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Review Article

Solubility Enhancement, Formulation and Evaluation of Solid Tablet of Tinidazole

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Abstract:

To attain the necessary concentration of medication in the systemic circulation for the predicted pharmacological response, solubility the phenomenon of solute dissolving in solvent to produce a homogeneous system is a crucial characteristic to consider. The primary challenge in developing formulations for both novel chemical entities and generics is their low water solubility. Formulation scientists face a significant obstacle in solubility. The Classification of Biopharmaceutics states that APIs from Classes II and IV have reduced bioavailability, dissolution, and solubility. The article covers a range of technologies that can be used to make drugs that aren't very water-soluble more soluble. These include crystal engineering, pharmaceutical salts, drug nanocrystals, solid dispersion methods, polymeric micelle preparation, cosolvents, micelles, microemulsions, and emulsion formation. Physical and chemical drug modifications, crystal engineering, salt formation, solid dispersion, surfactant use, micronization, solid dispersions, nano sizing, cyclodextrin complexation, and other advanced methodologies are primarily described in this review. Other methods also contribute to improving solubility and bioavailability. It was an effort to talk about different complexation methods and to quickly point out their possible uses, as well as their technical and economic limits.

Keywords: Solubility, BCS Classification, Solubility enhancement, poorly soluble drugs

Introduction:

The solubility of a chemical substance is defined as its ability to dissolve in a certain solvent, whether that solvent is solid, liquid, or gas. This allows the solute to create a uniform solution in the solvent. A substance's solubility is very sensitive to changes in solvent, temperature, and pressure. The saturation concentration, at which further addition of solute has no effect on the solution's

concentration, is a measure of a substance's solubility in a certain solvent [1]. A liquid, either one component or a combination of two, is often used as the solvent. It is more common to talk about a solid solution than a gaseous one. One end of the spectrum is very soluble (totally miscible), like ethanol in water, while the other end is extremely weakly soluble, like silver chloride in water. Compounds that are not soluble or just extremely slightly soluble are sometimes referred to be insoluble. The competing processes of dissolving and phase joining (such as solid precipitation) produce solubility, which happens under dynamic equilibrium. When both processes remain constant in rate, we say that there is solubility equilibrium [2]. A so-called supersaturated solution, which is metastable, may be produced when equilibrium solubility is surpassed under certain circumstances. A substance's solubility is distinct from its dissolving or liquefying capabilities, since the former might be the result of either dissolution or a chemical reaction. As an example, whereas hydrochloric acid does not dissolve zinc, it does dissolve zinc chloride, which in turn dissolves hydrogen, when the two combine chemically. Particle size and other kinetic parameters are irrelevant to solubility; with sufficient time, even very big particles will dissolve [3].

Drug detection data shows that the percentage of poorly soluble pharmaceuticals has been rising over the last several years, with 70% of new prescriptions exhibiting low aqueous solubility. Because of their poor solubility and slow dissolving rate in gastrointestinal fluids, these medications' oral formulations have a limited in vivo bioavailability. Accordingly, in vitro dissolution and boosting the bioavailability and speed of dissolving poor solvable pharmaceuticals constitute a significant challenge for pharmaceutical specialists and an important topic in medication development. The medicinal agent has to be in a water-soluble form at the site of absorption in order to be submerged [4]. When it comes to absorption in living organisms, the solubility and permeability are encouraging variables. Solubility improvement strategies may make them better.

Biopharmaceutical Classification System

Among the many scientific methods for categorising pharmaceutical compounds according to their solubility and permeability, BCS is among the most widely used. Aqueous solubility and intestinal permeability are two important parameters that control the extent and rate of oral medication absorption.

Various formulations and their ratios according to BCS classification have been developed, as shown in Figure1, in light of the current environment of the pharmaceutical developing market. The U.S. Food and medication Administration's Biopharmaceutics Classification System (BCS) is a tool for estimating the intestinal medication absorption [5]. Solubility and intestinal permeability are the characteristics that this approach uses to limit the prediction. The solubility of an instant release substance is determined by its

highest-dose strength. For a medicine to be classified as very soluble, it must be able to dissolve in 250 mL or less of water at pH levels between 1 and 7.5, regardless of the dosage strength. The 250 mL volume estimate is based on the standard technique for bioequivalence studies, which involves giving a medicinal product to human volunteers who are fasting along with a glass of water. A comparison to the intravenous injection is used to classify intestinal permeability. Oral administration accounts for 85 percent of the most popular medications in the United States and Europe, making all of these considerations crucial. Class I medications are very soluble and highly permeable; class II drugs are less soluble but highly permeable; class III drugs are low soluble but highly permeable; and class IV drugs are low soluble but poorly permeable [6].

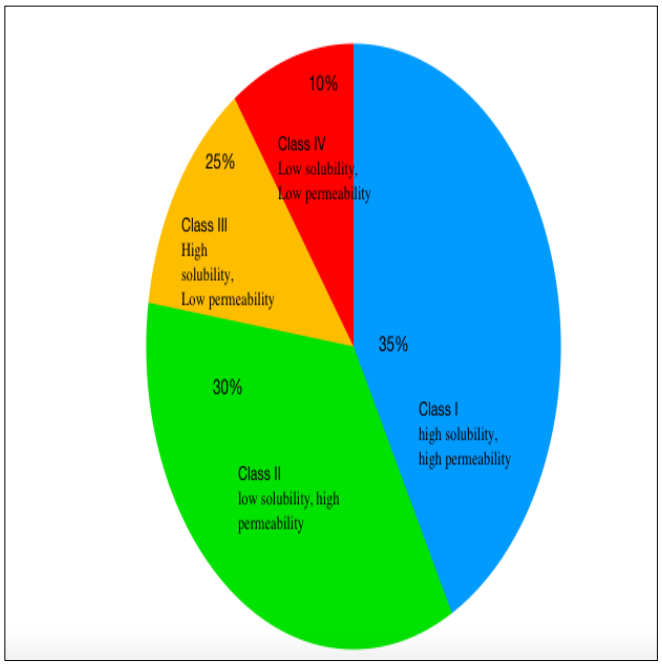

Figure.1 The oral medication delivery frontier is beset by solubility difficulties. Oral absorption is measured by drug permeability and solubility according to the biopharmaceutical classification system. Available drugs on the market are shown as a percentage.

The medicine is considered very soluble and has a pH range of 1.0 to 7.5 when its full potency dissolves in 250 mL or less of the aqueous standard; otherwise, it is considered to have ingredients that are not very soluble. Scientists in the biopharmaceutical industry are always working to perfect a physiologically imitating system that can accurately predict in vivo performance by matching parameters including stomach pH, food content, and peristalsis. From 1960 to 1970, there were a lot of breakthroughs in biopharmaceutical research. A lot of studies showed how different formulation and dissolving factors affected the bioavailability of drugs. The first dissolving test instrument, USP instrument I (basket type), was produced in 1970 for the accurate assessment of any formulation's dissolution rate. Subsequently, USP Apparatus II (paddle type) was created [7]. This device has allowed us to extrapolate the formulation's in vivo performance from its in vitro testing. The in vivo performance of dosage forms has been enhanced, however, due to the fact that the in vivo performance of every formulation is dependent on a number of factors.

The solubility of a substance is defined by the International Union of Pure and Applied Chemistry (IUPAC) as the ratio of a given solute to a given solvent in a saturated solution. You may express solubility in a variety of ways, including concentration, molality, mole fraction, mole ratio, and more. Many diverse ways of expressing solubility have emerged as a result of its extensive usage from various perspectives. Mass (in grammes of solute per kilogramme of solvent or grammes per deciliter of solvent), molarity, molality, mole fraction, and similar descriptors are the most frequent ways that concentration is described. The solubility of a solute in a given solvent under certain circumstances is the greatest equilibrium quantity that may dissolve per amount of solvent [8]. The simplicity of this kind of solubility expression is its main drawback; on the one hand, it is independent of the solvent and any other species present (the common ion effect, for example). Solubility constants are sometimes used to characterise saturated solutions of ionic substances that have a poor solubility. There has been a process of balance. It summarises the equilibrium between the salt's dissolved ions and its undissolved salt. The numerical value of the solubility constant is affected by temperature, much like other equilibrium constants. This constant's value is often unaffected by other species in the solvent. One theoretical model that attempts to explain how polymers dissolve is the Flory-Huggins solution theory. Two empirical approaches for predicting solubility are the Hansen Solubility Parameters and the Hildebrand Solubility Parameters. Other physical variables, such the enthalpy of fusion, may also be used to predict solubility. An indicator of a compound's differential solubility between a hydrophilic (water) and hydrophobic (octanol) solvent is the partition coefficient (Log P). To rank compounds according to their hydrophilicity (or hydrophobicity), one may take the logarithm of these two numbers. Table 1 shows the criteria that USP and BP have specified for classifying solubility, which are independent of the solvent utilised [9].

Chemical structure and solution conditions are the primary determinants of a drug's solubility. The quantity of the medication, its crystal energy, the number of hydrogen bonds, its ionizability, and its lipophilicity are all defined by the molecular assembly. Solution conditions are affected by ionic strength, cosolvents, time, temperature, additives, and pH. The production of new drugs may be severely hindered by pharmaceutical chemicals that are poorly soluble in water.

To be effective, a "good compound" has to access the dormant focuses at the target place. The absorption, permeability, and potency of compounds are influenced by how they dissolve. Compounds with a poor water solubility tend to be very powerful and porous [10].

Table 1: USP and BP solubility criteria.

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Importance of Solubility

In terms of cost-effectiveness, least sterility limitations, convenience of administration, high patient compliance, and flexibility in the creation of dosage forms, oral ingestion is the most convenient and widely used mode of drug delivery. Consequently, a growing number of generic medicine manufacturers are focusing on creating oral prescription formulations that are bioequivalent. But low bioavailability is the biggest problem with oral dosage form formulation. Multiple variables influence the oral bioavailability, such as the drug's solubility in water, its permeability to water, the pace of dissolution, the presence of first-pass and presystemic metabolism, and the likelihood of efflux mechanisms. Limited permeability and poor solubility are the most common reasons for limited oral bioavailability. For other kinds of dosing, such as parenteral formulations, solubility is also crucial [11]. Achieving the necessary concentration of the medication in the systemic circulation to generate the requisite pharmacological reaction is dependent on many factors, one of which is solubility. Oral administration of medications with poor solubility in water often requires large dosages to achieve therapeutic plasma concentrations. The main challenge in developing formulations for both novel chemical entities and generics is their low water solubility. At the site of absorption, any medicine that is to be absorbed must be present as an aqueous solution. For pharmaceutical formulations in a liquid state, water is the preferred solvent. Due to their weak acidity or basicity, the majority of the medications have limited solubility in water. A significant portion of the new chemical entities (NCEs) created for the pharmaceutical industry—over 40%—are almost insoluble in water. Inadequate and unpredictable bioavailability as well as gastrointestinal mucosal toxicity are consequences of these medicines' delayed absorption and poor water solubility [12]. If a drug is to have any pharmacological impact after being given orally, its solubility is the most important characteristic that will restrict how fast it may reach the desired concentration in the circulation. For formulation scientists, the solubility problem is one of the biggest obstacles. Particularly for oral-drug delivery systems, increasing a drug's solubility and, by extension, its oral bioavailability, is a major obstacle in the drug development process. To improve the solubility of medications that are not very water-soluble, there are a lot of methods that have been documented in the literature and are readily accessible. Several factors are taken into account while selecting the methods, including the characteristics of the medicine, the kind of

excipients to be used, and the planned dose form. Inadequate bioavailability is a common side effect of medications with poor water solubility and slow dissolving rate in the watery gastrointestinal fluids [13].

Parenteral formulations and other non-oral dose forms rely heavily on solubility. To prolong therapeutic plasma concentrations after oral administration of drugs with limited water solubility, a large dose of the agent is often necessary. To absorb any pharmaceutical substance, it is necessary to be in an aqueous media at the site of absorption. Liquid medicinal formulations are best prepared using water as the solvent. The biggest challenge for those working on medicinal formulations is the sluggish solubility of the molecule in water. Fewer medications dissolve in water because they are either weakly basic or weakly acidic. According to research in the pharmaceutical industry, about 40% of NCEs (new chemical entities) are water insoluble [14].

Improving the solubility of drugs is the most difficult aspect of the drug development process. To increase the solubility of medications that are not very water-soluble, there are a number of methods that have been detailed in the literature. The properties of the medicine, the kinds of dosage forms desired, and the selected excipient all play a role in determining which of these methods is best.

A lack of bioavailability occurs due to the aqueous gastrointestinal fluids' slow dissolving rate and poor solubility. For drugs classified as class II (low solubility and high permeability) by the BCS, improving the drug's solubility and dissolving rate in gastrointestinal fluids may increase its bioavailability. Since the rate-limiting step for BCS class II medications is not absorption but rather drug release from the dosage form and solubility in stomach fluid, improving solubility leads to an increase in bioavailability. Poor absorption and bioavailability, inadequate solubility for intravenous dosage, difficulties during development that increase research costs and timelines, and the patient bearing the burden of repeated high-dose administration are all unfavourable effects of poorly soluble substances [15].

Techniques for Solubility Enhancement

Physical and chemical alterations of the medicinal ingredient are two main types of solubility enhancement approaches. Physical Alterations. Cryogenic procedures, drug dispersion in carriers, eutectic mixes, solid dispersions, solid solutions, and micronization are all ways to reduce particle size. Polymorphism, amorphous form, and cocrystallization are all ways to modify the crystal habit. Changes Made by Chemicals.

Variation in pH, buffering, derivatization, complexation, and salt production. Uncommon Approaches. Adjuvants such as surfactants, solubilizers, cosolvency, hydrotrophy, and new excipients are used in the supercritical fluid process [16].

Physical Modifications

Particle Size Reduction

Particle size determines how well a medicine dissolves in water. Particles of a large size have a smaller surface area and interact with the solvent less. Improving the drug's solubility may be achieved, in part, by decreasing its particle size, which in turn increases its surface area.

Micronization

Manufacturing medication particles via a physical approach, often on a nano scale. Crystallisation, freeze-drying, spray-drying, and milling are some of the most common techniques used to increase the solubility of BCS class II medicines.

Mechanical procedures, such as grinding, milling, and crushing, are used to decrease the size of heavy particles. These methods utilize friction, pressure, attrition, shearing, or impact to accomplish the reduction. Mills, both ball and jet, as well as high-pressure homogenizers, are used for mechanical micronization. When it comes to micronization, dry milling is where it's at [17].

Instead than increasing the equilibrium solubility of the medication, micronization increases the dissolving pace. Researchers have shown that by lowering the size and increasing the surface area of medications that are poorly soluble in water, they may improve their solubility and bioavailability.

Nanosuspension

A colloidal dispersion containing sub-micron drug components stabilised by a surfactant is known as a nanosuspension. Nanosuspensions are made by the processes of wet milling and homogenization. The active component is defragmented by milling while a surfactant is present.

Advantages of Nano suspension [18]

- Enhancement of drug solubility and its bioavailability
- Higher drug loading
- Suitable for hydrophobic drugs
- Passive drug targeting
- Reduction in dosage
- Increase in drug’s physical and chemical stability.

Nanosuspension Preparation Techniques: Both "bottom-up" and "top-down" techniques may prime a Nanosuspension.

Bottom-up technology refers to a method of constructing nanoparticles using processes including microemulsion, melt emulsification, and precipitation.

Top-down technology include methods that break down larger particles into smaller ones, such grinding and high-pressure homogenization [19].

The precipitation approach is used to create submicron sized medication particles that have low solubility. This process involves dissolving drug molecules in one solvent and then adding a surfactant to make them insoluble in the second solvent. An ultrafine crystalline or amorphous drug may be produced by rapidly supersaturating the drug in a solution by solvent mixing. The creation of nuclei and subsequent crystal development are the two stages that make up this method. The weather has a major impact on these.

A low crystal growth rate and a high nucleation rate

are essential requirements for the creation of a stable suspension [20].

A three-step process known as high-pressure homogenization begins with dispersing drug powders in a stabilising solution to create a pre-suspension. Then, the pre-suspension is homogenised using a low-pressure, high-pressure homogenizer, which is sometimes used for the previous preparation. Finally, the nano suspensions are subjected to 10–25 cycles of final homogenization at a high pressure until they reach the desired size.

Aqueous medium homogenization (Dissocubes) Homogenization in Nanopure and other non-aqueous mediums [21].

Milling Techniques

(a) Media milling

Nanoparticles of pharmaceuticals may be created in media milling by introducing impaction between the drugs and the milling medium, which releases enough energy to break down the particles. This method calls for a grinding chamber that is filled with the medication, a stabiliser, grinding tools, and an appropriate buffer, such as water. To make the suspension, the grinders spin at a high cutting speed. One big problem with this approach is that it leaves behind residues in the final product [22].

(b) Dry grinding

Using a pearl ball mill and the wet grinding process, nano suspensions were first created. Dry milling is being used to create them. This method involves dispersing a poorly soluble medication in a liquid media, then dry grinding it with soluble copolymers and polymers to create a nano suspension.

Lipid Emulsion/Microemulsion Template

Emulsions may be easily diluted to make nano suspensions by moulding them via water and a partially miscible solvent in accordance with a dispersed phase. Medications that are slightly miscible with water or soluble in volatile organic solvents may be processed using this approach. Furthermore, nano suspensions may also be made using microemulsion templates. Oil, water, and an immiscible stabiliser fluid (cosurfactant or surfactant) make up the physical components of a microemulsion. During the internal phase, the drug molecules are either introduced as a microemulsion or saturated with pharmaceuticals from an informal mixture. Water, taurodeoxycholate sodium salt, butyl lactate, and lecithin are the main ingredients in the microemulsion procedure that produces glisofulvin nanosuspensions [23].

Microprecipitation -High-Pressure Homogenization (Nano Edge)

This technique is a unification of the high-pressure homogenization and microprecip- itation technique. This process involves the precipitation of breakable constituents that succeed through fragmentation.

Nanojet Technology

"Reverse flow" describes this method. One component of nanojet technology is a chamber that divides a suspension current into two or more independent sections. As high-pressure colloids, both streams are present. As a result of the impact, the procedure's strong shear force demonstrates a decrease in particle size. Atovaquone nano-

suspensions are created by means of the micro fluidification process. A relatively large number of microparticles is produced as a consequence of the method's primary constraint, which is a high number of cycles over the microfluidizer. Studying the effectiveness and safety of NCEs in a preclinical setting may be facilitated by using nanoparticle methods as a screening strategy. To make already-existing NCEs more bioavailable with less side effects, drug delivery methods based on nanoparticles might be useful. [24]

2.1.2. Modification of the Crystal Habit

Crystal engineering: Crystal engineering involves researching and developing methods for creating and using crystalline solids with specific molecular and ionic compositions. An intriguing solid-state structure with intriguing electrical, optical, and magnetic characteristics may be rationally designed via crystal engineering by taking advantage of noncovalent interactions between ionic or molecule components. The drug's solubility in luminal fluids and the size of its particles determine its surface area. The crystallisation conditions or comminution processes, such impact milling or fluid energy milling, determine this particle size, which is crucial to the medication dissolving rate.

Because of their heterogeneity, charges, and cohesiveness, the particles produced by comminution processes may impede downstream processing and product performance. To achieve high purity powders with predetermined particle size distribution, crystal habit, crystal shape (crystalline or amorphous), surface nature, and surface energy, crystal engineering methods are created for controlled crystallisation of pharmaceuticals. The crystallisation conditions may be adjusted to create polymorphs with varied packing arrangements by changing the solvents, stirring, or adding additional components to the crystallising drug solution [25]. Therefore, physicochemical characteristics including solubility, dissolving rate, melting point, and stability might vary across polymorphs of the same medicine. Because of the inherent polymorphism in most pharmaceuticals' structures, it is best to create the drug's most thermodynamically stable form in order to guarantee consistent bioavailability throughout the product's shelf life, regardless of the storage circumstances. Chloramphenicol palmitate suspensions are a paradigmatic example of how polymorphism affects bioavailability. When given the same dosage, the metastable polymorph of chloram-phenicol palmitate resulted in much greater blood levels than the stable polymorph. Another research discovered that oxytetracycline tablets made from the form a polymorph dissolved far more slowly than tablets made from the form B polymorph. Thirty minutes after administration, tablets containing form a polymorph dissolved about 55% of the drug, but tablets containing form B polymorph dissolved almost completely, at 95% [26]. Improving the solubility rate is another goal of the crystal engineering strategy, which includes making hydrates and solvates. It is feasible to ensnare solvent molecules within the crystal lattice

while crystallisation is taking place. The crystal that forms when water is used as the solvent is called a hydrate. When another solvent is used, it is called a solvate. diverse solvates have vastly diverse effects on a drug's solubility and rate of dissolution. For instance, glibenclamide's solubility and dissolution rate were shown to be greater in the pentanol and toluene solvates that were separated, compared to the two nonsolvated polymorphs. Hydrates may dissolve more quickly or more slowly than the anhydrous form, depending on the specific case. In most cases, the anhydrous form will dissolve more quickly than the hydrate. As an example, theophylline anhydrate dissolved more quickly than its hydrate counterpart. The hydrate version of the medicine may dissolve more quickly than the anhydrous version in certain situations. The dissolving rate of erythromycin dihydrate differed significantly from that of monohydrate and anhydrate forms. The presence of potentially harmful organic solvent residues makes solvates an unattractive choice for pharmacological and medicinal applications. Additionally, there are daily exposure limitations for all organic solvents used in formulated preparations. With a thorough understanding of crystallisation processes and the molecular characteristics of active pharmaceutical components, crystal engineers may use a variety of strategies to increase solubility and dissolution rate. The medication is dissolved in a solvent and then controlled precipitation with an antisolvent (often water) is used to create nanoparticles [27].

When it comes to medications that aren't very soluble, pharmaceutical cocrystals provide a fresh perspective. They consist of a novel crystal structure formed by the arrangement of two or more different molecules, the combined qualities of which are often better than those of the individual components. Cocrystals of pharmaceuticals are created when a solid cocrystal former is mixed with a molecular or ionic medication under room temperature and humidity. The most common way for their preparation is the gradual evaporation of the components (cocrystal formers) from a drug solution; however, other acceptable approaches include sublimation, melting growth, or the ball mill grinding of several solid cocrystal formers [28]. Canine studies on the oral absorption profile, stability, dissolution, and suspension stability of carbamazepine: saccharin cocrystal compared well to crystal forms of carbamazepine alone. After just 5 minutes, the water solubility of fluoxetine HCl succinic acid cocrystal increased by around threefold, according to a separate investigation by Childs et al. The dissolving profile of the itraconazole L-malic acid cocrystal was found to be comparable to that of the commercially available formulation [29]. Some of the more conventional ways of crystallisation include grinding and milling, desolvation, evaporation, crystallisation from solutions, and sublimation. Modern crystal engineering techniques, such SCF technologies, are gradually displacing them in the production of pharmaceutical solids that meet certain requirements for stability and rate of dissolution. Melt sonocrystallization is a new method that

employs ultrasound to create hydrophobic drug molecules' hydrophobic drug molecules in a porous, rapidly dissolving particle form. According to these promising findings, crystal engineering approaches should be used more often to improve the solubility of medications that are not easily soluble in water. Salt generation, solvent dielectric constant changes, chemical drug modification, hydrate or solvate usage, soluble prodrug use, spherical crystallisation, ultrasonic wave application, and chemical modification are other methods that improve the solubility of pharmaceuticals that are weakly water soluble [30].

Hydrates/solvates: Adducts of molecules that include solvent molecules in their crystal structure are called solvates. A hydrate solvate is one in which water serves as the solvent.

Polymorph: When two or more compounds have distinct crystal structures but the same chemical content, we say that they are polymorphs. Because their network architectures and molecular conformations are different, the compounds' physicochemical properties are also different. In order to improve their solubility, several medicines may undergo polymorphism and crystallise into different polymorphic forms [31].

2.1.3. Drug Dispersion in Carriers Eutectic Mixtures

Although most compounds do not exhibit phase compatibility when combined to form a new entity, there are certain fractions at which the compounds inhibit crystallisation of one another, leading to a system with a lower melting point than the sum of its parts.

Solid Dispersion

The use of a hydrophilic matrix in conjunction with a hydrophobic medicament causes the two substances to molecularly scatter into either crystalline or amorphous particles.

Solvent evaporation method: Solvent evaporation occurs when the medication and carrier have been fully dissolving in an organic solvent. Example: furosemide with eudragits is in a thick form that has been powdered, sieved, and dried.

Hot-melt extrusion method: This process makes use of a co-rotating twin-screw extruder to manufacture carriers and active medicinal ingredients for hot-stage extrusion. The drug concentration dispersion is 40% w/w. various dosage forms, such as sustained-release pellets, are made using it.

Kneading technique: The process begins by turning the drug carriers into a paste with water. Then, the drug component is added and the combination is compressed for a certain amount of time. Once the mixture has dried, it is passed through a sieve.

Co-precipitation method: The co-precipitation approach involves adding a certain amount of the medication to a carrier solution while stirring the mixture continuously using a magnetic stirrer. It is important to keep the solution out of direct sunlight throughout this process. To avoid water loss caused by complicated structures, the precipitates are filtered via a vacuum and allowed to dry at ambient temperature [32].

Melting method: Here, the medication and its

carrier are ground together using a mortar and pestle. Once the components have been mixed, the mixture is heated until it reaches the melting point of each one. Then, it is cooled until it becomes a solid mass. For example, albendazole and urea are added to the mixture after crushing and sieving it.

Co-grinding method: The medicine and carrier are mixed in a blender at a certain speed and for a set amount of time. The next step is to move the mixture to the vibration ball mill section, where steel balls are introduced. For samples such as chlordiazepoxide and mannitol, pulverisation is performed and then the material is removed and kept at room temperature.

Gel entrapment technique: An organic solvent is used to dissolve hydroxyl propyl methylcellulose, which is then employed to form a translucent gel. The medication ingredient is then liquefied inside the gel by applying sonication for a predetermined duration. Following the removal of the organic solvent from the vacuum, the solid dispersions are reduced in size using a mortar and pestle and then separated by sieving [33].

Spray-drying method: The minimum effective dose of a medicine that can be dissolved in water using a suitable solvent and carrier. To prepare a clear solution, sonication or other suitable procedures are mixed and used. The solution is then spray-dried in a spray drier.

Lyophilization technique: The idea was to use this method instead of solvent evaporation. Molecular mixing techniques like this one entail combining medicinal chemicals with their carriers, dissolving them in a universal solvent, freezing them, and then subjecting them to sublimed heat to create a lyophilized molecular dispersion. .

Melt agglomeration process: The binder serves as a carrier to prepare the solid dispersion, which sets this procedure apart from others. On the other hand, solid dispersions may be made by either using a high shear mixer or heating the drug compound, binder, drug, and excipient to a temperature equal to or greater than the drug's melting point. By spraying the molten binder over the heated excipient, the medicinal component is distributed. One piece of alternative equipment that may be used with a rotary processor is a high-content binder and simple temperature control [34].

Solid Solutions

When two components are mixed, they crystallize together in a single homogeneous phase, considered a solid solution.

They are of two types: substitutional solid solutions (random and ordered), and interstitial solutions.

Substitutional: The condition where solute atoms occupy some space in the regular lattice sites of the parent metal (solvent) e.g., random (Cu-Ni) or ordered (Cu-Au).

Interstitial: The condition where solute atoms occupy the space in interstitial positions e.g., (steel C solute atoms in Fe).

Solid solutions can generally attain a quicker dissolution rate than the corresponding eutectic mixture [35]

Solubilization by Surfactants Microemulsion

Microemulsions are clear, transparent, unstable mixtures of two immiscible liquids—for example, water and oil. Emulsions are alleviated through an

interfacial film formed by surfactants.

Components of microemulsion

Aqueous phase: The aqueous phase most often used is water. It is necessary to modify the pH of the water phase in order to accommodate the phase behaviour. The aqueous phase of parenteral microemulmsions containing sodium chloride, glycerol, dextrose, and sorbitol must be isosmotic to blood in order for the mixture to be administered intravenously.

Oil phase: The choice of oil is based on the nature of the medicine and the mode of administration. It is expected that the oil will have high solubilization capacity for that medication. The surfactant tail assembly may be inflated when the oil undergoes shape changes. Their penetration is amplified for both saturated and unsaturated fatty acids. By penetrating the stratum corneum's extracellular gaps and breaking up the thick lipids, these fatty acids will enhance permeability. Unsaturated fatty acids use oleic acid to improve skin penetration, and the efficacy of this augmentation varies from drug to drug. One famous fatty acid ester that increases permeability is isopropyl palmitate [36]. There has been a recent trend towards using semi-synthetic oils instead of their natural counterparts due to their superior stability. To create a functional oil/water microemulsion arrangement, drugs with poor solubility in water must be soluble in the dispersed oil phase. A higher oil concentration causes the microemulsion droplets to be larger.

Surfactant: Compounds that possess a hydrophilic head and a hydrophobic tail are known as surfactants. Their presence at system interfaces causes changes to interfacial tension. They are present, albeit in low quantities. During the production of a microemulsion, the primary goal of the surfactant is to reduce the interfacial tension between the two systems to a minimal value. This facilitates the dispersion process. To make the microemulsion fit correctly, it gives it the right lipophilic nature. A surfactant is a molecule that can bring together polar and nonpolar groups. The value of the hydrophilic lipophilic balance (HLB) is used to choose a surfactant molecule. Based on this HLB value, we may infer whether the emulsion is oil-in-water or water-only [37].

Co-surfactants: Amphiphilic co-surfactants build up at the interfacial layer, which they then penetrate to enhance the interfacial film's fluidity. In order to create a microemulsion, single-chain surfactants must lower the interfacial tension of oil/water. To make the contact more fluid, chain alcohols are employed in conjunction with co-surfactants. As permeation enhancers, ethanol and medium-chain 1-butanol are used. The most important thing to think about is the surfactant-co-surfactant connection.

Classification of microemulsion

Depending on the composition, microemulsions are classified into three kinds:

- Oil-in-water microemulsions (o/w)
- Water-in-oil microemulsions (w/o)
- Bi-continuous microemulsions

The interface of the components in the three microemulsions must be stabilized with an adequate mixture of surfactants and/or surfactants

as a stabilizing agent [38].

Methods for the preparation of a microemulsion:

(i) Phase titration method (ii) Phase inversion method.

Self-Emulsifying Drug Delivery Systems (SEDDS)

This method is used to address the issue of limited bioavailability in drugs that are both poorly soluble and very porous. This technology is capable of liquefying hydrophobic medicinal compounds. A self-emulsification in situ emulsion is the result of the interaction between the SEDDS components and the gastrointestinal fluid upon delivery into the lumen of the gastrointestinal system. This interaction causes the production of a fine micro/nanoemulsion. The medication becomes more soluble and is then transported via lymphatic channels, avoiding the hepatic first-pass action. Various in vivo characteristics of the lipid formulations have been associated to the bioavailability-enhancing characteristic.

Processes for self-emulsification:

- Self-nano emulsifying drug delivery system (SNEDDS)
- Self-micro emulsifying drug delivery system (SMEDDS)

Composition of a self-emulsifying drug delivery system:

Active Pharmaceutical Ingredients (APIs): To improve the solubility of medications that aren't highly water-soluble, a self-emulsifying drug delivery method is often used. This is especially true for BCS class II pharmaceuticals as itraconazole, naproxen, vitamin E, mefanimic acid, danazol, nifedipine, simvastatin, etc. [39].

Excipients used in SEDDS:

- Oils
- Surfactants
- Co-surfactants
- Viscosity enhancers
- Polymers
- Antioxidant agents

Complexation

A complex is formed when two or more molecules form an entity via a shared link; this development is unconnected to any specific balance. Reason being, this is dependent on relatively weak forces, such as hydrophobic contacts, London forces, and hydrogen bonds.

Completion of Stanching

Typically, aromatic compounds' overlapping planar domains give rise to Stanching complexes, which remove water via strong hydrogen bonding connections caused by the nonpolar groups. Anthelmintic, benzoic, pyrene, salicylic, methylene blue, nicotinamide, ferulic, theobromine, gentisic, naphthalene, purine, and caffeine are the specific particles that are known to form stanching complexes [40].

Inclusion Complexation

A nonpolar particle or a portion of the guest particle is introduced into the cavity of various particles or a molecular assembly (the host) in order to create

an inclusion complexation. An ideal fit between the host cavity and the guest molecules is the primary physical need for inclusion complexation. With just the right amount of room for the guest molecule and a sufficiently tiny host particle cavity, it should be able to eliminate water as the binding of water to the nonpolar domains of both the host and guest molecules diminishes. There are three kinds of naturally occurring CDs: α-, β-, and γ-cyclodextrin. In order to increase solubility, cyclodextrin is used in complexation. It is a molecular event that cyclodextrin takes physical form. One guest particle may form a stable relationship with cyclodextrin by combining via a cavity. The arrangement of the hydroxyl group inside a particle causes the cyclodextrin molecule to have hydrophilic shallow exterior activities and hydrophobic interior activities. Positions for either a one-step or a sequential two-step reaction involving structural change are examined in the inclusion complexation of cyclodextrin. By forming an inclusion complex, cyclodextrins make medicinal compounds more water-soluble. Increased drug solubility is achieved when cyclodextrin is combined with several drugs, such as clofibrate, rofecoxib, melarsoprol, celecoxib, cyclosporin A, taxol, etc. [41].

APPROACHES FOR MAKING OF INCLUSION COMPLEXES

Physical blending method

By mechanically stirring the medication and CDs together, a solid physical combination may be easily produced. To get the necessary particle size on laboratory scale, the CDs and medicine are mixed thoroughly using trituration in a mortar. The mixture is then passed through an appropriate sieve. Physical mixes are often prepared on an industrial scale by thoroughly mixing the medicine with CDs in a fast mass granulator, typically for 30 minutes. In the chamber, where the temperature and humidity are carefully regulated, these physical mixes are pulverised and kept.

Kneading method

To make a paste, this technique involves immersing CDs in a small quantity of water or hydroalcoholic solutions. The aforementioned mixture is then mixed with the medicine and left to knead for an allotted period. After being kneaded, the mixture is allowed to dry and, if necessary, sieved. The complexation approach was used to improve nimesulide's solubility, according to Parik et al. using a mortar and pestle allows for laboratory-scale kneading. Machines like extruders make kneading a breeze on a massive scale. This approach is widely used for making inclusion complexes since it is easy, inexpensive, and common.

Co-precipitation technique

Here, the medicine and CDs are complexes that are co-precipitated. This procedure involves adding the necessary dosage of medication to the CD solution. Light is shielded from the contents while the system is maintained under magnetic agitation with regulated process parameters. In order to preserve the structure water from the inclusion complex, the precipitate that forms is separated using vacuum filtration and then allowed to dry at room temperature. Research on gliclazide-bete-

cyclodextrin inclusion complexes has been conducted by Moyano et al. about their solid-state properties and their dissolving properties. By introducing organic solvents at extremely rapid temperature changes, this method keeps a drug-CD solution near saturation. Inclusion complex-forming substance precipitation is the means by which it is acquired. Pulverising or filtering the fluid while heating it produces the powders. Unfortunately, this process isn't very appealing on an industrial scale because of its poor yield, the dangers of employing organic solvents, and the lengthier preparation time needed for bigger scale [42].

Solution/solvent evaporation method

To make the solid powdered inclusion compound, this approach calls for first dissolving the drug and CDs in two solvents that are compatible with each other. Then, the two solutions are mixed to create a molecular dispersion of the drug and complexing agents. The solvent is then evaporated under vacuum. In most cases, the CDs' watery solution is only mixed with the drug's alcohol solution. After a day of stirring, the resultant mixture is vaporised under vacuum at 45 ºC. A 60-mess sieve was used to filter the ground up dry substance. As an alternative to the spray drying approach, this procedure is easy to implement and costs less whether done in a lab or on a massive scale.

Neutralization precipitation method

Here, the medication is dissolved in alkaline solutions (such as sodium/ammonium hydroxide) and then mixed with an aqueous solution of CDs; the process is based on the neutralisation approach, which precipitates inclusion compounds. Using agitation and a hydrochloric acid solution, the resulting clear solution is neutralised until it reaches the equivalence point. At this same time, in conjunction with the creation of the inclusion compound, a white precipitate is being created. After filtration, the precipitate is allowed to dry. Improving piroxicam's solubility by beta-cyclodextrin complexation has been investigated by Doijad et al. One disadvantage of this approach is that it may degrade medications that are sensitive to acids and alkalis [43].

Milling/Co-grinding technique

The medication and CDs may be mechanically ground and milled to create solid binary inclusion compounds. The drug and CDs are well combined before being ground for the appropriate amount of time in an oscillating mill. The drug-CD binary system may also be prepared by using the ball milling technique. After loading a 60-mesh sieve with the mill's contents—balls of varying sizes and running it at a certain speed for a certain amount of time, the mill is discharged. Because it does not involve the use of harmful organic solvents, this technology is better from an economic and environmental perspective than competing alternatives. In the physical mixing approach, all that's needed is blending; however, in co-grinding, you also need to create a significant combined attrition and impact effect on the powder blend.[44]

Atomization/Spray drying method

The pharmaceutical industry often use spray-drying as a means to transform liquid ingredients into a dry powder. Because it removes water, it also

works as a preservation strategy, making stored goods more stable. One of the most common ways to extract the inclusion complex strating from a solution is by using this procedure. The combination goes through a rapid elimination process with the help of a propionate solvent and forms complexes very efficiently. In addition, the controlled particle yielding of the finished product from this process enhances the complicated drug's dissolving rate. For dry powder inhalation, Vozone et al. have created budesonide complexes in cyclodextrins and characterised the particle aerodynamics of these solid forms. The atomization/spray drying process has the extra benefit of forming a perfect complex between the drug and CDs via adequate and efficient interaction, but it also has the drawbacks of causing heat stress and having a poor yield of the final product [45].

Lyophilization/ Freeze drying technique

The lyophilization/freeze drying method is thought to be an appropriate way to obtain an amorphous, porous powder with a high degree of drug-CD interaction. By first freezing and then drying the drug-and CD-containing solution at decreased pressure, this method removes the solvent system from the mixture. Using this approach, it is possible to effectively transform thermolabile chemicals into complex forms. The procedure is time-consuming, and the powdered product does not flow well. One alternative to solvent evaporation is the lyophilization/freeze drying procedure, which involves molecular mixing of the medication and carrier in a shared solvent [46].

Microwave irradiation method

This method makes use of a microwave oven to trigger a chemical reaction between the medication and the complexing agent. A circular bottom flask is used to dissolve the medication and CD in a certain molar ratio using an organic solvent and water combination. For a brief period of one to two minutes at 60 ºC, the ingredients are heated in a microwave. Following the completion of the reaction, a sufficient quantity of solvent mixture is added to the reaction mixture mentioned above in order to extract any remaining free drug and CD that has not been complexed. Whatman filter paper is used to separate the precipitate that is so formed, and it is then dried in a vacuum oven at 40 ºC for 48 hours. In order to create the fast-solving formulation, Deshmukh et al. used a variety of superdisintegrants to create inclusion complexes of ziprasidone hydrochloride with beta-cyclodextrin and hydroxypropyl beta-cyclodextrin. The microwave irradiation process has a shorter reaction time and a better product yield, making it a new choice for industrial scale preparation.

Supercritical anti solvent technique

It was in the late 1980s when this technique was first proposed. A multitude of methods have been created and protected in the realm of supercritical fluid-assisted particle design since the first findings by Hannoy et al. in 1879. As an anti-solvent for the solute and a solvent for the organic solvent, carbon dioxide is used in the supercritical fluid antisolvent approach. Supercritical CO2 is useful for processing heat-labile medications because of its low critical temperature and pressure.

Additionally, it is cheap, non-combustible, and easy to remove from polymeric materials after the process is finished; consumers are not harmed by the little quantity of carbon dioxide that remains trapped within the polymer. One novel and effective approach to increasing the bioavailability of medicinally active substances is the supercritical particle production technique. Also, a novel alternative approach for manufacturing medicinal cyclodextrin complexes has been suggested, and it involves supercritical fluid operations. The enhanced mass transfer and higher solvating power of supercritical carbon dioxide have led to its suggestion as a novel complexation medium. This technique is among the most cutting-edge ways to create a solid-state drug-CD inclusion complex. There is a significant starting cost, but the approach is non-toxic as it does not use organic solvents, the procedure is rapid, and the maintenance cost is modest. The results are encouraging. This method involves dissolving the drug and CD in a suitable solvent, followed by pumping the solution into a pressure vessel under supercritical conditions via a nozzle (i.e., spraying into a supercritical fluid anti-solvent). The anti-solvent quickly diffuses into the liquid solvent, while the carrier solvent counter-dives into the anti-solvent. The combination becomes supersaturated, leading to the precipitation of the solute, and the solvent is transported away by the supercritical fluid flow[47]. This is because the expanded solvent has lower solvent power than the pure solvent.

Cyclodextrins as permeation enhancers

Not only may CDs improve solubility, but they can also stabilise and increase membrane permeability. When cyclodextrins are present, they increase the permeability across biological membranes. In the presence of CDs, Masson46 found that medicines with low water solubility had an enhanced ability to permeate. In order to facilitate drug transport across biological membranes, which have a lipophilic surface, these substances function as permeation enhancers. Because CDs have both hydrophilic and lipophilic properties, this is also possible with them. By interacting with the nasal epithelium, CDs may affect the tight junction and the lipid and protein composition of the membrane, which promotes the penetration of the membrane and makes them more effective nasal permeation enhancers.In pulmonary drug delivery systems, CDs may potentially be used as a permeability enhancer. The pace and amount of bacterial death are connected to the achievement of a high maximum concentration compared to the least inhibitory concentration when using rifampicin, an antibiotic that is so-called concentration-dependent. When nebulized with suitable pulmonary deposition, the rifampicin-CD inclusion combination may enhance drug transport to the lungs, and when supplied as an aerosolized solution, it can attain the requisite concentration of drug in the lining fluid of the bronchoalveoli [48].

Peptide Complexation

There are several benefits to delivering genetic materials, peptide hormones and growth factors, medications that are poorly soluble in water, DNA, and RNA using protein nanoparticles. Because of their stability and simplicity of manufacturing,

protein nanoparticles have many benefits over alternative colloidal carriers. Using a simple, inexpensive, and environmentally friendly synthesis procedure, nanoparticles of proteins from different sources may be created. These nanoparticles will have a greater chance of being used in living organisms since they consume less chemicals compared to nanoparticles made of other materials. In addition, increasing the water solubility of bioactive compounds and medications by complexation will lead to improved absorption and greater bioavailability. Because of this, the medicine may be taken at a lower dosage while still producing the intended effect, and the risk of adverse effects is reduced. The bioactive compounds will become even more resistant to digestion after the bioconjugate is formed. The use of this method will lead to better health care for people.

In their study, Chang et al. found that by enhancing the hydrophobic encapsulation of curcumin in egg white protein nanoparticles, they were able to decrease the degradation ratio and preserve the antioxidant activity of the encapsulated curcumin. A nanoconjugate with improved antibacterial, antioxidant, and anticancer action was created by a nanoassembly of lysozyme-conjugated curcumin, according to another work by Prathap et al. Indomethasone, a nonsteroidal anti-inflammatory medicine with low water solubility, was complexed with casein hydrolysate to increase its water solubility (Figure 2). Peptide complexation also has the potential to increase the water solubility of medicines that aren't very water-soluble [49].

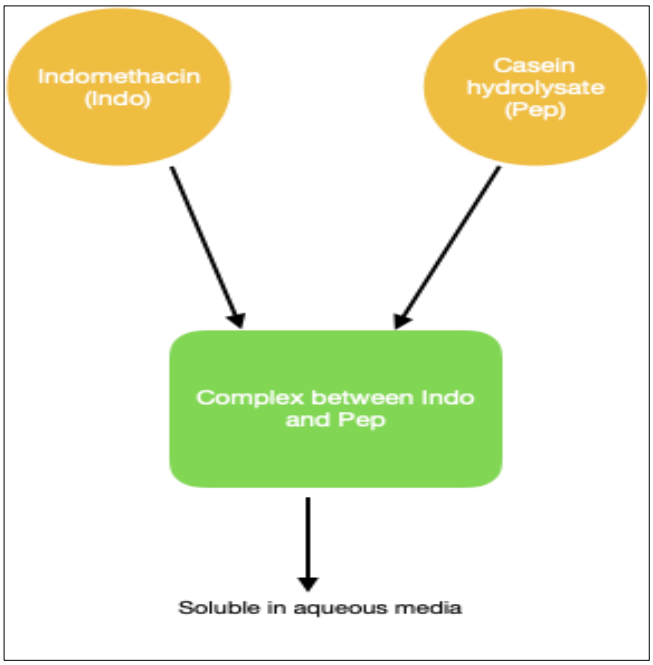

Figure 2. Enhancement of drug solubility of poorly aqueous soluble drugs through complexation with peptides

Cryogenic Techniques

To improve the pace of drug dissolution, scientists have devised cryogenic ways to create nanostructured amorphous drug particles with a high degree of porosity at very low-temperature circumstances. Nozzle type (capillary, rotary, pneumatic, or ultrasonic), liquid level (above or below), and cryogenic liquid composition (hydrofluoroalkanes, N2, Ar, O2, or organic solvents) are the defining characteristics of cryogenic innovations. Spray freeze drying, air freeze drying, vacuum freeze drying, and lyophilization are some of the drying procedures that may be used to create dry powder after cryogenic processing [50].

Cryogenic fluids sprayed with a freezing spray. Spray freezing cryogenic fluids was a technique developed by Briggs and Maxvell. A boiling agitated fluorocarbon refrigerant was used to

atomize the medication and carrier (mannitol, maltose, lactose, inositol, or dextran) in water. If you want your water solution to be more evenly distributed, you may use a sonication probe in the stirred refrigerant. Spray Freezing into Cryogenic Liquids (SFL). Amorphous nanostructured drug powder aggregates with a high surface area and excellent wettability have been produced using SFL particle engineering technology. To achieve rapid freezing and strong atomization into microdroplets, it uses direct liquid-liquid impingement between the automated feed solution and cryogenic liquid. Afterwards, the particles are frozen and lyophilized to create micronized powders that are dry and easy to work with [51].

Spray Freezing into Vapor over Liquid (SFV/L). Fine, highly wettable drug particles are generated by freezing drug solutions in cryogenic fluid vapours and then removing the frozen solvent. It is common practise for atomized droplets to begin freezing in the vapour phase prior to contact with the cryogenic liquid during SFV/L. The drug becomes supersaturated in the unfrozen areas of the atomized droplet when the solvent freezes, allowing for the nucleation and growth of tiny drug particles [52].

United Rapid Freezing (URF) has been developed. One new cryogenic technique, ultra-rapid freezing, uses solid cryogenic ingredients to build nanostructured medication particles with an increased surface area and the surface shape of choice. Instantaneous freezing and lyophilization (to remove solvent) result in micronized drug powder with enhanced solubility when drug solutions are applied to solid surfaces of cryogenic substrates. The pharmaceutical components are unable to crystallise or separate when subjected to ultra-rapid freezing, resulting in solid solutions and amorphous drug-carrier solid dispersions that are highly mixed [53].

Chemical Modifications

pH Adjustment

This is very important for how well drugs dissolve in water. The drug's solubility in water may be affected. Changing the pH of a solution allows one to manipulate the drug molecules' charge states. Solutes with low solubility tend to precipitate out of solutions when the pH is low enough that individual molecules do not have any net electric charge. At what pH is the net charge zero? That's the isoelectric point, frequently shortened to IEP.

Hydrotrophy

The solubilization process known as hydrotrophy increases the water solubility of the first solute by introducing a significant concentration of the second solute, the hydrotropic agent. Alkali metal salts of different organic acids make up hydrotropic agents, which are ionic organic salts. To "salt in" a solute is to add a salt that makes it more soluble in a particular solvent, while to "salt out" a solute is to add a salt that makes it less soluble. The "salting in" of non-electrolyte substances, referred to as "hydrotropic salts," is caused by a number of salts that include big cations or anions that are very soluble in water. This process is termed "hydrotropism." When there are a lot of additives, the solubility in water increases, which is called

hydrotrophy. Complexation including a modest interaction between the weakly soluble medications and hydrotrophic substances such sodium benzoate, sodium acetate, sodium alginate, and urea is more intimately linked to the process by which it enhances solubility [48]. It is known that hydrotropes may self-assemble in water. Many different types of substances have been found to display hydrotropic behaviour, making it difficult to classify hydrotropes based on their chemical structure. Some compounds that may be specifically mentioned include ethanol, aromatic alcohols such as resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids such as caffeine and nicotine, ionic surfactants such as diacids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene. The chemicals that have been examined the most often are aromatic hydrotropes that have anionic head groups. The availability of interacting pi (π) orbitals and isomerism contribute to their huge quantity, and their efficient hydrotrope activity. Salts of aromatic amines, such procaine hydrochloride, are examples of uncommon hydrotropes having cationic hydrophilic groups. On top of making chemicals more water-soluble, they can affect how surfactants aggregate to form micelles, how multicomponent systems manifest phase-wise in relation to nanodispersions and conductance percolation, whether surfactants and polymers become cloudy, and much more besides [54].

Co-Crystallization

Non-ionic supramolecular materials may form compounds with co-crystals. Without changing the chemical structure of APIs, they may be used to solve problems with physical qualities including medication solubility, bioavailability, and stability. The weak forces in co-crystals are intermolecular interactions like π-π stacking and hydrogen bonding, which are formed when two or more distinct molecular units are used in their preparation. It is well acknowledged that co-crystallization is a viable approach for optimising medication features since it changes the molecular interaction and composition of medicinal substances. Any active pharmaceutical ingredient (API) from an acidic, basic, or ionizable group may crystallise via the several paths provided by co-crystals. Because of their lack of ionizable functional groups, molecules with poor pharmacological profiles may benefit from this [55].

Co-Solvency

Reduced medication solubility in water is a common side effect of newly created entities as their structural complexity increases. It is common practise to use a combination of solvents to increase a compound's solubility in water when its therapeutic dosage is much lower. The drug's solubility in water is increased with the introduction of co-solvents, which provide several nonpolar groups. Pharmaceutical formulations sometimes call for the use of co-solvents, which may improve drug solubility in certain cases [56].

Salt Formation

Medications with an acidic or basic pH are less

soluble in water than their salt counterparts. Solubility improvement via salt creation is the preferred technique for the development of parenteral administration.

Nanotechnology in Pharmaceuticals

Nanotechnology has the potential to improve the water solubility of medications. Extensive research and use of structures and materials at the nanoscale (up to 100 nm) constitute nanotechnology. Because micronized materials tend to clump together, reducing the effective surface area for dissolving, micronization alone is insufficient to improve solubility and oral bioavailability for a number of NCEs [57].

The use of nanotechnology in the process of nanonization

Nanotechnology for nanonization:

- Nanomorphs
- Drug nanocrystal

Miscellaneous Methods

Supercritical Fluid Technology

Supercritical fluid technology was employed for the first time industrially in the early 1980s in the pharmaceutical sector. During that period, SCF technology was used in pharmaceutical industries for developing pharmaceutical materials through crystallization and precipitation. The SCF. Method is safe, eco-friendly, and cost-effective. The low operational parameters (pressure and temperature) make SCFs attractive for pharma research. An SCF survives as a single phase above its critical pressure (Pc) and temperature (Tc) [58].

Micellar Solubilization

One method of solubilization, known as micellar solubilization, involves adding the component to or onto micelles. Micelles' capacity to increase the water solubility of less soluble substances is their most notable feature. An example of solubilization in this context would be the gradual breakdown of a molecule into a less active, more stable isotropic solution by reversible interactions with surfactant micelles in water. When a compound's water solubility is plotted against the concentration of surfactant, it is often found that the drug's solubility decreases until the surfactant concentration reaches the critical molecular concentration (CMC). Solubility increases linearly with surfactant concentration after concentrations beyond the CMC, suggesting that solubilization plays a role in micellization. The micellar solubilization approach is used to increase the solubility and bioavailability of drugs that are weakly water-soluble, such as glimepiride, rosiglitazone, glyburide, repaglinide, pioglitazone, and glipizide [59,60].

Other miscellaneous methods are as follows:

• Direct capsule filling • Electrospinning method • Dropping method solution

Dropping solution method

Round particles are produced from melted solid dispersions using the dropping process, which also facilitates the crystallisation of certain substances. Pipetting a solid dispersion of a melting drug-carrier combination onto a plate causes it to solidify into spherical particles, a process often used in laboratory-scale production. Particle size and form are affected by variables like melt viscosity and

pipette diameter. To ensure that the melt solidifies into a spherical form upon dropping onto the plate, it is crucial to control the temperature, since viscosity is strongly temperature-dependent [61].

Direct Filling

One way to prevent grinding-induced changes in the drug's crystallinity is to fill hard gelatin capsules directly with the liquid melt of solid dispersions. Compared to the powder-fill method, this one yields greater fill weight and content homogeneity, and when cooled to room temperature, the molten dispersion solidifies within the capsule, decreasing operator exposure to dust and cross-contamination. The direct capsule filling approach did not work with PEG because the water-soluble carrier dissolved at a faster rate than the medication, creating drug-rich layers on top of the dissolving plugs and blocking their ability to dissolve further [62].

Electro spinning method

The polymer industry's electro spinning technology clearly incorporates nanotechnology and solid dispersion technology. This method involves applying a potential of 5–30 kV to a stream of a drug/polymer solution in liquid form. Fibres with diameters below one micron are produced when electrical forces triumph over the surface tension of the drug/polymer solution at the air interface. Collecting the generated fibres on a spinning mandrel or a screen produces woven fabric when the solvent evaporates. Variables such as electric field intensity, feeding rate, surface tension, and dielectric constant determine the fibre diameters [63].

Conclusion:

Formulation design, solid particle techniques, crystal engineering, micronization, solid dispersions, particle size reduction technologies, nanosizing, cyclodextrins, drug complexation, micelles, microemulsions, cosolvents, polymeric micelles, pharmaceutical salts, prodrugs, solid state alternation, drug nanocrystals, nanomorph technology, and a few relevant research reports and recent advances are all part of this review's critical summary. Formulation development relies on the solubility enhancement approach of poorly water-soluble pharmaceuticals to provide therapeutic activity and medication bioavailability at the target location. Oral absorption of medications with low water solubility is dependent on how quickly the drug dissolves in water, and solubility is the most fundamental prerequisite for GIT absorption. Screening programmes in the pharmaceutical sector have shown that roughly 40% of NCEs encounter different challenges throughout development and formulation. Low bioavailability and low water solubility are the major causes of this. A major obstacle in the field of pharmaceutical formulations is improving medication solubility and bioavailability. Class II and IV APIs are characterised by low water solubility, decreased bioavailability, and poor dissolution, as per the biopharmaceutical classification system. To make the medications more soluble, you may use any of the methods listed above, or a mix of them. If you want your formulation to achieve its goals—low manufacturing costs, improved patient compliance, reduced dosage frequency, and adequate oral

bioavailability—you need to choose your solubility augmentation approach wisely. The desired dosage form (tablet or capsule formulation), strength (immediate or modified release), and regulatory requirements (maximum daily dose of any excipientsand/or drug, approved excipients, analytical accuracy, etc.) are all factors to consider when choosing a method to enhance solubility. Other drug characteristics to consider include chemical nature, melting point, absorption site, physical nature, pharmacokinetic behaviour, and so on. Solubility enhancement is seeing a number of recent trends, with new processes and excipients being developed to aid molecules with low solubility. Extensive research is focused on better understanding these molecules and developing formulations that target them.

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