Opinion/Perspective
Sciences of Pharmacy

Impact of Preparation Method in Co-Amorphous System

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[The author informations are in the declarations section. This article is published by ETFLIN in Sciences of Pharmacy, Volume 1, Issue 1, 2022, Page 34-40. https://doi.org/10.58920/sciphar01010041]

Received: 20 May 2022
Revised: 20 June 2022
Accepted: 24 June 2022
Published: 28 June 2022

Editor: Angi Nadya Bestari

Keywords: Co-amorphous, co-amorphous method, solvent evaporation method, milling techniques, quenching methods.

Abstract: The co-amorphous solid dispersion system is one of the methods to improve the physicochemical characteristics and stability of a drug. With the appropriate material ratio and preparation method, a co-amorphous solid dispersion system can increase the bioavailability of the drug due to an increase in solubility. In addition, the co-amorphous system will maintain its amorphous shape longer than a single compound. However, using unsuitable materials and methods for co-amorphous fabrication will precipitate them and diminish their bioavailability. As a result, exploring the fundamentals of co-amorphous manufacturing methods is essential. This article discusses the physicochemical properties and solubility of co-amorphous mixtures prepared by solvent evaporation, milling, and quenching methods. Scopus, PubMed, and Google Scholar literature were obtained using the keywords 'co-amorphous preparation', 'co-amorphous method', 'solvent evaporation for co-amorphous preparation', 'milling methods for co-amorphous preparation', and 'quenching method for co-amorphous preparation'. We excluded literature whose application was not in the medical field. Based on the findings, the co-amorphous preparation methods have their respective advantages and disadvantages. Solvent evaporation can only be used on a small scale. Milling techniques are laborious and time-consuming but have a large yield and less chemical destruction, while the quenching method is only intended for thermostable compounds.

Introduction

The bioavailability of a drug is very dependent on its solubility and permeability. High solubility accelerates the availability of drugs in free form, so it is fast to be absorbed. This provides better clinical efficacy than drugs with low solubility. Several methods have been used to increase drug solubility, such as microemulsions, nanoparticles, coatings, amorphization, etc. (1). Among these methods, amorphization is the best method for increasing solubility, which also affects the increase in bioavailability (2). However, the amorphous form of a drug has high internal energy, so it is not stable either in storage or during the manufacturing process. Over time, the amorphous form will change to crystalline, with lower solubility (3).

The drug is mixed with other amorphous drugs to keep the drug in an amorphous form during storage or manufacturing. This solid dispersion system is known as co-amorphous (4). A stoichiometry ratio between components and an appropriate preparation method will produce a more stable physical and chemical mixture through unique molecular interactions depending on the compound being mixed (5). In addition, the co-amorphous system can also improve solubility compared to a single compound (2). And more beneficial is a mixture of two drugs that have the same pharmacological effect and produce a synergistic effect, thereby increasing the therapeutic efficacy (6).

However, an improper mixture of drugs and preparation methods will only cause them to precipitate and can reduce the bioavailability of each other. Molecular interactions between materials may occur due to the influence of the storage environment and the manufacturing process (7). Therefore, it is necessary to study the co-amorphous system's drug

mixtures and preparation methods and their effect on the preparation properties to understand the co-amorphous system better. This review systematically describes the preparation method and physicochemical properties of the co-amorphous system from a molecular interaction perspective.

Type of Co-Amorphous Preparation Method

According to Chavan et al. (8), the preparation method for the co-amorphous system is divided into three main parts, which are the milling method (such as ball milling and cryo-milling), solvent evaporation methods (such as freeze-drying, spray drying, and rotating evaporation) and quench cooling. The methods used in co-amorphous preparation can be seen in Table 1.

Melt and Quench Cooling

Quench cooling is appropriate for materials that do not deteriorate easily when melted (32). The advantages of this method are straightforward. The molecular movement will slow down when the drug substance is under no clot. If the melting can be cooled quickly, then there is no chance of time to return to crystal form because the drug substance is frozen in an irregular state, and crystallization can be avoided. Therefore, in this method, the final product's enthalpy depends on the cooling speed (33). Still, the disadvantage of this method is that most crystalline substances are known to have high melting temperatures, so they cause easy degradation, and this method is rarely applied (12). In addition, chemical degradation may occur during melting due to high temperatures because the degradation product in glass transition temperature can be lower than the amorph product. Still, to overcome this problem, the alternative is to use heating under inert gas (34). This method has been proven to increase the solubility of atorvastatin, in a mixture with naringin (1:1), with an increased solubility by 56 times than before (35). Ritonavir-lopinavir (11), naproxen-indomethacin, and naproxen sodium-indomethacin (12) were reported to be more soluble.

Table 1. Preparation method of co-amorphous.

No	Method	CAM (co amorphous)	Result	Author
1.	Melt-quenching	Desloratadine-benzoic acid	Co amorphous desloratadine and benzoic acid (DES:BA) increased solubility and dissolution compared with pure desloratadine. The solubility increased 19.1 times, and dissolution increased 1.15 times. DES:BA can potentially improve the stability of the mixture.	(9)
2.	Freeze-dried	Quetiapine fumarate-nicotinamide (1:1, 1:2, 1:3)	The results showed that co-amorphous quetiapine fumarate and nicotinamide with a ratio of 1:1 increased solubility of quetiapine fumarate six times compared with pure quetiapine fumarate.	(10)
3.	Quench cooling	Ritonavir-lopinavir (1:1, 1:2, 2:1)	Solubility and flux from ritonavir and lopinavir have been demonstrated to be low. Co-amorphous of ritonavir and lopinavir was found to be significant in flux and solubility, with the solubility increase 3.8 times (1:1), 2 times (1:2), and 3.7 times (2:1) compared to their pure form.	(11)
4.	Quench cooling	Naproxen-indomethacin	The solubility and physical stability of the co-amorphous mixture were improved significantly.	(12)
5.	Solution crystallization	Repaglinide-saccharin	Co-amorphous repaglinide and saccharin showed high solubility. The solubility increased 18.2 times compared to pure repaglinide.	(13)
6.	Cryomilling	Sulfamerazine-deoxycholic acid (SMZ:DA), sulfamerazine-citric acid (SMZ:CA), and sulfamerazine-sodium taurocholate (SMZ:NaTC)	The dissolution test showed an improvement, with the increment of dissolution of 0.6 times (SMZ:DA), 3.1 times (SMZ:CA), and 10.2 times (SMZ:NaTC) compared with pure sulfamerazine.	(14)

7.	Solvent-assisted grinding (SAG) and neat grinding (NG)	β-azelnidipine-maleic acid	The solubility of the mixtures was increased 31 times (SAG) and 19.7 times (NG) compared with pure β – azelnidipine.	(15)
8.	Cryomilling	Simvastatin-lysine (S:L), glibenclamide-serine (G:S), and glibenclamide-serine-threonine (G:ST)	The mixture's solubility was increased 3 times (S:L), 2.8 times (G:S), and 3 times (G:ST) from their pure form.	(16)
9.	Solvent-assisted grinding (SAG) and dry ball milling (DBM)	Naproxen-arginine	Naproxen's solubility was increased 25.3 times (SAG) and 29.3 times (DBM), with the dissolution rate increase of 14.8 times (SAG) and 74.1 times (DBM) from pure naproxen.	(17)
10.	Quench cooling	Valsartan-nifedipine	The dissolution was increased 1,61 times compared to pure valsartan.	(18)
11.	Melt-quenching	Simvastatin-nifedipine	The simvastatin's and nifedipine's solubility were increased 3.7 and 1.7 times compared to pure simvastatin and nifedipine, respectively.	(19)
12.	Cryo-milling	Atenolol (ATE)-hydrochlorothiazide (HCT) (1:1)	The mixture's intrinsic dissolution rate and bioavailability were significantly enhanced.	(20)
13.	Quench cooling (ANQC), solvent evaporation (ANSE), and ball milling (ANBM)	Atorvastatin-naringin (1:1)	The highest solubility was obtained from the co-amorphous prepared by ANSE, with a drug release of 97%.	(21)
14.	Solvent-assisted grinding (SAG) and neat grinding (NG)	α/β-azelnidipine-oxalic acid (2:1, 1:1, and 1:2)	The co-amorphous of β-azelnidipine-oxalic acid (1:2) prepared by ND was the most improved mixture in solubility and stability.	(22)
15.	Ball milling	Carbamazepine (CBM)-citric acid (CA) (1:1)	The intrinsic dissolution rate of the mixture was improved 2.2 times than pure carbamazepine	(24)
16.	Solvent evaporation method	Lacidipine-spironolacton (1:6)	The result demonstrated that lacidipine release was increased in the co-amorphous solid dispersion.	(25)
17.	Ball milling	Mebendazole-aspartame	The result showed that the dissolution rates of mebendazole increased eight times compared with crystalline drug	(26)
18.	Ball milling	Carbamazepine-indomethacin-amino acids (arginine, phenylalanine, tryptophan, and tyrosine), (1:1 and 1:1:1)	The dissolution rate of all co-amorphous drug–amino acid mixtures were significantly increased over the respective crystalline and pure amorphous drugs.	(7)
19.	Ball milling	Nateglinide-metformin hydrochloride (1:1, 1:3, and 1:5) and dose ratio (120 mg:500 mg), till 6 h	The result showed a significant increase in dissolution of nateglinide in co-amorphous.	(27)
20.	Spray drying and hot melt extrusion	Indomethacin-arginine- copovidone	The solubility of indomethacin was improved both in a mixture with arginine or copovidone.	(28)
21.	Solvent evaporation	Loratadine-citric acid (1:1)	The solubility and dissolution of the co-amorphous system (1:1) were significantly greater than the individual amorphous form of loratadine. This system greatly improved the absorption and bioavailability of loratadine.	(29)

22.	Solvent evaporation	Atorvastatin calcium (ATC)-carvedilol (CVD)-glibenclamide (GLN)	There is no significant difference between ATC crystalline and amorphous. The solubility of CVD and GLN was improved in the co-amorphous form.	(30)
23.	Solvent-drop grinding	Pyrimethamine (PIR)-Fumaric acid (FUM)	The mixture's solubility declines as the concentration of FUM increases.	(31)

Milling Method

Milling methods such as ball milling and cryo-milling are the most widely used because they produce stable co-amorphous, easy handling, and low chemical degradation. The final product's properties depend on the drug's temperature, thermal stability, and T_g (Jensen et al., 2014). Process efficiency increases if the grinding temperature is below T_g of the drug, and liquid nitrogen is usually used to reduce the processing temperature. However, implementing this method is laborious and time-consuming, especially with the possibility of contamination with crystal impurities (7, 8). High mechanical pressure, homogeneity, load build-up, phase transformation issues, and temperature are crucial aspects that must be controlled during the process. Product stability is dependent on these settings since the drug crystallizes when the processing temperature exceeds T_g drug, and a higher temperature might enhance the molecular mobility of the drug, causing phase separation. Aside from adhering the product to the walls of the grinding chamber, this tends to exacerbate recrystallization and expense. As a result, this technique must be restricted to thermally stable drugs and co-formers with high T_g (36).

Cryo-Milling

This procedure is typically carried out in a vibration ball mill. Ball glass is soaked in nitrogen liquid to ensure cryogenic conditions. After grinding, they are placed in a desiccator and allowed to reach room temperature. Milling temperatures are significant for solid-state transitions (37). In T <Tg, the material becomes fragile, and a disorganized state form is preferred by mechanical activation. Cryomilling is more effective than conventional dry milling in producing co-amorphous solid dispersion (7). Many research has been conducted employing this approach to increase the solubility of drugs such as sulfamerazine, atenolol, hydrochlorothiazide, simvastatin, and glibenclamide (6, 14, 16).

Dry Ball Milling

When a drop of solvent is injected during grinding, it acts as a medium to promote molecule diffusion and facilitate component reactions. The study found that dry milling produced entirely amorphous salts, whereas adding water resulted in crystal synthesis (38). The solubility of naproxen was successfully increased by using this method (17). In Wairkar et al. (2015)'s study, the use of Ball Milling for the co-amorphous process (6 hours) on nateglinide-metformin hydrochloride at a ratio of 1:1, 1:3, and 1:5 showed a significant increase in nateglinide dissolution. This is due to amorphism in nateglinide, increasing the change of hydrogen interactions (proton exchange between nateglinide and metformin). Nateglinide was completely amorphized and stabilized by metformin HCl (27). Dipeptides and amino acids can also be used as co-former in the ball milling method to improve the dissolution and stability of drugs. Lobmann et al. (2013) reported that using amino acids such as arginine, phenylalanine, tryptophan, and tyrosine can increase the solubility of carbamazepine and indomethacin (7).

Solvent Evaporation Method

The solvent evaporation technique was widely utilized to produce a co-amorphous system in which the active pharmaceutical component and co-former are stoichiometrically combined and dissolved in a solvent that can dissolve both. Solvent evaporation has increased lacidipine's and spironolactone’s solubility and dissolution rate, with an increased solubility of 1.5 times better than pure lacidipine (25). The benefit of this approach is that it may be utilized for thermolabile materials. However, this method requires a more reactive solvent to dissolve API and conformer. Because of circumstances like hydrogen bonds that will not always occur, the pace of creation of co amorphous is slower.

Freeze Dried and Spray Drying Method

The freeze-drying method is known as lyophilization, which involves reducing pressure to remove the solvent in the active medicinal component. This method is not suitable for materials with T_g below -40°C. This method produces a more uniform mixture size (10).

Because the amino acid could not be transformed into an amorphous state, spray drying is the ideal method for drug-amino acid combinations. Lenz et al. 2015 and 2016 reported that using arginine as the co-former successfully increased the dissolution rate of indomethacin prepared by the spray drying method (28, 39).

Conclusion

The co-amorphous preparation methods have their respective advantages and disadvantages. Solvent

evaporation can only be used on a small scale but is safe for thermolabile drugs. Milling techniques are laborious and time-consuming but have a large yield and less chemical destruction, while the quenching method is only intended for thermostable compounds.

Declarations

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Acknowledgment

The author expressed his gratitude to Mrs. Prof. Dr. rer. nat. Anis Yohana Chaerunisaa, Apt., as a lecturer in drug stability, has provided material and instruction in writing this review article.

Conflict of Interest

The authors declare no conflicting interest.

Data Availability

Not applicable.

Ethics Statement

Not applicable.

Funding Information

Not applicable.

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How to cite: Soyata, A., Kenti, K., Sutoro, M., Sagita, N.D.. Impact of Preparation Method in Co-Amorphous System. Sciences of Pharmacy. 2022; 1(1):34-40