CO-AMORPHOUS DRUG DELIVERY SYSTEM

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ABSTRACT

Co-amorphous solids have been employed as a potential method for delivering medications that aren't very water-soluble throughout the past few decades. In comparison to single amorphous constituents, co-amorphous solids with pharmacologically important medicinal compounds or excipients have better physical stability, solubility, dissolution, and bioavailability. We have outlined current developments in co-amorphous solids' physical stability as well as their in vitro and in vivo performances in this study. The importance of molar ratio, molecular interaction, and mobility in determining the physical stability of co-amorphous solids has been highlighted. An in-depth discussion of how co-amorphous materials impact physicochemical qualities in vitro and in vivo is provided in this review.

Keywords: *Co-amorphous system, amorphous solid dispersion, polymers, miscibility, phase separation, stability.*

1. INTRODUCTION

The conversion of potential novel chemical entities (NCEs) into viable medicine is complicated by their poor physicochemical qualities, such as low solubility and permeability. Slow dissolution and limited bioavailability are symptoms of low solubility. A lot of work is needed to increase solubility, dissolution, and eventually bioavailability. Converting crystalline drugs to amorphous forms increases apparent solubility and dissolution, which frequently increases bioavailability. In contrast to crystalline solids, amorphous solids (glass) may contain short-range molecular organization but lack long-range molecular packing order or well-defined molecular conformation. Amorphous materials are more reactive than their crystalline counterparts due to the presence of high internal energy and improved molecular mobility, which causes thermodynamic instability Due to stability issues, however, the actual solubility advantage of these high-energy forms is frequently lost because of amorphous systems' propensity to recrystallize or devitrify into an ordered crystal lattice.

In order to get around many medications' low water solubility, amorphous drug delivery devices have received a lot of attention from academics and the pharmaceutical industry. In a nutshell, the same solid substance can be crystalline or amorphous, and amorphous pharmaceuticals show a much greater solubility and dissolution rate than their crystalline counterparts. Because they are thermodynamically unstable, pure amorphous highly soluble medicines have a physical instability that makes them more likely to recrystallize into the less soluble crystalline form. A prominent area of interest in amorphous research and development is the stability of the amorphous form through the use of excipients, as solely pure amorphous pharmaceuticals sometimes appear to be unfeasible in drug delivery systems. The use of co-amorphous formulations, mesoporous silica, and polymer-based glass solutions are a few strategies that have been proposed in earlier investigations. The co-amorphous technique is the one that has lately attracted the most attention in the pharmaceutical industry since it offers the potential to address the drawbacks of the other two strategies. A review of the state-of-the-art in co-amorphous medication formulations is what this study aims to do.

Solid polymer dispersions have been the subject of some systematic methods for predicting and designing amorphous mixtures. Single glass transition (Tg), which has been experimentally discovered, is a sign of drug-

polymer miscibility. Other techniques for determining miscibility in drug-polymer solid dispersions include calculating solubility parameters, using partition coefficients, rheological techniques, measuring melting point depression, and computational techniques based on X-ray powder diffraction (XRPD) data. Furthermore, miscibility in drug-polymer blends may be evaluated using lattice-based solution models, such as Flory-Hugin's theory, for which the Flory-Huggins interaction parameter () can be taken into account as a measure of miscibility. An indicator of adhesive forces between the medication and polymer would be a negative (or barely positive) value that produced a negative (or slightly positive) enthalpy of mixing between the components and overall negative free energy of mixing.

1.1.WHAT ARE CO-AMORPHOUS FORMULATIONS?

Glass solutions, which are a subclass of solid dispersions, include mesoporous silica, co-amorphous formulations, and glass solutions based on polymers. This section offers a brief explanation of the intricate categorization of solid dispersions because the use of this phrase in the pharmaceutical industry is so erratic. The definition of solid dispersion given by Chou and Riegelman3 in 1971 is "a dispersion of one or more active ingredients in an inert carrier at the solid state prepared by the melting (fusion), solvent, or melting-solvent method." This definition suggests that solid dispersions can be divided into different groups based on the quantity and nature of their solid-state phases. Solid dispersions can come in a wide variety of forms, including eutectic mixes, solid solutions, glass solutions, and glass suspensions, as shown in Table 1. Chou and Riegelman3 and Laitinen et al. offer a more thorough explanation of the many kinds of solid dispersions.

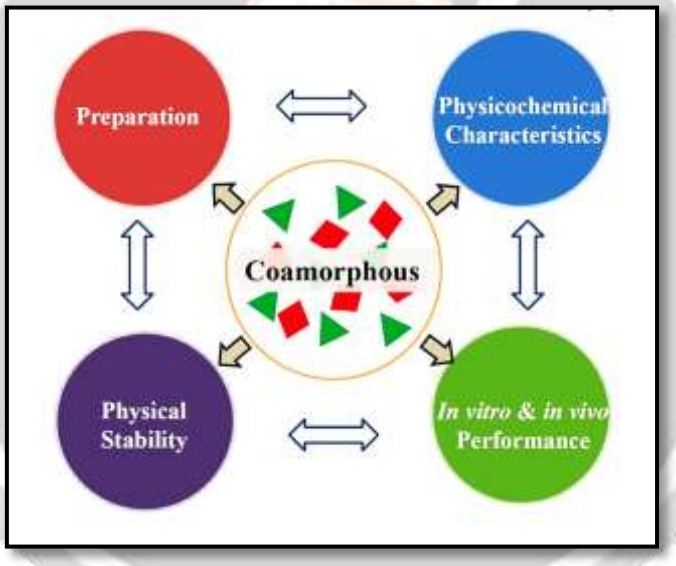

Fig 1:Co-amorphous Formulation

1.2.HISTORY OF CO AMORPHOUS SYSTEM AND ITS CLASSIFICATION

Since a long time ago, amorphous systems have been described that use small molecules like urea, citric acid, and tartaric acid as amorphous stabilisers (Ford and Rubinstein, 1981; Liu et al., 2004; McGinity et al., 1984). Chieng et al. did, however, invent the term "co amorphous" in 2009 (Chieng et al., 2009). This word was created to distinguish an amorphous mixture made up of two tiny molecules from PASD. CAM is described as "a multi-component single phase amorphous solid system lacking periodicity in lattice and associated by weak and discrete intermolecular interactions between the components" (Suresh et al., 2014). They have short-range interactions comparable to amorphous systems of single component systems, such as hydrogen bonding of carboxylic acids, phenols/alcohols, and carboxamides. However, the primary way in which this system varies from cocrystal, salt, or eutectic is due to its amorphous nature, which is indicated by the presence of a broad hump (referred to as an "amorphous halo" in the X-ray diffractogram) (Grohganz et al., 2013). Citing an increase in solubility and dissolution rate brought on by the stabilisation of both medicines' amorphous forms by intermolecular hydrogen bonding, Yamamura et al. created the first drug-drug CAM by combining cimetidine

with naproxen (Yamamura et al., 2000; Yamamura et al., 1996). This possibility was increased when Lu et al. reported using small molecule excipients such citric acid to stabilise the amorphous form of indomethacin. By raising the mixture's Tg through salt production or intermolecular interactions, the amorphous drug was stabilised. There have also been studies of other small compounds, such as sugars, amino acids, nicotinamide, urea, and carboxylic acids (Lu and Zografi, 1998; Serajuddin, 1999). Small molecule-based CAM has been divided into drug-drug and drug-excipient combinations in the sections below.

2.TECHNOLOGIES FOR THE PREPARATION OF CO-AMORPHOUS SYSTEMS:

The literature has provided descriptions of many methods for making amorphous medicines. These strategies may be further separated into two categories, namely thermodynamic disordering processes and kinetic disordering processes, depending on the mechanism at play. The medication is introduced into the thermodynamic route in a melt or solution, which is a thermodynamically stable non-crystalline state. It is necessary to either precipitate the drug from the solution, followed by solvent removal, to acquire the amorphous drug, or the melt must be quenched and subsequently vitrified to produce the drug in its amorphous form. The crystalline substance undergoes direct solid-state conversion into its amorphous form as part of the kinetic route. This can be accomplished by continually introducing crystal disorders and flaws throughout a milling operation by shear pressures, crushing, and impact. Both methods have generally been explained for the creation of amorphous blends. Because the co-amorphous drug formulation strategy is still in its infancy, the bulk of investigations have concentrated on gaining a fundamental knowledge of these systems through the use of small-scale preparative methods such quenching, solvent evaporation, and ball milling. Since only modest sample quantities are needed for screening, all of these procedures are appealing since they offer quick and simple methods of (co-)amorphization. Due to the ability to create and study the co-amorphous systems in situ within a differential scanning calorimeter (DSC), quenching also provides the opportunity to swiftly evaluate crucial physicochemical characteristics including Tg, miscibility, and recrystallization.

3.DEVELOPMENT OF CO AMORPHOUS SYSTEM:

Subtypes of solid dispersions include co-amorphous systems. Co-amorphous mixes were grouped into a solid-dispersion subtype of glass solutions according to the stabilising agent used in a method described by Dengale et al. Since the other types of glass solutions are polymer- or mesoporous silica-based, the co-amorphous drug system method is more particularly a mixture of two or more low molecular weight components that create a homogenous amorphous single-phase system. Since Yamamura et al. indicated that cimetidine may be a possible amorphous carrier and dissolving enhancer for acidic non-steroidal anti-inflammatory medications (NSAIDs) due to salt production, multiple co-amorphous systems have been created (Table 1) utilising various techniques of manufacture., i.e., quenched cooling, kinetic activation, solvent evaporation, and spray drying. The component combinations that can be used are constrained by the preparation techniques used; for example, the drug(s) may deteriorate at the temperatures necessary for co melting, making it difficult to choose a common solvent for solvent evaporation or spray drying techniques. The potential applicability of this multi-component system as a better physicochemical alternative to PASD has increased attention in it during the past 10 years. However, the creation of CAM is not straightforward since choosing the right co-former is a time-consuming procedure that necessitates a thorough analysis of the co-former's crystallisation propensity. Similar to this, additional factors like manufacturing and stability must be carefully taken into account before CAM is transformed into an appropriate dosage form.

3.1.CO-FORMER SELECTION:

The choice of co-former is an important stage in the creation of CAM since it determines the final product's stability and pharmacological efficacy. Co-formers might be low molecular weight excipients or prospective drug molecules. The selection of medication candidates that can work together to build a seamless system poses the biggest hurdle for creating drug-drug CAM. Quantum mechanics may be applied to this process to validate the development of co-amorphous mixture through molecule interactions by identifying distinct molecular interactions in FTIR and Raman spectra and by revealing insights into the near range order of amorphous systems. Using quantum mechanics, Lobmann K et al. looked at how the CAM system of indomethacin and naproxen formed heterodimers.

3.2.PREPARATION METHODS:

There are many known lab-scale preparation techniques for amorphous systems. These preparation techniques may be divided into three categories: thermal (melt quenching), solvent evaporation, and milling (Figure 2). The manufacture of indomethacin: cimetidine and naproxen: cimetidine CAM using ball milling, co-evaporation, and quench cooling were recently compared by Lim W et al. They came to the conclusion that the structural qualities of the finished product were discovered to be caused by the preparation methods, underscoring the significance of the physicochemical properties of pharmaceuticals and excipients, which often define the preparative technique. A few research have described the use of scalable techniques, such as spray-drying, freeze-drying, and ultrasonic extrusion, for synthesizing co-amorphous formulations to establish industrially more practical manufacturing processes. Inkjet printing has also been applied to the creation of co-amorphous indomethacin-arginine systems in order to produce printed fabrications that provide flexible and more individualized dosages and, as a result, the creation of quickly absorbing customized medications.

3.3.SCALE UP:

A CAM system scaling up and manufacturing for commercialization present a significant obstacle. Today's preparation techniques are for lab scale and can produce items weighing a few milligrams to a few grams. The medication may recrystallize from its amorphous state as a result of many processing variables, including temperature, moisture content, solvent characteristics, mechanical stress, and thermal stress. The preparation process is also essential for achieving the intended outcome, which is a stable amorphous product with increased bioavailability. In general, the physicochemical characteristics of the medicine and its co-former—where the melting point and thermal stability of the constituents play a significant role—are crucial factors in the selection of a logical and practical production technique. For screening or optimisation tasks when scale-up is not anticipated, melting procedures are used due to the possibility of non-homogeneity of the end product, where presence of even a tiny proportion of unreacted components may impair the performance of the product, use of jacketed vessels and heat transfer coil systems may not be effective in scaling up of molten technique. The use of melt techniques for CAM preparation is restricted by these problems in addition to in-line deterioration and uneven mixing.

3.4.CHARACTERIZATION (CAM):

Advanced characterization methods are needed to qualitatively and quantitatively characterize the miscibility, phase separation, crystallinity, moisture or solvent residue, molecular interactions, molecular mobility, surface chemistry, and morphology of CAM Understanding the performance and stability of CAM often involves the use of thermal, moisture sorption, and diffractometric instruments. In order to comprehend the stability characteristics of the amorphous system, dielectric spectroscopy, isothermal microcalorimetry, and thermomechanical methods are also used. The primary use and other vibrational spectroscopic methods are to examine molecular interactions between CAM components, and structural changes during phase separation, and to measure crystallinity.

3.5.EVALUATION OF PHARMACEUTICAL AND BIOPHARMACEUTICAL PROPERTIES:

According to an analysis of CAM's stated pharmacokinetic studies, the increased AUC is most likely caused by better solubility. Many CAM showed a significant change in Cmax and AUC. The effects of several CAM medication systems on Cmax varied from 1.3 to a 30-fold increase, while improvements in AUC ranged from 1 to 5 folds. The solubility advantage of amorphous systems was also noted, and this led to a considerable decrease in Tmax. Poor solubility of the medication may have impaired the drug's ability to pass through the GI membrane in the case of P-gp substrates, which in turn restricts the concentration of the drug that can pass into the enterocyte by preventing the saturation of efflux transporters. The enhancement of medications' physicochemical qualities, which are essential for their pharmaceutical and biopharmaceutical performance, is the main driver for the creation of CAM. More than 35 research on CAM has shown improvements in solubility, dissolution, and stability. An excellent example is the CAM system of ritonavir and indomethacin, which exhibits improved chemical stability and is supported by the absence of any additional peak in chromatograms of prepared binary amorphous systems and degrades at 40^0C immediately after being converted into an amorphous form. At all tested temperatures (i.e., 4^0C, 25^0C, and 40^0C), this system's physical stability exhibited superior physical stability for a maximum period of 90 days.

3.6.FORMULATION:

The majority of CAM systems may be formulated into tablets or capsules and are typically meant for oral use. For CAM to be transformed into the final dosage form, it must overcome difficulties such as the sticky and soft character of the product, difficulty in pulverizing and sifting, poor flow, poor compressibility, and stability of the amorphous form of the drug under mechanical pressure. Additionally, these variables may affect how the amorphous drug product dissolves and maintains its stability. Additionally, only a small number of reported CAM were reported to have been formed and stabilized through molecular interactions like hydrogen bonding, charge-assisted interactions, etc. Therefore, mixing CAM with excipients for tablet preparation may hinder amorphous drugs' physical stability and dissolution rate.

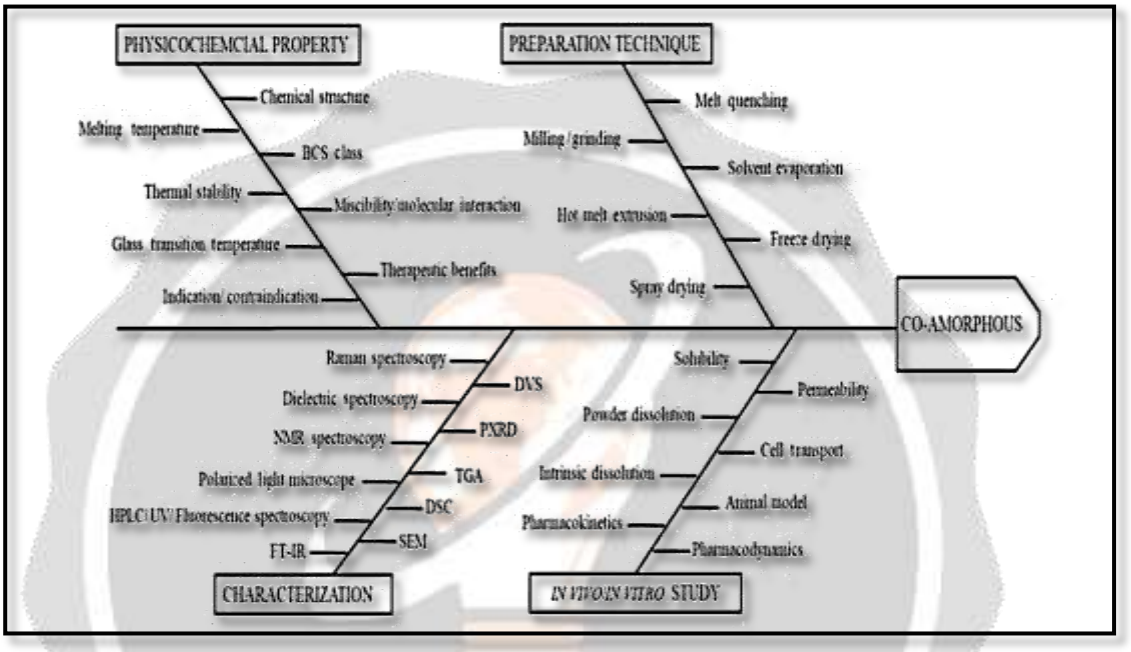

Fig 2: Fishbone Diagram of Co-Amorphous Formulation Development

Developing a resistant co-amorphous formulation with the appropriate pharmacological performances seems to depend on choosing the right co-formers. The co-former selection for co-amorphous systems should be conducted rationally and methodically, based on a complete understanding of the physicochemical characteristics of a medication and its co-former. An in-depth study is needed to clarify the co-amorphous systems' stabilization processes since it is still highly challenging to forecast the physical stability of co-amorphous formulations

4. CONCLUSION:

The last and most important point is that only a few numbers of stabilized co-amorphous delivery methods have been tested in vivo. As a result, it appears that despite intense study spanning two decades, issues with amorphous formulations' dry state stability are still a problem. by using infrared spectroscopy, intermolecular interactions have been experimentally verified. The main weakness in choosing a stabilizing excipient for co-amorphous formulations has been that the intermolecular interaction and miscibility have typically only been examined on an explanatory basis. This is due to the fact that the miscibility of compounds in amorphous formulations has been estimated by calculating various solubility parameters and experimentally determined with DSC. There are relatively few numbers of instances where excipient selection has been made in a predictive manner.

5. REFERENCE:

1. Co Amorphous Systems: A Product Development Perspective, , Rahul B Chavan, Rajesh Thipparaboina, International Journal of Pharmaceutics (2016).
2. Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. Int J Pharm. 2008;364(1):64-75. doi: 10.1016/j.ijpharm.2008.07.023
3. Chen Y, Yu L. Co-amorphous drug delivery systems: a review of preparation, stability, and pharmaceutical applications. J Pharm Sci. 2016;105(2):441-458. doi: 10.1016/j.xphs.2015.12.004
4. Löbmann K, Laitinen R, Strachan C, Rades T, Grohganz H. Advances in amorphous solid dispersion technology: stabilizing poorly soluble drugs. Eur J Pharm Biopharm. 2019;139:189-200. doi: 10.1016/j.ejpb.2019.04.022
5. Bhattacharjee S, Bhardwaj V, Roy S. Co-amorphous drug delivery systems: a promising approach for enhancing drug solubility and bioavailability. Expert Opin Drug Deliv. 2019;16(8):837-854. doi: 10.1080/17425247.2019.1621068
6. T. Vasconcelos , S. Marques , J. das Neves and B. Sarmento , Adv. Drug Delivery Rev., 2016, 100 , 85 —101
7. H. D. Williams , N. L. Trevaskis , S. A. Charman , R. M. Shanker , W. N. Charman , C. W. Pouton and C. J. Porter , Pharmacol. Rev., 2013, 65 , 315 —499.
8. Savjani KT, Gajjar AK, Savjani JK. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm
9. https://www.hindawi.com/archive/2012/195727/
10. https://www.sciencedirect.com/science/article/pii/S0169409X01000989
11. T. Vasconcelos , S. Marques , J. das Neves and B. Sarmento , Adv. Drug Delivery Rev., 2016, 100 , 85 —101
12. https://www.sciencedirect.com/science/article/pii/S0378517302001953
13. Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: I. A thermodynamic analysis. J Pharm Sci [Internet]. 2010 Mar;99(3):1254–64.
14. https://linkinghub.elsevier.com/retrieve/pii/S0022354915327180
15. Jensen, K.T., Blaabjerg, L.I., Lenz, E., Bohr, A., Grohganz, H., Kleinebudde, P., Rades, T., Lobmann, K.,2016a. Preparation and characterization of spray-dried co-amorphous drug–amino acid salts. J Pharm Pharmacol 68, 615–624.
16. Kaushal, A.M., Gupta, P., Bansal, A.K., 2004. Amorphous drug delivery systems: molecular aspects, design, and performance. Crit Rev Ther Drug Carrier Syst 21, 1-62.
17. Masuda, T., Yoshihashi, Y., Yonemochi, E., Fujii, K., Uekusa, H., Terada, K., 2012. Cocrystallization and amorphization induced by drug–excipient interaction improves the physical properties of acyclovir. Int JPharm 422, 160-169.
18. Alhalaweh, A., Alzghoul, A., Kaialy, W., Mahlin, D., Bergström, C.A., 2014. Computational Predictions of Glass-Forming Ability and Crystallization Tendency of Drug Molecules. Mol Pharm 11,3123-3132.
19. Beyer, A., Radi, L., Grohganz, H., Lobmann, K., Rades, T., Leopold, C.S., 2016. Preparation and recrystallization behavior of spray-dried co-amorphous naproxen–indomethacin. Eur J Pharm Biopharm104, 72-81.
20. Grohganz, H., Lobmann, K., Priemel, P., Jensen, K.T., Graeser, K., Strachan, C., Rades, T., 2013.Amorphous drugs and dosage forms. J Drug Deliv Sci Technol 23, 403-408.