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APPROSPECTIVE SCHEMATIC PROCESS OF VARIOUS TECHNIQUES ON SOLID DISPERSION – A REVIEW

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ABSTRACT: -

For enhancement of solubility and dissolution rate of poorly soluble drugs, abundant commercially viable methods are available such as liquisolid, in which a drug in solution state or dissolved drug is adsorbed over insoluble carriers. Therefore, to progress the bioavailability of poorly water-soluble compounds like biopharmaceutical classification system class II and class IV drugs, polymer matrices of various origins can be used. A series of dosage forms known as "solid dispersions" are used to refer to a method of dispersing a medication in a physiologically inert matrix, typically in order to improve oral bioavailability. In this process, there are many techniques that which perform on solid dispersion. Various methods such as grinding, co-precipitation, lyophilization, and spray drying are available to prepare solid dispersion in which the drugs are present in the amorphous state.

Keywords: -

Solubility enhancement, BCS classification, oral bioavailability, poorly water-soluble drugs, amorphous solid dispersions.

INTRODUCTION:

Biopharmaceutics classification system (BCS): - Was introduced by us Food and Drug Administration (FDA) and it classifies the drug into four classes according to solubility and permeability. Solubility impediments are faced as the class II and class IV of the system facing dissolution as the rate-limiting step for the absorption of the drug due to low solubility[(1)].

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

Solubility is a significant physicochemical factor affecting the absorption of a drug and its therapeutic effectiveness. Formulation development would lead to failure if the drug has poor aqueous solubility. The low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently need inadequate bioavailability. The venture to improve the solubility and dissolution of hydrophobic drugs remains one of the trickiest tasks in drug development[2].

For enhancement of solubility and dissolution rate of poorly soluble drugs, abundant commercially viable methods are available such as liquisolid, in which a drug in solution state or dissolved drug is adsorbed over insoluble carriers[3]. To improve wettability and solubility of various lipophilic substances surfactants can also be used in formulations[4]. Micronization of the drug is not ideal because the micronized product has the propensity of agglomeration, which leads to reduced effective surface area for dissolution. however solid dispersion is the mainly promising method for formulators because of its simplicity of preparation, ease of optimization, and reproducibility[5].

The term 'solid dispersion' has been employed to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually to enhance oral bioavailability[6].

"The dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting [fusion], solvent, or melting-solvent method" is the definition given by Chiou and Riegelman to solid dispersion systems. In contrast to the matrix, which is hydrophilic, the medication is hydrophobic. Simple eutectic mixes, solid solutions, glass solutions, suspensions, amorphous precipitation in a crystalline carrier, compound or complicated forms, and so on can all be considered types of solid dispersions[7].

Absorption of the drug and its therapeutic effectiveness are affected by solubility which is a significant physicochemical factor. Poor aqueous solubility can lead to failure in the formulation development process. The main reason behind the adequate bioavailability of the drug is its low dissolution rate and low solubility in an aqueous medium. Most of the drug substances were innovated by the venture to improve the solubility and dissolution of hydrophobic drug substances remains one of the trickiest tasks in drug development. Dissolution of drugs in an aqueous medium like gastric fluid is important for better absorption and bioavailability for orally administered drugs. Therefore, to progress the bioavailability of poorly water-soluble compounds like biopharmaceutical classification system class II and class IV drugs, polymer matrices of various origins can be used[8].

Enteric polymers have been used historically as tablet coatings to delay drug release until after the formulation has existed in the stomach. Ideally, the enteric coating dissolves rapidly when the pH of the gastrointestinal milieu reaches the threshold of the pH, where the polymers become soluble[9].

HPMCAS (Hydroxy propyl methyl cellulose acetate succinate), polyvinyl acetate, HPMCP (Hydroxy propyl methyl cellulose phthalate and polymethacrylates. These polymers are used in the amorphous solid dispersion for enteric coating[10]. Many polymers in particular cellulose derivatives, are effective crystallization inhibitors, delaying nucleation and suppressing crystal growth[11].

Thus, in contrast to enteric coatings drug may be released from the Amorphous Solid Dispersion (ASD) formulations at the low pH conditions of the gastric compartment followed by rapid polymer dissolution and release of the remaining drug in simulated intestinal fluid[12].

ASDs of drug enteric polymers are fundamentally different from enteric coatings in that the drug is blended with the polymer in the ASD formulation, where by the molecular level mixing of the drug and polymer can impact the polymer dissolution process and vice-versa[13].

Polymer dissolution is complex and involves the following steps;

- Ingress of water into the polymer matrix.
- Disentanglement of polymer chains.
- Release of polymer at the surface and diffusion across the aqueous boundary layer[14].

Increasing number of poorly water-soluble drug candidates is one of the most pressing issues in the pharmaceutical industry[15].

Low aqueous solubility prevents the active pharmaceutical ingredient from being bioavailable and biologically active one of the approaches for dissolution enhancement is creating amorphous solid dispersion achieving super saturation of active pharmaceutical ingredients[16]. An alkalizer has a reasonable pH modification in preparation for the micro pH modification of a weakly acidic drug[17]. In recent years, there has been an increase in the number of APIs that have low solubility leading to limited oral bioavailability[18]. However, supersaturated solutions are thermodynamically meta-stable/unstable and tend to undergo crystallization[19].

Drug polymer interaction may include pie-pie interaction, ionic interaction, and hydrogen or halogen bonding, with non-specific interaction between hydrophobic groups thought to be important for crystallization inhibition in an aqueous environment[20].

The use of solid dispersion can improve the solubility or dissolution rate of poorly water-insoluble drugs. Various methods such as grinding, co-precipitation, lyophilization, and spray drying are available to prepare solid dispersion in which the drugs are present in the amorphous state[21]. Fakuda *et al* performed spray dried solid dispersion was prepared by using enteric coating polymers (Hydroxy propyl methyl cellulose phthalate) and very fine hydrophilic silica particles as additives in the formulations. These solid dispersions were found to have good drug dissolution properties and the amorphous state of a drug was well maintained under dry conditions[22].

The mechanism by which the solubility and dissolution rate of the drug is augmented includes the particle size of the drug being abridged to submicron size or to the molecular size in the case where the solid solution is achieved. The particle size reduction usually enhances the rate of dissolution; the change from crystalline to amorphous form, the very soluble and highly energetic state; finally, the wettability of the drug particle is enhanced by the dissolution carrier. Regardless of these promising advantages, the application of solid dispersion in the pharmaceutical industry has certain boundaries[23].

With the recent dawn of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has increased sharply and the formulation of poorly soluble compounds for oral delivery currently presents one of the most frequent and utmost challenges to formulation scientists in the pharmaceutical industry. Only small amounts of solid dispersion products are commercially existed. This is due to their poor physical characteristic for dosage formulation. The solid dispersions prepared by employing water-soluble carriers are soft and tacky masses which is hard to handle, particularly in capsule-filling and tablet-making development e.g., pulverization, sieving, and mixing[24].

Various hydrophilic carriers such as polyethylene glycol [PEG], polyvinyl pyrrolidine [PVP], hydroxypropyl cellulose, hydroxypropyl methylcellulose, gums, sugar, mannitol, urea, hydroxypropyl methylcellulose phthalate, glaciers, eudragits and chitosan has been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[25].

METHODS FOR ENHANCING SOLUBILITY OF POORLY SOLUBLE DRUGS:

I. Chemical Modifications:

1) Salt Formation
2) Co-crystallization
3) Co-solvency
4) Hydrotropy
5) Use of novel solubilizer
6) Nanotechnology

II. Physical Modifications:

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      vii. Dropping Method

III. pH adjustment

IV. Supercritical fluid process

V. Liquisolid technique

VI. Polymeric alteration[26,27,28,29,30,31,32,33].

I.Chemical modification:

1) Salt formation:

Many times, an API cannot be formulated in its pure form due to various issues of instability. Thus, they are converted to solid forms such as salts, co-crystals, solvates, hydrates, and polymorphs. Each of them imparts a different physiochemical property and affects performance characteristics stability, bioavailability, purification, and manufacturability of the drug in their own better way. Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. Salts are formed when a compound is ionized in solution. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Acidic or basic drugs converted into salt have more solubility than the respective drug. Ex. Aspirin, Theophylline, Barbiturates. A commercially available example of this approach is Progesterone; a water-insoluble steroid that is solubilized in peanut oil[34].

2) Co-crystallization:

Co-crystallization modifies the interactions between molecules and is a potentially useful substitute for improving the quality of drugs. An improved meaning of a co-crystal would be "a multicomponent crystal formed between two solid compounds under ambient condition, where at least one component is acceptable molecule or ion". Several physical, chemical, or physiological shortcomings of an API are addressed via co-crystallization. The co-valency mechanism reduces the interfacial tension, which facilitates the dissolving of a non-polar solute. Analytical methods and sensible physicochemical evaluations, which include solubility and stability assessments can be utilized to determine which co-crystal is most suitable. The only difference between solvates and cocrystals is the physical state of the components. If one of the components is liquid and the other is solid then it is termed as solvate but on the other hand, if both exist in solid form then they are termed as cocrystals. Pharmaceutical Co-crystals consist of two components that are the API and the co-crystal former(s)[35].

3) Co-solvency/Solvent Blending:

By lowering the interfacial tension between the hydrophobic solute and the aqueous solution, it improves the solubility of poorly soluble drugs by adding a water-miscible solvent, in which the drug has good solubility. Pharmacological forms are invariably liquid. The low-solubility medication was increased by the co-solvent by about a thousand times compared to the simple medicines. For compounds that are highly crystalline and have a high solubility in the solvent mixture, or for lipophilic molecules that are weakly soluble, a co-solvent method might be suitable. Due to the low toxicity of many c0-solvents and their comparatively higher solubility of nonpolar medicines, parenteral dosage forms have been its primary application. Commonly used cosolvents Glycerol, propylene glycol, PEG 400, Dimethyl Sulfoxide, Dimethyl Acetamide, Ethanol, and n-octanol are the commonly used cosolvents[36].

It is a highly helpful tactic to utilize co-solvents to increase the solubility of poorly soluble medications. The most popular low-toxicity cosolvents used in parenteral administration include propylene glycol, glycerine, and polyethylene glycol. Dimethylacetamide (DMA) and dimethyl sulfoxide (DMSO) have been used as cosolvents extensively due to their significant solubilization capacity for poorly soluble medicines and their relatively low toxicity[37].

Advantages:

- It is easy to formulate, produce, and evaluate, and it has a high solubilization capability for poorly soluble medicines.

Disadvantages:

- Toxicity and tolerability of the amount of solvent used must be taken into account.
- The chemical stability of the insoluble substance is worse than in a crystalline state, as it is with all solubilized forms[38].

4) Hydrotropy:

Is a solubilization occurrence in which a significant amount of the solute is added, increasing the solute's water solubility. The process via which it increases solubility is more directly associated with complexation, which is a weak interaction between weakly soluble medicines and hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, and urea. Ionic organic salts are hydrotropic agents. The hydrotropic agent and solute interact weakly in hydrotropic solutions, which lack colloidal characteristics[39,40].

It is a solubilization event in which the aqueous solubility of the original solute increases upon the addition of a significant amount of the second solute. The process via which it increases solubility is more closely associated with complexation, which is a weak interaction between the weakly soluble drugs and hydrotropic

agents such as sodium benzoate, sodium acetate, sodium alginate, and urea. Ionic organic salts are hydrotropic agents. Hydrotropic solutions have a weak contact between the hydrotropic agent and the solute and do not exhibit colloidal features[41].

Advantages:

- Hydrotrophy has a high selectivity and doesn't require emulsification, and its solvent

nature is independent of pH.

- It does not need the use of organic solvents or the preparation of an emulsion system[42].

5) Use of novel solubilizer:

Various solubilizing agents can also increase the solubility of poorly soluble drugs. Examples of conventional solubilizers that increase the solubility of hydrophobic API include dendrimers, PEG 400 Sepitrap, Soluplus Povacoat, and polysorbates. Sepitrap is a new kind of soluble eighty percent of the solubilizers in Sepitrap TM (a microencapsulated solubilizer for solid dose delivery) desorbed in less than five minutes, making the medicinal ingredient soluble. The drug-to-sediment trap ratio (2:1) can be utilized without formulation limits and is effective in increasing the rate of dissolving while also leaving the tablet properties unaffected.

Dendrimers: They are recognized for their three-dimensional, monodispersed, highly branching macromolecular nanoscopic architecture with numerous reactive end groups produced by reiterative sequences of processes. They also function as solubilizing agents to host both hydrophilic and hydrophobic medicines. Dendrimers are regarded as static multimolecular micelles, and even at greater solvent concentrations, their micellar structure is stable. Because of their micellar behavior, dendrimers are used to solubilize hydrophobic drugs. Dendrimers probably make hydrophobes more soluble because of the hydrophobic interactions between their terminal functional groups and hydrophobes. Polyamidoamine (PAMAM) and polypropylenemine (PPI) dendrimers are the most widely used types of dendrimers. Many researches, PAMAM dendrimers have the greatest attention in solubilization. Poly (propylene)imine dendrimers (PPI) constitute an equally important family of dendrimers reported first by Brabander and Meijer. These dendrimers closely resemble PAMAM dendrimers (except repeating units)[43].

6) Nanotechnology:

Nanotechnology is the study and application of materials and structures at the nanoscale level, or less than 100 nanometers(nm). Since micronized products have a very small effective surface area for dissolving, oral bioavailability enhancement micronization is insufficient for many new chemical entities with restricted solubility; thus, the next stage is nanonization[44].

Nanonization was the next step that was performed. Preparation techniques such as high-pressure homogenization, vacuum deposition, high-temperature evaporation, and grinding may be employed[45].

I. Physical modification:

1.Particle size reduction:

Drug solubility and drug particle size are frequently inextricably linked. The surface area to volume ratio rises as particle size decreases. Greater solubility results from greater interaction with the solvent made possible by a larger surface area. Drug particle size and bioavailability of poorly soluble medications are frequently correlated. Reducing particle size increases surface area, which enhances dissolving characteristics and opens up more formulation and delivery options[46].

The drug's particle size and solubility are also correlated. Particle size can be decreased to increase surface area, which enhances the drug's dissolving ability. Poorly soluble drugs bioavailability is frequently correlated with their drug particle size. Milling processes, such as colloid mills and jet mills, are used to reduce particle

size. This is not appropriate for drugs with high dosage numbers since the drug's saturation solubility remains constant. Micronization and nanosuspension are two methods for reducing particle size[47].

A. Conventional method of particle size reduction:

The traditional method of reducing particle size involves several methods, including cutting, compression, impact, attrition, and combined impact and attrition. The active component is broken down by mechanical stress in conventional particle size reduction techniques like comminution and spray drying. Thus, solubility improvement is now possible through an affordable, scalable, and effective method of particle size reduction. However, the medication product frequently experiences large quantities of physical stress from the mechanical forces inherent in communication, such as milling and grinding, which may cause deterioration. When processing thermosensitive or unstable active substances the possibility of thermal stress during communication and spray drying is also taken into account. It is not possible to increase the solubility of poorly soluble drugs up to a desirable level.

B. Micronization:

This method of high energy particle size reduction can reduce coarse particles to smaller than 5µ diameter particles. The development of a uniform dosage form requires a consistent and narrow particle size distribution, which is produced by micronization. Particle size decreases as micronization takes place, increasing surface area and solubility. The type of micronization procedure utilized affects the quality of the therapeutic material that has been micronized, including form, size distribution, agglomeration behavior, and powder flow. The methods most frequently used to produce micronized medication particles are mechanical mixing, spray drying, and supercritical fluid (SCF) technology. The Noyes-Whitney postulations state that one common way to increase the bioavailability of poorly water-soluble medicinal compounds is to administer the drug in micron size.

Techniques for Micronization

- Jet milling /fluid energy mill or micronized
- Rotor stator colloid mills
- Microprecipitation & micro crystallization
- Controlled crystallization
- Supercritical fluid technology
- Spray freezing into liquid[48].

Advantages of micronization:

- Gives uniform particles with narrow particle size distribution and an increase in surface area.

Disadvantages:

- High energy process, disrupts the drug crystal lattice, and in the final product, amorphous or disordered regions are present.
- Disordered/Amorphous regions are thermodynamically unstable and upon storage in hot and humid conditions these are susceptible to recrystallization[49].

C. Nanosuspensions:

Drugs that are poorly soluble and insoluble in water and oils are treated with this method. A biphasic system made up of nanoscale particles suspended in an aqueous medium is called nanosuspension. Surfactant stabilizes nanoscale medication particles for oral and topical use, as well as parenteral and pulmonary administration. The solid particle size distribution in nanosuspensions is typically smaller than one micron. Particle sizes range from 200 to 600 nm on average. This procedure was used for buparvaquone, amphotericin and paclitaxel, tarazepide, and atovaquone. There are several ways to make nanosuspensions, such as using nanopores, nanocrystals, dissocubes, and nano edges[50].

Advantages:

- The size of drug particles is reduced which increases the surface area, which in turn increases dissolution, solubility & bioavailability.
- Nanosuspension increases drug permeability.
- Nanosuspension increases the duration of the action of residence.
- Nanosuspension increases bio adhesion of drug
- It exerts the advantage of high drug loading.
- Avoidance of organic solvent.

Disadvantage:

- The main problem suffered in nanosuspension is instability due to crystal growth, agglomeration, and Ostwald ripening[51].

2)Modification of crystal habit:

The ability of a solid material to exist in two or more distinct crystalline forms with various lattice configurations is known as polymorphism. Different crystalline forms are called polymorphs. Drugs in crystalline form have the same chemical makeup, but they differ in their physiochemical characteristics, such as stability, solubility, texture, melting point, and destiny. In a similar vein, amorphous drugs are preferable to crystalline ones. Because of its larger surface area and high energy content. The arrangement of several solid medication forms. Amorphous > Metastable polymorphs > Stable polymorphs[52].

3)Complexation:

It is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry[53].

Two types of complexes:

i) Stacking complexes: The non-polar portion of the medication is kept out of touch with water due to the interaction between the non-polar area and the complexing agent. Although stacking produces a distinct solution, it might be mixed or homogeneous.

ii) Inclusion complexes: They form when a nonpolar molecule or a portion of a molecule is inserted into the cavity of another molecule or collection of molecules. In complexation, cyclodextrins and their derivatives are frequently employed.

A. Physical mixture:

In this, the CDs or suitable polymer and drug are mixed thoroughly by trituration in a mortar and pass through an appropriate sieve to get the desired particle size in the final product. It is a simple trituration method.

B. Kneading method:

This method is based on soaking the CDs or suitable polymer with a small amount of water or hydroalcoholic solutions to convert them into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through the sieve.

C. Co-precipitate method:

The required amount of drug is added to the solution of CDs or a suitable polymer. The complex was kept under magnetic agitation with controlled process parameters. The complex is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature to avoid the loss of the structure water from the inclusion complex. This method applies to industry[54] .

4) Inclusion of Complex Formulation Based Techniques:

When a nonpolar molecule or nonpolar portion of one molecule (referred to as a guest) lodges inside the cavity of another molecule or collection of molecules (referred to as the host), inclusion complexes are created. Host molecules called cyclodextrins are often utilized. The host's cavity needs to be both big enough to fit the visitor and tiny enough to remove water. Several techniques, including kneading, co-precipitation, neutralization, co-grinding, spray drying, and microwave irradiation, are used to prepare solid inclusion complexes[55].

A. Lyophilization/Freeze-Drying Technique:

In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CDs or suitable polymer at reduced pressure. Lyophilization in great measure was dependent on the unique properties of water and its role as the solvent, gas, diluent, plasticizer, and stabilizer. It is an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent.

B. Microwave Irradiation Method:

Involves the microwave irradiation reaction between a drug and a complexing agent using a microwave oven. The drug and CD in a definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for a short time of about one to two minutes at 60 ºc in the microwave oven. After the reaction completes, an adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed-free drug and CD. The precipitate is separated by Whatman filter paper and dried in a vacuum oven at 40 ºc for 48 hrs.

5) Solubilization by surfactants:

Surfactants are molecules with polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. Anionic, cationic, zwitterionic, or non-ionic might be polar groups. The hydrophobic center of the micelles might get crowded with tiny polar molecules when they are introduced. The solubilization process is crucial to both natural and industrial processes. Surfactants facilitate the dissolving of lipophilic medicines in aqueous medium, hence lowering surface tension and improving drug solubility. Drug suspensions are stabilized with the use of surfactants. Micelle formation, also known as micellization, occurs when the concentration of surfactants exceeds their critical micelle concentration (CMC), which is typically in the range of 0.05-0.10%. this primarily leads to increased solubility of poorly soluble drugs.

A. Microemulsions:

A microemulsion is an optically clear preconcentrate, isotropic, thermo dynamically stable transparent, translucent system, containing a mixture of oil, hydrophilic surfactant, and hydrophilic solvent that dissolves a poorly water-soluble drug. The criteria for the selection of surfactant are HLB and non-toxicity. On contact with water, the formulation self-emulsifies and forms a very clear emulsion of small and uniform oil droplets containing the solubilized poorly soluble drug. Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with the incorporation of proteins for oral, and parenteral. Oil-in-water (o/w) microemulsion is the most suitable formulation, which is expected to increase the solubility by dissolving compounds with low water solubility into an oil phase. They can also enhance oral bioavailability by reducing the droplet size (< 100 nm), and hence increase the rate of absorption due to surfactant-induced permeability changes[56].

B. Self-emulsifying drug delivery systems:

Uses the concept of *in situ* formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents, and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). Self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant that form oil-in-water microemulsions on mild agitation in the presence of water. These novel colloidal formulations on oral administration behave like oil-in-water microemulsions.

6) Drug dispersion in a carrier:

A mixture of two crystalline solids that results in a new crystalline solid is called a solid solution. Because the two components crystallize together in a homogenous one-phase solution, a mixed crystal is created. Therefore, compared to basic eutectic systems, it is anticipated to produce substantially higher rates of dissolution. Amorphous precipitation: amorphous precipitation is the result of a medication precipitating in an inert carrier in an amorphous state. In this particular system, the drug's higher energy state typically results in significantly faster rates of dissolving compared to the comparable crystalline forms[57].

i) Fusion Process:

The carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Other factors that may play a role include the solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties. Disadvantages Exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is thermoliable[58].

ii) Solvent Method:

The carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum. As the solvent is removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The co-precipitate is then dried under a vacuum to drain out any solvent freely adhering to the particle. Removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and less sensitive procedures like spectroscopy, gravimetry and can be used to demonstrate complete solvent removal[59].

iii) Fusion-Solvent Method:

Carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. The Method is useful for drugs with high melting points or that are thermolabile.

iv) Spray Drying:

The carrier and the active ingredient are dissolved and suspended in a suitable solvent. This solvent is evaporated by drying it to applying a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.

v) Lyophilization (Spray Freeze Drying Method):

This method has been successfully developed to prepare solid dispersions at ambient temperature and avoid heating during the preparation of thermosensitive drugs; spray freeze drying (SFD). SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried.

This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area[60].

vi) Hot-melt Extrusion:

This is a method of choice in the polymer industry. But Speiser and Huttenrach were the first persons who use this technology for pharmaceutical purposes. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. The Active ingredients and the carrier are fed into the heated barrel of extruder at a constant rate. When the mixture of the active ingredient and the carrier is conveyed through heated screws, it is transformed into its "fluid-like state". This state allows intimate and homogeneous mixing by the high shear of extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drugs that are somewhat thermolabile to be processed[61].

vii) Dropping Method:

Solid dispersion of a melted drug carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size, and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped on the plate it solidifies to a spherical shape[62].

III. pH adjustment:

A pH shift could cause a poor water-soluble medication to potentially dissolve in water. The buffer capacity and tolerability of the chosen PH are crucial factors to take into account to assess the solubility using this method. The solubility of a drug is increased by soluble excipients that raise the PH of the surrounding environment within the dosage form to a range higher than the Pka of weekly acidic pharmaceuticals; conversely, alkalizing excipients may increase the solubility of weekly basic drugs.

Advantages of pH adjustment:

- Simple to formulate and analyze.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages of pH adjustment:

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity both local and systemic related with the use of a non-physiological pH and extreme pH should be considered.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations of crystalline solids. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms[63].

IV. Super critical fluid process:

Non-volatile solvents can be dissolved by supercritical fluids (SUFs), with carbon dioxide serving as the critical point. It is affordable, safe, and environmentally beneficial. A single phase of a SCF is present above its critical pressure and temperature. Because SCFs have qualities halfway between those of a pure liquid and a gas, they are suitable for product processing. Furthermore, with little variations in operating temperature, pressure, or both around the critical points, the density, transport characteristics (like viscosity and diffusivity), and other physical characteristics (like dielectric constant and polarity) alter significantly. Lately, the food sector has identified and utilized the unique processing capabilities of SCFs, and these capabilities have been extended to medicinal applications. Supercritical solvents such as nitrous oxide, water, ethanol, ammonia,

propane, ethylene, propylene, and propane are frequently employed. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Impregnation or infusion of polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES) and supercritical antisolvents processes (SAS)[64].

Advantages of supercritical fluid process

1. The low operating conditions (temperature (375^0C) and pressure (22MPa) make it attractive for pharmaceutical research.

2. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. Current SCF processes have demonstrated the ability to create nanosuspensions of particles 5-2 micro meter in diameter.

3. The flexibility and precision offered by SCF processes allow micronization of drug particles within narrow ranges of particle size, often to sub-micron levels.

V. Liquisolid methods:

Both absorption and adsorption occur when the drug dissolved in the liquid vehicle is introduced into an inert carrier material that has a porous surface and fibers in its interior, such as cellulose. Specifically, the liquid is first absorbed in the interior of the particles and is then captured by its internal structure; after this process reaches saturation, the liquid is adsorption into the internal and external surfaces of the porous carrier particles. Next, the liquisolid system has the desired flow characteristics due to the coatings materials large specific surface area and high adsorptive qualities. Powders of silica microcrystalline and amorphous cellulose can be utilized as coating materials[65].

Advantages of Liquisolid methods:-

1. Provides acceptably flowing and compressible powdered forms of liquid medications.

2. Method improves the solubility, and bioavailability of orally administered water insoluble and is applicable in industry.

3. Useful for the formulation of oily drugs/liquid drugs.

4. Drug release can be modified by using different carriers and additives like PVP, PEG 6000, Hydroxy Propyl Methyl Cellulose Eudragit, etc.

5. Several poorly soluble drugs can be formulated into the system.

6. This system is specifically for powdered liquid medications.

7. Production cost is low compared to that of preparation of soft gelatin capsules.

Disadvantages of the liquisolid method

1. It requires recipients of high adsorption properties and high specific surface area.

2. It does not apply to high-dose insoluble drugs (>100 mg)[66,67].

VI. Polymeric alteration:

Polymorphs are several crystalline forms of a medication that may have various characteristics. Physical and chemical stability, melting point, vapor pressure, shelf-life, dissolving rate, shape, density, biological activity intrinsic solubility, and bioavailability are only a few examples of the physicochemical characteristics that might differ amongst polymorphs. The three crystalline polymorphs that are stable, unstable, and metastable are associated with a higher energy, greater surface area, solubility, bioavailability, and efficacy. In terms of bioavailability, it is preferable to transform a medicine during its shelf-life from crystal forms into metastable or amorphous forms within a range of actual storage circumstances[68,69].

Different techniques for co-crystallization: - Solvent evaporation, Grinding, Slurry Co - Crystallization, Solvent drop grinding (Modification of Grinding), High throughput co-crystallization, Hot melt extrusion, and Sono crystallization method.

Co Crystals Characterization Parameters: - Solubility, Maximum wavelength, Stability, Intrinsic dissolution, Bioavailability, Melting Point, Melt (Hot stage microscopy), Scanning Calorimetry (DSC), XRD, Vibrational spectroscopy[70].

Polymers are used in solid dispersions:

Polymers

S.NO	Drugs	Polymers	Methods	Authors
1.	Sildenafil citrate	Kolliphor®P188 (K188), Kollidon®30 (K30), Kollidon®-VA64 (KVA64)	Solvent evaporation method	Mohammed F. Aldawsari, Md. Khalid Anwer, Mohammed Muqtader Ahmed, Farhat Fatima, Gamal A. Soliman, Saurabh Bhatia, Ameeduz Zafar and M. Ali Aboudzadeh.
2.	Rosuvastatin Calcium	Hydroxypropyl methylcellulose, ethyl cellulose, Carbopol, Acacia Gum	Kneading method	Lovepreet Kaur, Taranjit Kaur, Amar pal Singh, Ajeet pal Singh. 2021,13(6).
3.	Lornoxicam	Sodium hydroxide (NaOH), Potassium dihydrogen phosphate(KH_2PO_4)-Hydroxy propyl methyl cellulose (HPMC), crystalline cellulose (MCC), Polyvinyl pyrrolidine (PVP) Polyethylene glycol (PEG), Dicalcium phosphate (DCP), Pregelatinized starch (PGS), Methanol	Solvent evaporation method	N. Sri Raviteja, D. Naga Latha, B. Sowmya, Ch V. Prasada Rao and P. Renuka Tejasvi. 2014, 8(4), 601-608.
4.	Diazepam	Poloxamer 407	Solvent method	Md. Sariful Islam Howlader, Jayanta

		(Lutrol 127). HPMC 6 cps, HPC, and reagent grade methanol.		Kishor Chakrabarty, Khandokar Sadique Faisa, Uttom Kumar, Md. Raihan Sarkar, Mohammad Firuz Khan. 2012,1(12), 423-430.
5.	Meloxicam	Poloxamer 188, Anhydrous methanol, sodium lauryl sulfate.	Melting method	Anmar Adham Issa, Daniela Marchidan, Victor Cojocaru, Valentina Anuta.
6.	Febuxostat	Kolliphor P 237 and Eudragit RLPO, Silicon dioxide, and magnesium stearate, Avicel PH 102	Solvent evaporation method	M. Sanjana Reddy, P. Tripura Sundari. 2018, 5(12), 1-11.
7.	Clonazepam	Poloxamer 407 (Lutrol 127), Kollicoat IR, and Kollidon VA 64 were gifted by BASF, PEG 6000 (Loba Chemie, India), reagent grade methanol.	Solvent evaporation method	Md. Armin Minhaz, Md. Mofizur Rahman, Md. Qamrul Ahsan, Abul Bashar Ripon Khalipha and Mohammed Raihan Chowdhury. 2012,1(2).
8.	Isradipine	Hydroxy propyl methyl cellulose, Sodium hydroxide, Hydrochloric acid, KH_2po_4, HPLC	Spray Drying	Hai Van Ngo, Phul Kien Nguyen, Toi Van Va, Van Thanh Tran ,2016;513(1-2);148-152.
9.	Ethenzamide	Polyhydroxy ethyl acrylamide,	Co-Crystallization	Derek S. Frank, Adam J. Metzger. 2019;16(2);682-688.
10.	Carbamazepine, Nifedipine	Poly vinyl alcohol, Tri ethylene glycol, Mono ethyl ether.	Co-Crystallization	Thao T.D Tran and Phuong H.L, Tran 2020;12(8);1679.
11.	Griseofulvin, Phenytoin	Hydroxy propyl methyl cellulose phthalates, (Hp-50 &Hp-55) cellulose acetate phthalate, carboxy methyl ethoxy ethyl cellulose, Hydroxy propyl methyl	Hot melt extrusion	Thao T.D. Tran & Phuong H.L. Tran 2020;12(8);1679.

		cellulose acetate succinate.		
12.	HDPE/ZNO Nanoparticles	(HDPE) High-density poly ethylene. Polyethylene oxide (PEO)	Melt mixing	M. Salzanode luna, M. Galiza, J. Wojnarowicz, R. Rosa, W. Lojkowski, C. Leonelli, D. Acierno, G. Filippone.2014; 8(5);362-372.

Importance of hydrophobic and hydrophilic polymers in solid dispersions:

Recent research on solid dispersions suggests that this is a highly profitable strategy for increasing the rate of release and oral bioavailability of hydrophobic medications. Two factors strongly suggest that solid dispersions will play a bigger role in pharmaceutical research going forward: the rise in poorly soluble drug candidates and the significant advancements in solid dispersion production techniques over the past several years. Solid dispersion also has the benefit of not requiring toxicity studies because many of the carriers can be utilized or are already widely used as excipients in the pharmaceutical sector. This article offered a wealth of information regarding the use of solid dispersions to improve the oral bioavailability and release rate of poorly water-soluble drugs. It is also feasible to delay or slow down a drug's release pattern by carefully selecting the carrier when preparing a solid dispersion[71].

Enhancing drug dissolution rate and bioavailability can improve the wettability, and porosity, reduce particle size, and give an amorphous state.

Hydrophilic polymers are used as coatings, adhesives, fiber, films, and engineering plastics. Moreover, they are extensively employed as biomedical polymers for vascular grafts, implants, drug delivery, and ophthalmic applications. Hydrophilic molecules play an important role in the structure of cells and living things. Many proteins, carbohydrates, and other molecules inside the cell must be hydrophilic to help the cell carry out its functions.

Hydrophobic surfaces are manufactured by adjusting combinations of chemicals and monitoring the structural properties of solid surfaces. Hydrophobic surfaces reduce the potential adhesion of bacterial activities. They also show high cleaning activity. Hydrophobic surfaces bind to proteins more firmly done hydrophilic surfaces. Therefore, the presence of a hydrophobic polymer in solid dispersion may induced a chemical interaction between the polymer and the poorly water-soluble drug, which facilitated increased drug dissolution. The use of hydrophobic polymers in solid dispersion might facilitate molecular interactions with poorly water-soluble drugs for changing drug crystals to amorphous form.

In the case of limited dissolution rate of very poorly soluble drugs to decrease the drug recrystallization and increase the wettability[72].

Conclusion:

In this study, we provide evidence that introducing hydrophobic functionalities on water-soluble polymers via post-polymerization modification improves the stability of amorphous solid dispersion and supersaturated solutions of pharmaceuticals. Optimizing polymer design for amorphous solid dispersions is essential to prevent recrystallization from the amorphous phase and the solution.

Imparting hydrophobicity to water-soluble polymers has a dual effect of optimizing the performance of amorphous solid dispersion. In this amorphous phase, hydrophobic residues decrease hygroscopicity and protect interaction between polymer and pharmaceutical from interruptions by atmospheric water. In aqueous solutions, hydrogen bonding between polymer and bulk water competes with bonding between drug and

polymer, and tethering hydrophobic functionality on a water-soluble polymer can preferentially interact to stabilize supersaturated drug from precipitation.

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