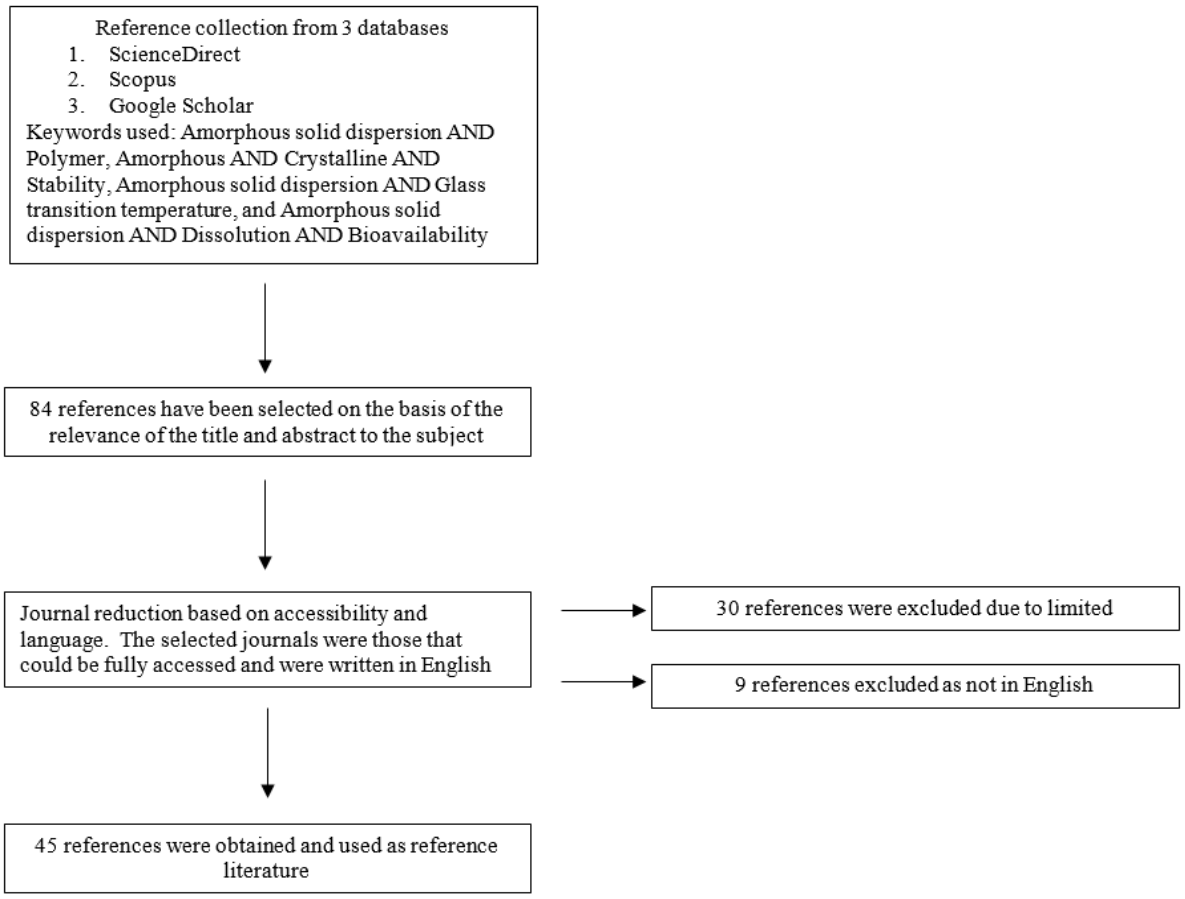

Figure 1. Flowchart of the review preparation process

The amorphous form has a higher free energy. Thus it has a higher solubility and dissolution rate.[16,17] The success of Amorphous Solid Dispersion (ASD) systems in enhancing drug solubility and dissolution has incentivised manufacturers to integrate such systems into their own product development. Table 2 illustrates the current incorporation of ASD systems in various commercial products.

The main issue of the amorphous form is its stability. Having higher thermodynamic activity makes it tend to reach its stability state by undergoing recrystallization. However, amorphous form is rarely used in practice. The amorphous solid dispersion (ASD) formulation is an alternate option to amourphous form.

This formulation increases drug solubility but has better stability.[11] The drug in ASD is molecularly dispersed in the polymer matrix to form amorphous crystals that are more stable than traditional amorphous forms. The ASD improve drug supersaturation and result in solubility enhancement.[17,18]

3.2. Formulation of Amorphous Solid Dispersion (ASD)

Polymer is an important excipient in

Table 2. Example of The Marketed Product Using Solid Dispersion

Brand Name	Drug (s)	Carrier(s)	Manufacturer
Cesamet	Nabilone	PVP	Valeant Pharmaceuticals
Sporanox	Itraconazole	HPMC	Janssen Pharmaceutica
Kaletra	Lopinavir/Ritonavir	PVP-VA	Abbot Laboratories
Nimotop	Nimodipine	PEG	Bayer Ltd.
Fenoglide	Fenofibrate	PEG/Poloxamer	Santarus, Inc.

PVP: Polyvinylpyrolidone; PVP-VA: Polyvinylpyrolidone-co-vinylacetate; PEGS: Polyethylene Glycol; HPMC: Hydroxypropyl Methyl Cellulose

the ASD system. Therefore the success of ASD formulation will be determined by the selection of the type and proportion of polymers and additives.[19] Various studies have been carried out to develop ASD systems in different polymer bases. The development is not limited to commercial active substances[20,21] but also natural active compounds.[22,23]

a. Polymer Selection

Polymer selection is essential in ASD formulation as the characteristics of ASD are directly influenced by the properties of the polymer such as solubility, viscosity index, carrier capacity, and molecular weight. In addition, the chemical structure can also affect the molecular interaction between the drug and the polymer.[13] Furthermore, it also can provide sterical hindrance that prevent inter-molecular interaction between drug molecules.[24,25] The use of different polymers in the resveratrol ASD system showed a different enhancement in solubility. Povidone can increase the solubility of resveratrol up to 100-fold at low drug loading (DL) (<30%). However, at a higher DL, both solubility and the dissolution rate dramatically reduced. On the other hand, copovidone has a higher carrier capacity so it can be formulated with up to 50% DL. Carrier capacity can affect the ratio of drug and polymer required in the formulation. Less carrier capacity brings more polymer needed to achieve optimal drug amorphization.[26]

Polymer selection is not only limited to its structure. Polymers as macromolecules have several grades and molecular weights (MW) which govern their physical properties. Polymers with high molecular weight tend to swell and form a viscous layer around the matrix thereby inhibiting drug diffusion. Research showed that ASD systems using high MW Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) hand a lower dissolution rate than systems using low BM

Table 3. Research Related to Amorphous Solid Dispersion

API	Carrier	Method	Key Findings	Reference
Carvedilol	PVP, PVP-VA	Spray drying	The drug-polymer ratio affected the solubility and dissolution rate of carvedilol. It took at least a 1:2 drug-polymer ratio to develop a stable carvedilol ASD.	(13)
Resveratrol	Soluplus, Poloxamer 407	Solvent casting	The molecular weight of the polymer affected the dissolution rate of the drug. Polymers with high molecular weight tend to have high viscosity and prolonged drug release.	(26)
Curcumin	TPGS, HPMC	Solven evaporation	Solid dispersion increased the solubility of curcumin across the pH of the gastrointestinal tract.	(30)
Atorvastatin	HPC, Sodium Crosscarmelose, Sodium Starch Glicolate, Kolliphor RH40	Solvent evaporation	ternary system of ASD containing surfactants was more stable because surfactants form micelles and inhibited drug recrystallization during dissolution	(31)
Efavirenz	HPMC, HPMCAS, PVA, PVP-VA, Soluplus	Vacuum compression molded	ASD system with DL less than the theoretical limit, the dissolution rate was controlled by the polymer and did not undergo recrystallization	(19)

API: Active Pharmaceutical Agent; ASD: Amorphous Solid Dispersion; PVP: Polyvinylpyrolidone; PVP-VA: Polyvinylpyrolidone-co-vinylacetate; TPGS: Tocopherol Polyethylene Glycol Succinate; HPMC: Hydroxypropyl Methyl Cellulose; HPC: Hydroxypropyl Cellulose; HPMCAS: Hydroxypropylmethylcellulose Acetate Succinate

HPMCAS.[26,27] The same agreement were also obtained in several other studies.[28] However, not all polymers show different dissolution profiles at different MWs. The ASD system using PVP and PVP/VA with various MWs showed that the drug dissolution behavior was controlled by the type of polymer rather than the MW.[13]

b. Polymer-drug Ratio

Polymer-drug ratio (PDR) significantly affects the saturation level of the ASD system by altering the thermodynamic equilibrium of the system (discussed in the next section). The ratio can be prepared in the range of 1:1 to 5:1 and can even be surged up to 10:1.[29] The selection of the ratio can be based on the characteristics of the polymer, the active substance being dispersed, as well as the bulk burden on the final product in the formulation. Different drug might exhibit different characteristics at the same drug-polymer ratio. The Lasidipine ASD system with soluplus carrier required a PDR of at least 2:1 to maintain saturation. Using polymer at a 1:1 ratio could not maintain drug saturation during dissolution and caused 85% of the drug to precipitate in the first 4 hours.[8] Adding more polymer increases the interaction between the drug and the polymer, followed by system stabilization and maintains its saturation.[26] Table 2 shows studies related to ASD formulation.

Although different studies showed a proportional correlation between solubility and the amount of polymer,[13] adding more polymer did not always boost the dissolution rate. At a certain point, the polymer conversely reduces the drug dissolution rate because it forms a dense diffusion layer, thereby inhibiting drug release from the matrix.[10] For this reason, selection on polymer type and proportion plays important in ASD formulations. These characteristics also open opportunities for ASD systems to be developed as a controlled-release dosage form by modifying the type and amount of polymer.

3.3. Stability of Amorphous Solid Dispersion

Recrystallization and phase separation is the preeminent forms of instability in ASD systems. This instability causes the dispersed active substance to form a crystalline structure so that it loses its superiority. Stability maintenance is done through two main mechanisms, crystallization inhibition, and plasticizing effect.

a. Crystallization Inhibition

Drug crystallization occurs through 2 stages that take place simultaneously. The process begins with forming a crystal nucleus due to drug molecules aggregation. It continues with crystal growth as more and more drug molecules migrate to the nucleus surface. ASD can undergo crystallization in both the solid and solution state. Solution-state crystallization is more prevalence due to its higher molecular mobility. Indeed, crystallization requires sufficient activation energy to overcome the interfacial tension of the drug molecules so that nucleation can occur.[18,32] For this reason, crystallization never arises until the ASD system reaches a certain degree of saturation. Polymers exert crystallization inhibitory effects in two ways: increasing the saturation of the drug and lowering the molecule mobility. Molecular interactions are factors that directly affect the mobility of drug molecules. Both drugs and polymers can interact through several molecular interaction such as hydrogen bonds, van der Waals, electrostatic, ionic, or hydrophobic. The interactions restrain the drug molecules' mobility and stabilize the ASD. The dispersion of drug molecules in the matrix also reduces the concentration of free drugs in the solution since drug-polymer interactions limit interactions between drug molecules.[28,29]

Soluplus is a synthetic polymer that is increasingly utilized as a solid dispersion carrier owing to its numerous benefits. As an amphiphilic polymer, it has potential as a drug carrier with diverse characteristics. Prior research has demonstrated that Soluplus can improve solubility by retaining drug supersaturation in the gastrointestinal tract

while also avoiding aggregation caused by recrystallization during dissolution.[34,35] Indeed, Soluplus has been proven to enhance drug permeability in other studies.[36]

b. Anti-plasticization Effect

Thermodynamically, anti-plasticization can be defined as a decrease in the free energy of a system caused by an increase in the glass transition temperature (T_g). The decrease in free energy means a higher energy barrier that the drug must overcome to undergo recrystallization.[37] An ASD system will consist of at least a drug and a polymer, each with a different T_g. The final T_g of the bulk will be determined by the proportion of each component in the system and its T_g value. Combining low T_g drug with a high Tg polymer will result in a final T_g lays somewhere between the T_g values of its components. In other words, the polymer will provide an anti-plasticization effect by increasing the T_g of the drug, while the polymer itself undergoes plasticization.[38]

Previous study indicated that as the amount of polymer increased, an increase in T_g was observed in the ASD system of fenofibrate with HPMCAS. By reducing DL from 30% to 15%, the T_g of the system escalated to 70-80ºC, depending on the polymer grade used.[38]

3.4. Dissolution Behaviour of ASD System

a. The Influence of Polymer Type and Drug-Polymer Ratio

Dissolution is a biopharmaceutical stage that is directly affected by drug solubility. Based on the Noyes-Whitney equation, the dissolution rate (dC/dt) is proportionally influenced by the discrepancy between the drug solubility (C_s) and the dissolved drug (C).[17]

$$\frac{dC}{dt} = k\,(Cs - C)$$

Therefore, higher drug solubility will expand the gradient leading to a higher dissolution rate. Both polymers and drug in the ASD system have different solubility. Thus, as the same as T_g, the final solubility of the system will be controlled by the proportion of each component. Both polymer and drug will also undergo dissolution which can occur congruently.[39,40] However, this can only happen if there is enough polymer to control the dissolution. Finally, the dissolution rate of the ASD system $(dC/dt)_{ASD}$ will be determined by the dissolution rate of the polymer $(dC/dt)_{polymer}$ as well as the proportion of drug $(X)_{drug}$ and polymer $(X)_{polymer}$.

$$\left(\frac{dC}{dt}\right)_{\text{ASD}} = \frac{\left(\frac{dC}{dt}\right)polymer\ .\ Xdrug}{Xpolymer}$$

The ASD system possesses high stability as the amount of polymer is much higher than the drug, as the molecular mobility of drug can be diminished to the lowest. Hence, there is no recrystallization, or the dissolution rate of the system is much higher than the crystallization rate.[41] Ritonavir in the PVP-VA system with 25% DL showed a dissolution rate controlled by the polymer. However, increasing the DL above significantly changed the dissolution rate due to the recrystallization rate faster than dissolution. The polymer will dissolve initially before the drug. When the polymer begins to deplete, the undissolved drug molecules start to aggregate to form a thin layer on the surface of the bulk. This layer provides a physical barrier since the poorly water-soluble drug makes the remaining beneath unable to dissolve.[17,41] As discussed in the preceding subsection, each polymer has a different carrier capacity. Thun, polymer type, and drug-polymer ratio provide a consequential impact on ASD formulation.

b. The Use of Surfactants as Ternary Systems

One of the most challenging restraints in developing an ASD system is DL capacity. Binary systems with high DL have more tendency to experience recrystallization, especially during the dissolution process. During this process, the polymer matrix undergoes relaxation due to the water insertion, thus increasing molecular mobility, and the likelihood of recrystallization-also

known as solution-phase crystallization.[42,43] Current amorphous solid dispersion (ASD) formulations add a surfactant as a ternary drug-polymer-surfactant system. Surfactants provide a synergistic effect in enhancing dissolution and maintaining drug supersaturation.[15]

Surfactants significantly increase drug solubility and dissolution rate compared to binary drug-polymer systems.[26] A study on Ledipasvir at DL >5% caused only a tiny amount of the drug to be released. The addition of a surfactant maintained the dissolution rate with DL up to 30%. Surfactants improve wettability and work as co-solubilizers due to their amphiphilic properties.[44] Surfactants prevent drug recrystallization during the dissolution process by encapsulating drug molecules and forming a physical barrier that blocks drug intermolecular interaction.[40,45] Additionally, surfactants can bridge the interaction between drug and polymer to decrease the critical aggregation concentration, which increases apparent drug solubility. On the other hand, surfactant use must also be optimized because, at specific concentrations, surfactants can displace drug-polymer bonds and cause phase separation.[14]

4. Future Perspective

The primary issues faced by ASDs are the DL restrictions and the occurrence of recrystallisation during the dissolving process, leading to damage to the ASD system. Researchers have started exploring the use of surfactants as ternary systems. However, the intricacy of their interplay in the system demands better comprehension. Particularly, with the findings that certain surfactants stimulate recrystallisation and disrupt drug-polymer interactions. Further investigation is necessary to enhance the practicality of the established system since low drug loading eventually leads to a high mass of the bulk. The resilience of ASD in ternary systems with surfactants also requires examination, taking into account that surfactants have the potential to increase drug loading.

5. Conclusion

The formulation of amorphous solid dispersion (ASD) improves the solubility and dissolution rate of drugs by affecting the thermodynamic equilibrium of the drug in solution. This is the advantage of the ASD system, which distinguishes it from other formulation systems without changing the chemical structure of the active ingredient. The selection of polymer type, drug-polymer ratio, and manufacturing method must be considered in the pre-formulation. Additionally, the addition of surfactants can also be considered to enhance the stability of ASD.

Reference

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharm Res. 1995;12(3):413–20.
2. Childs SL, Kandi P, Lingireddy SR. Formulation of a danazol cocrystal with controlled supersaturation plays an essential role in improving bioavailability. Mol Pharm. 2013;10(8):3112–27.
3. Medarević D, Cvijić S, Dobričić V, Mitrić M, Djuriš J, Ibrić S. Assessing the potential of solid dispersions to improve dissolution rate and bioavailability of valsartan: In vitro-in silico approach. Eur J Pharm Sci. 2018;124(August):188–98.
4. Ibrahim AH, Rosqvist E, Smått JH, Ibrahim HM, Ismael HR, Afouna MI, et al. Formulation and optimization of lyophilized nanosuspension tablets to improve the physicochemical properties and provide immediate release of silymarin. Int J Pharm. 2019;563(March):217–27.
5. Li Y, Li C, Gao X, Lv H. Nitazoxanide in aqueous co-solvent solutions of isopropanol/DMF/NMP: Solubility, solvation thermodynamics and intermolecular interactions. J Chem Thermodyn. 2023;176(September 2022).
6. Gao L, Zhang XR. Pharmaceutical salt hydrates of vortioxetine with maleic acid and fumaric acid: Crystal

structures, characterisation and solubility performance. J Mol Struct. 2022;1250:1–10.
7. Sun X, Zhu J, Liu C, Wang D, Wang CY. Fabrication of fucoxanthin/2-hydroxypropyl-β-cyclodextrin inclusion complex assisted by ultrasound procedure to enhance aqueous solubility, stability and antitumor effect of fucoxanthin. Ultrason Sonochem. 2022;90(September).
8. Guan J, Jin L, Liu Q, Xu H, Wu H, Zhang X, et al. Exploration of supersaturable lacidipine ternary amorphous solid dispersion for enhanced dissolution and in vivo absorption. Eur J Pharm Sci. 2019;139(June).
9. Choi JS, Park JS. Design of PVP/VA S-630 based tadalafil solid dispersion to enhance the dissolution rate. Eur J Pharm Sci. 2017;97:269–76.
10. Chella N, Daravath B, Kumar D, Tadikonda RR. Formulation and Pharmacokinetic Evaluation of Polymeric Dispersions Containing Valsartan. Eur J Drug Metab Pharmacokinet. 2016;41(5):517–26.
11. Bhujbal S V., Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharm Sin B. 2021;11(8):2505–36.
12. Vullendula SKA, Nair AR, Yarlagadda DL, Navya Sree KS, Bhat K, Dengale SJ. Polymeric solid dispersion Vs co-amorphous technology: A critical comparison. J Drug Deliv Sci Technol. 2022;78(November).
13. Krstić M, Manić L, Martić N, Vasiljević D, Mračević SĐ, Vukmirović S, et al. Binary polymeric amorphous carvedilol solid dispersions: In vitro and in vivo characterization. Eur J Pharm Sci. 2020;150(March).
14. Song CK, Yoon I-S, Kim D-D. Poloxamer-based solid dispersions for oral delivery of docetaxel: Differential effects of F68 and P85 on oral docetaxel bioavailability. Int J Pharm. 2016;507:102–8.
15. Lu Y, Chen J, Yi S, Xiong S. Enhanced felodipine dissolution from high drug loading amorphous solid dispersions with PVP/VA and sodium dodecyl sulfate. J Drug Deliv Sci Technol. 2019;53(April).
16. Halász AS. Solubility as a Challenge in Drug Research and Development. In: Tihanyi K, Vastag M, editors. Solubility, Delivery and ADME Problems of Drugs and Drug_Candidates. Budapest: Bentham e-Books; 2011. p. 52–67.
17. Indulkar AS, Lou X, Zhang GGZ, Taylor LS. Insights into the Dissolution Mechanism of Ritonavir-Copovidone Amorphous Solid Dispersions: Importance of Congruent Release for Enhanced Performance. Mol Pharm. 2019;16(3):1327–39.
18. Surwase SA, Itkonen L, Aaltonen J, Saville D, Rades T, Peltonen L, et al. Polymer incorporation method affects the physical stability of amorphous indomethacin in aqueous suspension. Eur J Pharm Biopharm. 2015;96(June):32–43.
19. Jørgensen JR, Mohr W, Rischer M, Sauer A, Mistry S, Müllertz A, et al. Stability and intrinsic dissolution of vacuum compression molded amorphous solid dispersions of efavirenz. Int J Pharm. 2023;632(December 2022).
20. Xu H, Zhao T, Liu F, Zhang Y, Xie Y, Xiao X, et al. Dihydromyricetin solid dispersion: Preparation, characterization, and preservative effects on sturgeon fillets stored at 4 °C. Lwt. 2023;174(December 2022).
21. Nupur MA, Rahman MM, Akter K, Hanif KB, Sharna JF, Sarker MS, et al. Preparation and characterization of naproxen solid dispersion using different hydrophilic carriers and in-vivo evaluation of its analgesic activity in mice. Heliyon. 2023;9(5).
22. Sharma P, Ruchika, Dhiman P, Kumar R, Saneja A, Singh D. A solid dispersion of Citrus reticulata peel biowaste as an effective antiepileptic: Sustainable approach toward value addition and agro-industrial waste valorisation. J Drug Deliv Sci Technol. 2023;81(January).
23. Yu C, Zhang C, Guan X, Yuan D. Journal of Drug Delivery Science and Technology The solid dispersion of resveratrol with

enhanced dissolution and good system physical stability. 2023;84(October 2022).
24. Dengale SJ, Grohganz H, Rades T, Löbmann K. Recent advances in co-amorphous drug formulations. Adv Drug Deliv Rev. 2016;100(2016):116–25.
25. Yarlagadda DL, Sai Krishna Anand V, Nair AR, Navya Sree KS, Dengale SJ, Bhat K. Considerations for the selection of co-formers in the preparation of co-amorphous formulations. Int J Pharm. 2021;602(April).
26. Vasconcelos T, Prezotti F, Araújo F, Lopes C, Loureiro A, Marques S, et al. Third-generation solid dispersion combining Soluplus and poloxamer 407 enhances the oral bioavailability of resveratrol. Int J Pharm. 2021;595(November 2020).
27. Pinto JMO, Leão AF, Riekes MK, França MT, Stulzer HK. HPMCAS as an effective precipitation inhibitor in amorphous solid dispersions of the poorly soluble drug candesartan cilexetil. Carbohydr Polym. 2018;184(September 2017):199–206.
28. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47–60.
29. Shetty D, Yarlagadda DL, Brahmam B, Swapnil J, Lewis SA. Investigating the influence of the type of polymer on sustaining the supersaturation from amorphous solid dispersions of Apremilast and its pharmacokinetics. ournal Drug Deliv Sci Technol. 2023;
30. Xi Z, Fei Y, Wang Y, Lin Q, Ke Q, Feng G, et al. Solubility improvement of curcumin by crystallization inhibition from polymeric surfactants in amorphous solid dispersions. J Drug Deliv Sci Technol [Internet]. 2023; Available from: https://doi.org/10.1016/j.scitotenv.2020.138954
31. Torrado-Salmerón C, Guarnizo-Herrero V, Torrado G, Peña MÁ, Torrado-Santiago S, de la Torre-Iglesias PM. Solid dispersions of atorvastatin with Kolliphor RH40: Enhanced supersaturation and improvement in a hyperlipidemic rat model. Int J Pharm. 2023;631(December 2022).
32. Tian Y, Jones DS, Andrews GP. An investigation into the role of polymeric carriers on crystal growth within amorphous solid dispersion systems. Mol Pharm. 2015;12(4):1180–92.
33. Davis MT, Potter CB, Mohammadpour M, Albadarin AB, Walker GM. Design of spray dried ternary solid dispersions comprising itraconazole, soluplus and HPMCP: Effect of constituent compositions. Int J Pharm. 2017;519(1–2):365–72.
34. Nair AR, Lakshman YD, Anand VSK, Sree KSN, Bhat K, Dengale SJ. Overview of Extensively Employed Polymeric Carriers in Solid Dispersion Technology. AAPS PharmSciTech. 2020 Nov;21(8):309.
35. Tao C, Huo T, Zhang Q, Song H. Effect of Soluplus on the supersaturation and absorption of tacrolimus formulated as inclusion complex with dimethyl-β-cyclodextrin. Pharm Dev Technol. 2019 Nov;24(9):1076–82.
36. Linn M, Collnot E-M, Djuric D, Hempel K, Fabian E, Kolter K, et al. Soluplus® as an effective absorption enhancer of poorly soluble drugs in vitro and in vivo. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2012 Feb;45(3):336–43.
37. Wu W, Ueda H, Löbmann K, Rades T, Grohganz H. Organic acids as co-formers for co-amorphous systems – Influence of variation in molar ratio on the physicochemical properties of the co-amorphous systems. Eur J Pharm Biopharm. 2018;131:25–32.
38. Kallakunta VR, Sarabu S, Bandari S, Batra A, Bi V, Durig T, et al. Stable amorphous solid dispersions of fenofibrate using hot melt extrusion technology: Effect of formulation and process parameters for a low glass transition temperature drug. J Drug Deliv Sci Technol. 2020;58(November 2019).
39. Kaur N, Narang A, Bansal AK, Narang A, Bansal AK. Use of Biorelevant Dissolution and PBPK Modeling to Predict Oral Drug Absorption.

Eur J Pharm Biopharm. 2018;
40. Taylor LS, Zhang GGZ. Physical chemistry of supersaturated solutions and implications for 2 oral absorption. Adv Drug Deliv Rev. 2016;
41. Que C, Lou X, Zemlyanov DY, Mo H, Indulkar AS, Gao Y, et al. Insights into the Dissolution Behavior of Ledipasvir-Copovidone Amorphous Solid Dispersions: Role of Drug Loading and Intermolecular Interactions. Mol Pharm. 2019;16(12):5054–67.
42. Yen C-W, Kuhn R, Hu C, Zhang W, Chiang P-C, Chen JZ, et al. Impact of surfactant selection and incorporation on in situ nanoparticle formation from amorphous solid dispersions. Int J Pharm. 2021;607.
43. Correa-Soto CE, Gao Y, Indulkar AS, Zhang GGZ, Taylor LS. Role of surfactants in improving release from higher drug loading amorphous solid dispersions. Int J Pharm. 2022;625(May).
44. Saha SK, Joshi A, Singh R, Jana S, Dubey K, Joshi A, et al. An investigation into solubility and dissolution improvement of Alectinib Hydrochloride as a third-generation amorphous solid dispersion. J Drug Deliv Sci Technol. 2023;1–8.
45. Qian S, Li Z, Heng W, Liang S, Ma D, Gao Y, et al. Charge-assisted intermolecular hydrogen bond formed in coamorphous system is important to relieve the pH-dependent solubility behavior of lurasidone hydrochloride. RSC Adv. 2016;6(108):106396–412.