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REVIEW ON VARIOUS TECHNIQUES OF SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS WITH SPECIAL EMPHASIS ON CO-CRYSTALLIZATION

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ABSTRACT

The effectiveness and bioavailability of pharmacological substances are significantly influenced by solubility, especially for medications that are poorly soluble in water. Particle size reduction, salt generation, and solid dispersions are some of the methods that have been developed to improve solubility in order to address this difficulty. To increase solubility and dissolution rates without chemically altering the active pharmaceutical ingredient (API), co-crystallization has shown to be a very successful technique. One or more co-formers and the API are joined by non-covalent bonds such hydrogen bonds to produce cocrystals. Solubility, stability, and bioavailability are among the physicochemical characteristics of the drug that can be fine-tuned using this method. Solution crystallization, solid-state grinding, and solvent evaporation are among techniques that can be used to accomplish co-crystallization; each has unique benefits with regard to efficiency and scalability. Because of this, co-crystallization is a particularly useful and often used method for improving solubility in medication development.

KEYWORDS: Solubility, Co-crystallizations, BCS, API, Co-former, Dissolution.

INTRODUCTION

The best method for delivering the dose form is orally. The primary issue encountered while delivering the active drug orally is its bioavailability & Solubility. The maximum amount of solute that can dissolve in a given amount of solvent or amount of solution at a given temperature is known as solubility.[1] It refers to a transparent, homogenous molecular dispersion formed by the continuous interaction of two or more compounds. The greatest amount of solute dissolved in a solvent at equilibrium is how it is measured.[2] Various methods such as micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, co-crystallization etc. are commonly utilized for medication solubilization. A common problem in both formulation design and development and screening tests of novel chemical entities is the solubilization of poorly soluble medicines to reduce that problem various methods are used.[3]

Need of Solubility

A number of characteristics, the most important of which are the drug's poor water solubility and poor membrane permeability, can limit the absorption of the drug from the GI tract. An oral active drug must dissolve in stomach or intestinal fluids in order to pass through the GIT membranes and enter the systemic circulation.[4] Thus, increasing the solubility and dissolution rate of medications that are weakly water soluble and increasing the oral bioavailability of active substances are two fields of pharmaceutical research that concentrate on this goal. A scientific framework known as the BCS is used to categorize medicinal substances according to their intestinal permeability and water solubility. About the rate of BCS class II and IV medications so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs.[5]

BCS Classification

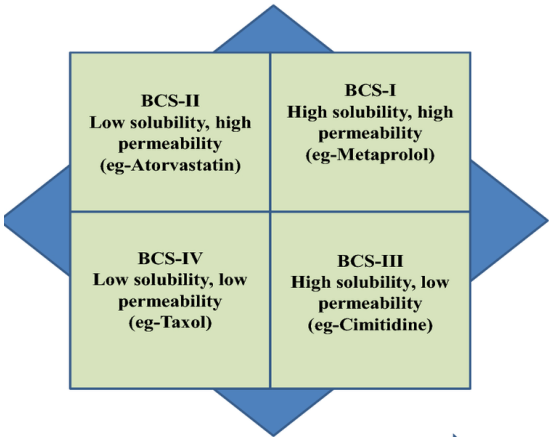

Figure 1: Provisional BCS Classification.

Class I

High Permeability and Solubility Drugs classified as class I exhibit high numbers for both absorption and dissolution. When at least 85% of a product dissolve within 30 minutes of in vitro dissolution testing across a range of pH values, nearly 100% absorption can be predicted for those Class I compounds formulated as immediate release products. As a result, in vivo bioequivalence data are not required to ensure product comparability. For example, metoprolol, propranolol, diltiazem, and verapamil.[6]

Class II

High Permeability, Low Solubility Drugs in class II have a low dissolution number and a high absorption number. Apart from a very large dose numbers, in vivo drug dissolution is then a rate-limiting step for absorption. Since these products' bioavailability is probably dissolution-rate limited, a relationship between in vitro dissolving rate and in vivo bioavailability may be seen. For instance, phenytoin, mefenamic acid, ketoconazole, danazol, and nifedinpine.[7]

Class III

Low Permeability, High Solubility The rate-limiting step in medication absorption in this class is permeability. The pace and volume of drug absorption for these medications vary greatly. There has been a suggestion that waiver criteria similar to those associated with Class I compounds may be appropriate, provided that the test and reference formulations do not contain agents that can modify drug permeability or GI transit time. Dissolution is likely to occur very quickly, but absorption is permeability-rate limited. For instance. Neomycin B,

Acyclovir, Cimetidine, and Captopril.[8]

Class IV

Low Permeability and Solubility These substances typically do not absorb well through the intestinal mucosa, and their very low oral bioavailability is predicted to be highly variable. In addition to being challenging to dissolve, these substances frequently exhibit insufficient permeability through the GI mucosa after dissolution. These medications frequently show significant inter- and intra-individual variability and are exceedingly difficult to synthesize.[9]

Factors Affecting Solubility

1) **Temperature:** A solid's solubility in a liquid is contingent upon its temperature. If heat is absorbed during the solution process, the solute's solubility rises as the temperature rises. For the majority of the salts, this is the case. The solubility of a solute will decrease as temperature rises if the solute releases heat during the solution process.
2) **Solute molecular structure:** A compound's solubility in a particular solvent can be significantly affected by even small changes to its molecular structure. For instance, adding a hydrophilic hydroxyl group can significantly boost a chemical's water solubility. Moreover, when a molecule is changed from a weak acid to its sodium equivalent, it dissolves in water with a notably greater degree of ionic dissociation.[10]
3) **Particle size of the solid:** A substance's solubility increases with decreasing particle size due to variations in interfacial free energy that occur during the dissolving of particles of different sizes. When the particles have a very small radius, the gain in solubility that occurs with a decrease in particle size stops, and any further decrease in size results in a fall in solubility.[11]
4) **Pressure:** The solubility of liquids and solids in water are not appreciably affected by increased pressure. The solubility of gases significantly increases with pressure. According to Henery's law, the increase in solubility is directly proportional to the increase in pressure.
5) **Stearic factors:** Solubility is also affected by dimension of structure and its configurations.[12]
6) **pH:** A weakly acidic drug's solution or its salt will have a higher concentration of unionized acid molecules if the pH of the solution is lowered. Because the solubility of the unionized species is lower than that of the ionized form, precipitation may therefore

occur. Conversely, a higher pH promotes precipitation in solutions containing weakly basic medications or their salts.

7) **Complex formation:** The addition of a third component that forms an intermolecular complex with the solute can enhance or reduce the solute's apparent solubility in a given liquid. The apparent change in the solubility of the original solute will depend on how soluble the complex is.[13]

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Techniques To meet the challenge posed by insoluble compounds, various technologies have emerged, and these technologies have made a difference. The following techniques for overcoming poor drug solubility are discussed:

I. Chemical modification

a) Salt formation
b) pH adjustment
c) Co-solvency
d) Hydrotropic
e) Solubilizing agents
f) Nanotechnology
g) Co-crystallization.[14]

II. Physical modifications

a) Particle size reduction
b) Micronization
c) Nanosuspension

III. Modification of the crystal habit

a) Polymorphs
b) Pseudo-polymorphs

IV. Complexation

V. Solubilization by surfactants

a) Microemulsions
b) Self-micro-emulsifying drug delivery system.[15]

VI. Drug dispersion in carriers

a) Solid solution

b) Solid dispersion.[16]

Chemical Modification

Salt formation: Many times, various instability issues prevent an API from being created in its purest form. The products of this conversion include polymorphs, solvates, hydrates, cocrystals, and salts. Salt production has been used to improve weak acids and bases, which are poorly soluble therapeutic candidates. When a material ionizes in solution, salts are created. It is effective in parenteral and other liquid formulations, as well as solid dosage forms. A salt is created when a basic or acidic medication is changed into a salt that is more soluble than the original basic medication. For example, whilst diclofenac sodium is soluble in water, diclofenac itself is not.[17]

By altering pH: Generally, the drug must remain in unionized form in order for the dosage form to be absorbed; however, occasionally, the medication is not soluble in the GIT (small intestine, stomach, and big intestine) fluids and solubility is the primary criterion for medication absorption; thus, the drug candidate's pH must be changed to enhance solubility. Drugs with higher pH values will dissolve or ionizable in stomach fluid, while lower pH drugs will dissolve in intestinal fluid.[18]

Co-solvent: It is well-known that the adding of an organic co-solvent to water can intensely change the solubility of drugs. Weak electrolytes and nonionic molecules have poor water by the adding water miscible solvent in which the drug has good solubility the solubility of a poorly water soluble drug can be improved frequently known as co solvents also known as solvent blending. Co-solvent formulations of poorly soluble drugs can be administered parenterally and orally. It is also commonly mentioned as solvent blending. Most co solvents have hydrogen bond donor and acceptor groups as well as small hydrocarbon areas. Their hydrophilic hydrogen bonding groups confirm water miscibility, while their hydrophobic hydrocarbon regions inhibit with waters hydrogen bonding network, reducing the overall intermolecular attraction of water.[19]

Hydrotropy: It refers to a rise in solubility in water brought on by a significant number of chemicals. Through complexation, which involves a mild interaction between the solute and hydrophobic agents (urea, sodium benzoate, and sodium alginate), it improves solubility. For

example, sublimation of theophylline using sodium alginate and acetate.[20]

Mechanism of action of Hydrotropes: Compounds with an anionic group and a hydrophobic aromatic ring or ring system are known as hydrotropes. Anionic groups and the ring system interact with the solution to be dissolved to promote hydrophilicity. The process of hydrotropy is linked to complexation, which is the interaction of hydrotropic substances such sodium alginate, urea, nicotinamide, and sodium benzoate with lipophilic medicines.[21]

Solubilizing Agents: Different solubilizing materials, such as PEG 400, can also increase the solubility of poorly soluble drugs. For example, PEG 400 increases the solubility of hydrochlorothiazide. The study and application of materials and structures at the nanoscale level, or 100 nanometres (nm) or less, is referred to as nanotechnology. Nanonization is the process of turning medication powder into nanocrystals, which range in size from 200 to 600 nm, for example. Amphotericin B. Currently, the fundamental methods for creating nanoparticles are

- Millin
- Homogenization in water (wet milling as in a colloid mill)
- Homogenization in non-aqueous media or in water with water-miscible liquids
- Precipitation
- Cryo-vaccum method.[22]

Nanotechnology

Nanomorph Without the need for physical milling or grinding processes, this technique transforms pharmaceuticals with limited water solubility from a course crystalline state into amorphous nanoparticles. Here, a chamber is filled with the drug ingredient suspension in solvent, and the mixture is quickly combined with another solvent. The drug substance precipitates as a result of this. The polymer stops the drug material particles from growing or aggregating, maintaining them in their nanoparticulate condition.[23]

Nanosuspensions - Colloidal dispersions of nanoscale drug particles stabilized by surfactants are known as nanosuspensions. These are biphasic systems made up of pure drug particles scattered over an aqueous vehicle with suspended particles less than one micrometre in diameter.[24]

Co-crystallization - "Solids that are crystalline materials composed of two or more

molecules in the same crystal lattice" is how the FDA defines cocrystals. A subset of cocrystals are known as pharmaceutical cocrystals. From relative obscurity, pharmaceutical cocrystals have quickly evolved is a class of crystal formations that has been extensively researched in relation to pharmaceutical science and engineering.[25] Similar to salts, cocrystals are solid forms that, if unique, may be subject to patents. They are also known to alter crucial physicochemical characteristics like solubility, stability, and bioavailability. As a result, they can be used as an API in formulations for either extended or immediate release.[26]

Co-crystallization is the area of maximal development and interest being diverted. Co-crystallization is only possible when certain physiochemical characteristics (Hygroscopicity, overall formulation solubility and compaction behaviour) is enhanced. In essence, co-crystals are made up of two parts: the former and the API. The former can now be any additional excipient or API that, when administered in combination, lowers the dosage and adverse effects. Therefore, altering the pharmaceutical qualities (chemical stability, bioavailability, solubility, melting point, moisture uptake, dissolution, etc.) will also alter the API, even if the latter remains unchanged.[27]

COCRYSTALS COMPONENTS

Cocrystal is composed of

- API (Active Pharmaceutical Ingredient)
- Co-former
- Solvent

Pharmaceutical ingredients - That have a direct biological effect or any other direct influence in the diagnosis, treatment, mitigation, or prevention of disease are known as active ingredients (APIs). Unlike polymorphs, which have a single API in the crystal lattice, cocrystals contain many APIs.[28]

Co-former - Any excipient or API that enhances the drug's physicochemical properties can be used as a co-former. Proper co-former selection and screening can enhance an API's solubility, dissolving rate, permeability, stability, and manufacturability. In order to meet regulatory criteria, the co-former must be safe, nontoxic, and free of substances that could cause cancer, mutagenesis, teratogenicity, etc.[29]

By selecting the molar or stoichiometric ratios of successful co-formers (1:1, 1:2, and 1:3), the ideal formulation can be found. For the manufacture of cocrystals, the 1:1 ratio is thought to be both safe and effective because ratios 1:2 and 1:3 demonstrated enhanced aqueous solubility and dissolving rate, but adding additional co-former grade is not safe.[30]

Solvent - Chemical A substance that dissolves another chemical to produce a mixed solution that is homogeneous is called a solvent. Both the API and the former should dissolve in the selected solvent in a cocrystal formulation.[31]

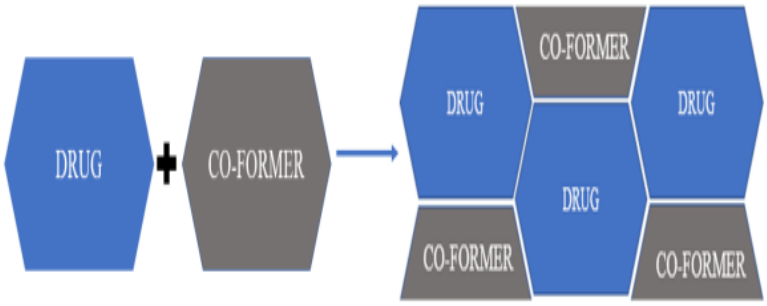

Figure 2: Schematic representation of cocrystal formation.[31]

SCREENING OF COFORMER - Research that has recently been published has used a range of strategies to identify the suitable conformer, including the following. Choosing co-formers and their compatibility with particular APIs is a major barrier to pharmaceutical crystal production.

- Supramolecular synthon
- Hansen solubility parameters
- Database of the Cambridge Structure (CSD)
- pKa models
- Hydrogen bonding propensity (HBP)
- Fabian's process
- Lattice energy calculations
- Conductor-like screening model for real solvents (COSMO-RS)
- Virtual cocrystal screening (Based on Molecular Electrostatic Potential Surfaces MEPS)
- Thermal analysis
- Measuring saturation temperatures
- Kofler contact method.[32,33]

Co-crystallization Method of preparation.[3]

A. CONVENTIONAL METHOD

1) Solvent evaporation method
2) Slurry method
3) Anti-solvent addition method or Anti-solvent co-crystallization
4) Grinding method

B. ADVANCED TECHNIQUE

1) Hot melt extrusion
2) Spray drying
3) Electrohydrodynamic atomization
4) Supercritical fluid technology
5) Microwave-assisted synthesis
6) High shear granulation
7) Ultra sound assisted solution

1. **Solvent Evaporation -** The simplest co-crystallization method is solvent evaporation. Using a proper stoichiometric ratio, the drug and co-former are dissolved in a common solvent and allowed to evaporate. The molecules' solution alters during evaporation as a result of hydrogen bonds forming between various functional groups, producing a product that is thermodynamically preferred. The intrinsic dissolution rate of benzoic acid, fumaric acid, and succinic acid was found to be higher when fluoxetine hydrochloride was combined with these co-formers. Co-formers of isonicotinamide, malonic acid, and maleic acid were used to create norfloxacin co-crystals. The method's drawback is the substantial amount of solvent it requires.[34]

2. **Grinding Method**

- **Solid-state grinding technique or neat grinding:** This process of co-crystallization doesn't use a solvent. The cocrystal is produced by admixing the right stoichiometric proportions of solid components, pressing and crushing them together using a mortar and pestle, ball mill, or vibrator mill. The typical grinding time is between thirty and sixty minutes. This technique can be used to manufacture a large number of cocrystals, and any failure is usually the result of using the incorrect settings. The specific surface area of interaction between the materials is increased for the formation of intermolecular bonds when the particle size is reduced. This has the advantage of higher selectivity as

compared to dissolution-based co-crystallization. It is easy to use and enables rapid cocrystal preparation .Cocrystal mixing experiments with several substances that can also produce cocrystals the API has been completed. In the latter scenario, a new conformer is added, which can be utilized to reveal different cocrystal alterations or gauge a cocrystal's stability in the presence of additional excipients.[35]

- **Liquid-assisted grinding, or solvent-drop grinding:** This technique, which modifies neat grinding by incorporating a tiny quantity of solvent into the grinding process, has been applied to improve crystalline systems' supramolecular selectivity, both polymorphic and stoichiometric. A very tiny amount of solvent (~a few tenths of an equivalent amount of solvent per mole of the component) is added after the two components have been mixed. Given that the solvent's little quantity does not contribute to the finished product, its action can be characterized as catalytic. Its benefits include enhanced performance, controllable polymorph formation, and better product crystallinity; also, a wide range of co-formers are appropriate for co-crystallization. The co-crystallization rate is increased by this technique, as some cocrystals demonstrated inadequate cocrystal formation performance after neat grinding for a sizable duration. The preparation time for high-purity cocrystals can be greatly decreased by using this technique.[36]

3. **Slurry method:** Slurry methods are straightforward procedures that require minimal volumes of solvent. In this process, the drug and co-former are fully mixed with the solvent. The resulting slurry solution is stirred as the co-crystallization process proceeds. The solvent is then allowed to evaporate at room temperature to provide the resultant cocrystals. The primary deciding factor in the co-crystallization process is the solvent selection.

Process involve in slurry method - Slurry method solvent reduced method, In this method, drug and solvent dissolved in suitable solvent in small amount to form muddy consistency, Solvent is allowed to evaporate in room temperature, Cocrystal are form.[37]

4. **Anti-solvent addition method -** If a material cannot be dissolved, it is referred to as an antisolvent. In this process, an organic solvent or buffer is added to the drug and coformer medium to supersaturate them. The extra fluid that is soluble in the medication and solvent need to combine for the cocrystal to precipitate. This procedure's drawback is the large amount of solvent required for preparation. Drug and solvent are mix well and then anti solvent is added, The solvent and the antisolvent must be miscible, creating phase, solvent is evaporated and cocrystal are formed.[38]

5. **Spray drying -** Spray dryers are used in the co-crystal manufacturing process. The process of turning liquids (solutions, suspensions, and slurries) into solid powders is continuous and only requires one stage. To achieve high-quality cocrystals, mix the drug and coformer solution in a standard evaporating solvent and then mist the mixture into a heated air stream to cause the solvent to evaporate. Due to its quick, continuous, and one-step nature, this technique is the most widely employed one. Consequently, the process of spray drying will offer a unique atmosphere. Spray drying was utilized by Urano et al. to produce co-crystals of clostazol-hydroxybenzoic acid (CLZ-HBA). The characteristics of CLZ-HBA co-crystals made by slurry, spray drying, and solvent evaporation were compared by the author. The results show that the spray drying method works well for dissolving CLZ and coformers was enhanced. This implies that poorly water-soluble pharmaceutical co-crystals could be successfully produced by the spray drying procedure.[39]
6. **Hot melt extrusion-** The most used processing method in the polymer and plastics sectors is HME. Its application in the pharmaceutical business began in the 1970s, while its introduction to the plastics industry dates back to 1930. HME is extensively used in the pharmaceutical industry to prepare granules, pellets, tablets with sustained release, transdermal, and transmucosal drug delivery systems. Implants, amorphous dispersion, and delivery method. But only in the past few years has its application for mechanochemical co-crystal formation come to light. HME is a continuous process that creates homogeneous pellets or strips by drawing materials toward a die at a constant screw speed and elevated temperature. The compact material packing and effective mixing that HME provides improve the surface contact between the drug and coformers, enabling co-crystal formation without the use of solvent.[40]
7. **Electrohydrodynamic atomization** - EHDA, also known as electrospraying, is a flexible technique that uses electrically charged fluids. It is derived from the electrospinning process, which creates micro- and nanofibers but also particles. It is easily operated in a continuous way and is reproducible since the process parameters may be controlled. It might therefore take the place of several unit operations in the pharmaceutical manufacturing process. The key benefits of EHDA over other traditional techniques (such nanoprecipitation) are its simplicity, one-step process, narrow size distribution, and ability to create particles without the need for stabilizers or surfactants. Furthermore, the products are gathered as dry powders with very little solvent residue. Wang et al., for instance, looked at the residual quantity of 1,2-dichloromethane in gathered polymeric

microparticles produced by EHDA with the use of mass spectrometry and gas chromatography.[41]

8. **Supercritical fluid technology -** Over the past ten years, supercritical fluid technology has grown significantly, especially in the materials processing industry where it is increasingly being suggested as a replacement for numerous traditional solvent-based processes. Supercritical fluid methods have been employed by multiple authors to produce micro and nanoscale particles of various materials, including polymers, oxides, metals, pharmaceutics, semiconductors, and superconductors. These materials find applications in nearly every industry, including plastics, energy, electronics, aerospace, pharmaceutics, and medicine. A supercritical fluid's density is related to its solvent power. A substance's density and solvating power approach those of a liquid above its critical point. As a result, tiny variations in the supercritical fluid's temperature and pressure will result in large changes in its density and solvent power, enabling the dissolution of a wide range of solutes in it. The capacity to induce the solute(s) initially dispersed in the liquid solvent is provided by the second fundamental attribute of supercritical fluids, namely, their miscibility with organic liquids. This creates a rivalry between two simultaneous phenomena.[42]
9. **Microwave-assisted synthesis -** When electromagnetic waves in the frequency range of 0.3 to 300 GHz contact with polar and polarizable materials, they cause "dielectric heating. "The molecules change direction in accordance with the microwave frequency as they align and orient themselves with the applied electric field upon irradiation. Molecular friction is produced by the recurrent alignment, randomization brought on by thermal motion, and realignment in the opposite direction. This friction is converted into heat. In 1986, microwaves were first used in synthetic chemistry. There have been studies on the use of microwave heating to create inclusion compounds from 2002 and 2004. A co-crystal loratadine inclusion complex was created in 2008 using microwave irradiation, and the results showed an increase in solubility and bioavailability. 2013 saw the report and demonstration of 1: 1 and 2: 1 caffeine–maleic acid cocrystals made by microwave technique, along with the impact of the solvent's dielectric characteristics on the microwave interaction. Caffeine acid phenethyl ester co-crystals with enhanced characteristics that were made using a microwave process were published in literature. In this work, we investigate the production of cocrystals of two sulfa medicines, sulfamethazine (SMT) and sulfamerazine (SMR), using microwave heating as the source of heating energy. However, we also show by comparison with normal

conductive/convective heating to the same temperature that the microwave heating is much more efficient in promoting the formation of co-crystals.+

10. High shear granulation

It was discovered that high-shear wet granulation was a workable technique for producing cocrystal grains. The duration of the solids' exposure to the granulation liquid (water), the volume of liquid, the granulator's impeller speed, and the excipients (hydroxyl propylcellulose, microcrystalline cellulose, and calcium hydrogenphosphate) utilized in the formulation all affected the development of cocrystals. The excipients had a significant impact on storage stability because they caused the formation of the weakly water-soluble salt calcium tartrate monohydrate at high relative humidity when calcium hydrogenphosphate was present. It's interesting to note that cocrystal formation improved compactability more than reference granules (pirace-tam and the corresponding excipients). Cocrystal formation resulted in a small decrease in drug release, most likely because the cocrystal was less soluble. When calcium hydrogenphosphate is present When compared to reference tablets, there was no discernible impact of cocrystal formation on compactability or drug release. The valuable, if intricate, process of making cocrystals by high-shear wet granulation was determined. Pre-formulation research on cocrystal formation is recommended since it may have an impact on compactability, drug release, and overall medication performance.[44]

Applications of Co-crystals in Pharmaceutical Industry

Sector Co-crystals have several advantages over other solid-state drug modification processes, such as complexation, solid dispersion, micelle solubilization, co-solvency, etc., in the pharmaceutical industry because of their simple manufacturing process. Experts think that the co-crystallization technique may have positive effects on the pharmaceutical industry's intellectual property landscape. Using coformers based on sugar for co-crystallization can hasten the pace of dissolution. Co-crystals of hydrochlorothiazide were made using sucrose as a coformer. The resultant co-crystal exhibited enhanced dissolving rates as well as flavor masking. When combined with APIs, nutraceuticals which are health-beneficial can offer greater overall health benefits.

Pharmaceutical experts have also shown a growing interest in multi-drug Co-crystal (MDC) in recent times. In some circumstances, MDC may be preferable to pure pharmaceutical components. discussed the advantages of employing the solvent evaporation process to produce the anti-diabetic medications glimepiride (Gli) and metformin (Met), including

improved solubility, bioavailability, and the capacity to stabilize unstable APIs through intermolecular interactions. Among the notable physicochemical changes shown by the research were improved solubility and dissolving rate compared to glimepiride, as well as decreased hygroscopicity and stronger accelerated stability than the parent medicine Met. During processing, co-crystals are also used to separate and purify the API. Drugs having a weak ionization character are frequently treated with co-crystallization techniques. Another function of co-crystals is crystallization inhibitor, prolonging the time that supersaturation is maintained during dissolution. In turn, this aids in boosting the drug's bioavailability and controlling its release.[45]

PHYSICAL MODIFICATIONS

1. Particle Size Reduction: Size reduction approaches utilizing different milling processes are well-established and are commonly included in formulation development procedures. The two basic methods for doing this are micronization and nanosuspension. Particle surface area grows as particle size decreases, increasing the solubility of the particle. The process of sonocrystallization is occasionally employed to reduce particle size as well.

2. Modification of Crystal Habit: The capacity of an element or compound to crystallize in more than one crystalline form is known as polymorphism. Despite having the same chemical makeup, different pharmacological polymorphs have distinct physicochemical characteristics, such as solubility, melting point, density, texture, and stability. Similar to this, an amorphous medication is usually preferable to a crystalline one because of the increased surface area and higher energy involved. The order in which the various solid drug forms dissolve is Amorphous > Metastable polymorph > Stable polymorph.[46]

3. Complexation: The association of two or more molecules to create a non-bonded entity with a precisely determined stichiometry is known as complexation. Relatively weak forces like London forces, hydrogen bonds, and hydrophobic contacts are necessary for complexation.7,12. Molecular complexes, polymers, inclusion complexes, chelates, EGTA, and EDTA are a few examples of complexing agents. cyclodextrins.[47]

4. Solubilisation By Surfactants: Molecules known as surfactants have separate polar and nonpolar sections. A polar group is joined to a hydrocarbon segment in the majority of surfactants. Anionic, cationic, zwitterionic, or non-ionic might be the polar group. The hydrophobic center of the micelles might get crowded with tiny polar molecules when they

are introduced. The solubilization process is crucial to both biological and industrial systems. Surfactants can boost a drug's solubility in an organic solvent while also lowering surface tension. The technologies that have emerged to address the problem of insoluble compounds are the main topic of this article, with a focus on solid dispersion. Despite the fact that partical size decrease, salt formation, etc. are sometimes employed to speed up the drug's dissolving rate; however, these methods have practical limitations, thus the intended improvement in bioavailability could not always be realized. Thus, formulation strategies are being investigated to improve the bioavailability of medications that are not very water soluble. Making a solid dispersion is one such formulation strategy that has been demonstrated to greatly improve the absorption of such medications. It has been shown that solid dispersion of an amorphous medication in a polymer matrix is a useful method for improving solubility and, consequently, bioavailability.[48]

SOLID DISPERSION - The concept of solid dispersion was first presented by Sekiguchi and Obi. The dispersion of one or more active substances in an inert carrier in a solid form is referred to as a "solid dispersion" and is commonly made using the solvent technique, fusion solvent method, or melting (fusion) method. But the concept can now be expanded to encompass specific nanoparticles, microspheres, microcapsules, and other drug dispersions in polymers made by any method. A few years later, Goldberg et al. reported that not all drugs in solid dispersion are necessarily presented in a microcrystalline state; rather, some drugs may be present as molecular dispersion in the matrix, which forms microcrystalline particles. Sekiguchi and Obi had proposed that the drug was present in a eutectic mixture in a microcrystalline state a solid solution[49].Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers.

Carriers for Solid Dispersions

Acids – Citric Acid, Tartaric Acid, Succinic Acid.

Sugars – Sucrose, Dextrose, Sorbitol, Maltose, Galactose, Xylitol.

Polymeric Materials – Polyvinyl pyrrolidone, PEG 4000 & 6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium Alginate, Dextrin, Cyclodextrin.

CLASSIFICATION OF SOLID DISPERSION

1. Simple Eutectic Mixtures
2. Solid Solutions
3. Glass Solution & Glass Suspension
4. Amorphous precipitation In Crystalline Carrier
5. Compound Or Complex Formation.[50]

CONCLUSION

Enhancing the solubility of poorly water-soluble drugs is a major challenge in pharmaceutical development, especially for oral formulations where solubility directly affects bioavailability. While several conventional methods exist, co-crystallization has emerged as a particularly promising approach. This technique allows for significant improvements in solubility, dissolution rate, and stability without chemically modifying the active pharmaceutical ingredient (API). By forming cocrystals through non-covalent interactions with suitable co-formers, it is possible to fine-tune the physicochemical properties of a drug to enhance its therapeutic effectiveness.

Co-crystallization is also advantageous due to its adaptability to various preparation methods such as solution crystallization, solvent evaporation, and solid-state grinding, offering both efficiency and scalability. Its growing application in drug development highlights its potential as a valuable strategy for improving the performance of poorly soluble drugs. As research progresses, co-crystallization is likely to play an increasingly important role in modern pharmaceutical formulation.

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