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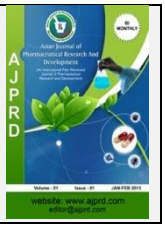

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Review Article

A Systemic Review on Techniques of Solubility Enhancement for Poor Water-Soluble Drugs

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A B S T R A C T

Background Investigating novel methods to improve solubility in order to increase drug absorption along with improving pharmaceutical formulations.

Main body of the abstract The limited water solubility of active pharmaceutical ingredients constrains their pharmacological efficacy. However, the solubility parameter must not be compromised, necessitating the use of various strategies to improve their bioavailability. The solubility of drugs significantly impacts their pharmacokinetics, pharmacodynamics, as well as other characteristics like drug distribution, protein binding, and absorption. This review article aims to provide a concise overview of both traditional and innovative techniques employed to enhance the solubility of medications that have low solubility. These methods encompass several physical and chemical techniques, such as reducing particle size, creating solid dispersions, Micronization using supercritical fluid technology, using cryogenic technology, utilizing complexation, employing hydrotrophy, employing crystal engineering, and developing solid self-emulsifying drug delivery systems. These various methods have contributed to improve the bioavailability of medications that are taken orally by enhancing the solubility of pharmaceuticals that have low water solubility.

Short conclusion Thereview offers comprehensive insights into tactics for enhancing solubility, along with the significance of solubility and the most recent strategies for augmenting it.

Keywords: Solubility, Bioavailability, Solubility Enhancement Techniques.

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INTRODUCTION

The bioavailability of a drug is depended on various factors such as the drug's aqueous solubility, rate of dissolution, permeability, susceptibility to efflux mechanisms, and first-pass metabolism[1]. Solubility refers to the quantity of a solute that may dissolve in a given amount of solvent at a given temperature and pressure, resulting a homogenous solution also solubility is define as the spontaneous interaction of two or more substances to produce a homogenous molecular dispersion[2-]. Solubility of drug may be expressed using a variety of concentration expressions such as parts, percentage, molarity, molality, volume fraction, and mole fraction[4].

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Oral administration is the one of the safest, reliable and acceptable routes for drug, and water-solubility of a drug have serious impact the oral bioavailability. Prior to absorption, a drug must be get in dissolved state at the location of absorption else its result to a suboptimal therapeutic response[5].

The Biopharmaceutics Classification System (BCS) is a scientific classification system that evaluates the in vitro dissolution and in vivo bioavailability of pharmacological products based on the intestinal permeability and water solubility of a medicinal ingredient. Based on the biopharmaceutical categorization system, the drug is categorized into four distinct classes, as shown in the table 1[6].

Table 1: Biopharmaceutical Classification System

Class	Solubility	Permeability	Absorption pattern	Drug Example
I	High	High	Well absorbed	Metoprolol, Diltiazem, Propranolol
II	Low	High	Variable	Phenytoin, Nifedipine, Danazol
III	High	Low	Variable	Cimetidine, Acyclovir, Captopril
IV	Low	Low	Poorly absorbed	Hydrochlorothiazide, Taxol, Furosemide

Compounds with low solubility (less than 10 mg/mL in water, for instance) may only partly, inconsistently, or slowly absorb, leading to a minimal response at the desired dose[7].

There has been a significant surge in the number of drug candidates that are insoluble in water throughout the drug development process. Specifically, more than 70% of new drug candidates exhibit poor water solubility. The limited capacity of this medicine class to disperse in gastrointestinal fluid and its poor water solubility significantly hinder its absorption when taken orally[8].

Drugs categorized as BCS class II, III, and IV have a limited potential to be absorbed orally. Various development in dosage forms to overcome solubility and improve the bioavailability of drugs; nevertheless, they all leading with some limitations. Hence, it is desired to enhance the solubility of drug by chemical alteration, physical approaches, particle technologies, and more. The objective of the article to review recent physical and chemical method that are used to enhanced the solubility of various drugs.

Main text

1. Physical Methods

Particle size reduction:

The solubility of drug is influenced by the ratio of its surface area to volume, which becomes greater as the size of the drug molecule decreases. The extensive surface area facilitates substantial interaction with the soluble solvent, hence enhancing solubility. Molecular size reduction procedures, such as contact and spray drying, apply greater mechanical pressure to generate dynamic chemical substances. The decrease in molecule size facilitates innovative, iterative, and economic enhancement of solubility. Thermosensitive materials are constrained by the fact that their size cannot be decreased by thermal transmission. Various size reduction techniques can be employed, contingent upon the nature of the material[9].

Micronization:

Micronization is a technique used to enhance the solubility of drugs by decreasing the size of particles. This enhances the rapidity at which the substance dissolves and improves its capacity to be absorbed by the body. The solution is micronized using jet mills and rotor stator coil mixing mills[10]. Micronization is a process that transforms the separated bulk of olive pomace, which is a dietary fibre, into a fine powder. This powder has enhanced solubility and yield[11].

Nanosuspension:

Nanosuspension technology has been identified as a viable option for the commercial transportation of hydrophobic pharmaceuticals. These machines are designed for compounds that exhibit poor solubility in both water and oil. Nanosuspensions are biphasic systems comprising of surfactant-stabilized medicines with nanoscale dimensions, which can be administered by topical, oral, or respiratory routes. The nanosuspensions typically exhibit an average particle size distribution within the range of 200 to 600 nm[12-13]. Nanosuspensions of Meclizine HCl, characterized by poor and variable bioavailability, were synthesised utilising the precipitation technique. This involved dissolving Meclizine in ethanol at room temperature and subsequently adding it to water containing stabilizers. In in-vitro research, a nanosuspension formulation with a particle size of 295 nm and a PDI value of 0.038 demonstrated enhanced dispersion by completely releasing the after 25 minutes[14].

Precipitation Technique:

The drug is initially dissolved in the solvent and subsequently in the antisolvent, resulting in the formation of a precipitate with enhanced solubility. The medicine has limited solubility in just a few numbers of solvents; therefore, it is crucial that the antisolvent does not combine with the solvent. This constraint imposes restrictions on the technology. It is important to exercise caution in order to prevent the inclusion of foreign substances during the process of crystal formation.[15].Enhancing the solubility and absorption via the mouth of danazol and naproxen nanosuspensions using precipitation technology[16-17].

Production of taxifolin nanoparticles with antioxidant properties utilising liquid antisolvent precipitation technique. This method enhances the separation of taxifolin nanoparticles by roughly 1.72 times and 3 times, respectively, and boosts the bioavailability by 7 times. Taxifolin, a flavanonol compound, may be synthesised as an antioxidant by the process of solubility using liquid antisolvent precipitation and dissolution of taxifolin nanoparticles. These quantities are around 1.72-fold and 3-fold more than the original amount of Taxifolin, respectively. The bioavailability of Nanoparticles of Taxifolin is sevenfold higher than that of the original Taxifolin. Nanoparticulate Taxifolin has a commendable antioxidant activity. compared to the first Taxifolin[18].

Media Milling:

Nanosuspensions were produced using a high shear media milling technique. The grinding medium, together with water, chemicals, and stabilizers, is introduced into the grinding chamber at a high shear rate and maintained at a regulated

temperature for a minimum duration of 2-7 days. The grinding media comprises glass, zirconia, or polystyrene. The collision generates a substantial shear force, which is employed to fracture the into particles that are nanoscale in size[19]. The crystallite size of the water-soluble bioflavonoid quercetin was reduced and its metastable equilibrium solubility, solubility, and bioaccessibility were improved using a milling process. The stabilizer employed in this study was hydrophobic modified starch, whereas quercetin nanoparticles were produced by media milling. The bioavailability of quercetin was assessed using the TNO dynamic intestinal model-1 (TIM-1), which simulates the conditions of the human intestine in a laboratory setting[20].

High Pressure Homogenization:

Homogenization technique was employed to create nanosuspensions of pharmaceuticals with low solubility. The drug and surfactant are forced through the nano-sized pore valve of the high-pressure homogenizer, resulting in the formation of cavities in the aqueous phase. This process converts the drug into nanoparticles[21].Amphotericin B, a polyene antifungal drug with low solubility, was synthesised using high-pressure Nanosuspension. Method of high homogenization. The data demonstrates enhanced dissolution in laboratory conditions and better absorption, distribution, metabolism, and excretion in living organisms, as well as increased solubility and availability in the body[22].

Combined Precipitation and Hominization:

High-pressure homogenization to produce nanocrystals after precipitation is an effective method to improve the solubility and dissolution behaviour of poorly soluble drugs[23]. Clarithromycin nanocrystals of BCS class II were synthesised using coprecipitation homogenization technique, with poloxamer 407 (2% w/v) and SLS (0.1% w/v) employed as stabilisers. The nanocrystals have a size of 460 ± 10 nm, which is rather tiny. Scanning electron microscopy (SEM) reveals that the nanocrystals have a cubic form, resembling the original particle morphologies. Furthermore, the nanocrystal structure remains unchanged from the drug, save for the presence of a peak. Density is a measure of the crystalline state and/or semi-amorphous form of a substance, which may be determined using techniques such as DSC thermogram and X-ray diffraction. The solubility of clarithromycin nanocrystals in vitro was enhanced in comparison to the dissolution of crude clarithromycin[24].

Ball Milling:

The production of amorphous materials is a crucial technique for enhancing the solubility of drugs. The amorphous form has a greater Gibbs free energy, resulting in enhanced solubility compared to the crystalline form[25]. Saquinavir, formerly a non-oral antiviral, has been reformulated to enhance its efficacy as an oral solution. The solubility of saquinavir mesylate in simulated saliva was measured both before and after the accident. It was found that the solubility rose by a factor of 9 after the accident. Thermal analysis and XRD revealed a little reduction in the melting point, from 242 to 236°C, as well as a progressive shift from a crystalline to an amorphous state, with some remaining crystalline structures[25].

Solid Dispersion:

Solid dispersions are employed as a technique to enhance the partitioning, dissolution, and gastrointestinal uptake of medicines with low solubility. An explosive is composed of a hydrophilic matrix and a hydrophobic material, which are two distinct components[26]. The use of weak acid fumed silica in the preparation of dispersion enhances the solubility of the hypertension drug telmisartan, which is an angiotensin II receptor antagonist. This results in a 1.19- and 1.15-fold increase in dissociation between pH values of 1.2 and 6.8[27]. The drug has poor solubility. Polyvinylpyrrolidone K30 (PVP) was created using the easily decomposable substance derived from polyethylene glycol 6000 and hydroxypropyl methylcellulose (HPMC)[28]. The solubility of telmisartan was enhanced by a factor of two when gold melt extrusion was employed using L-grade hydroxypropyl acetate succinate as a polymer material, as compared to the pure. Studies conducted on the release of telmisartan in vitro have demonstrated its conversion into amorphous material, leading to enhanced dissociation and stability[29].Quercetin extracts were made utilising heavy evaporation technique, incorporating Plasdone K-90, Plasdone K-30, and Eudragit RS-100. The solubility of quercetin was enhanced in the dispersion material compared to the pure solution. Both infrared spectroscopy and differential scanning calorimetry (DSC) provided evidence that the crystal structure of quercetin remained unchanged[30]. The use of solvent evaporation technology in dispersing products is a useful method for enhancing solubility and separation. However, it also has drawbacks that might impact safety, including expensive preparation costs and challenges in eliminating organic solvents. Residual crystallinity in carbamazepine dispersions observed by near-infrared spectroscopy[31].

Complexation:

A complex refers to the formation of an organisation consisting of two or more molecules that lack proper stoichiometry. London forces are dependent on feeble forces like hydrogen bonds and hydrophobic interactions. Some frequently employed ligands include cyclodextrin, caffeine, urea, polyethylene glycol, and N-methylglucamide. Cyclodextrins can enhance the solubility and separation of medicines. Cyclodextrins are cyclic oligosaccharides that are non-reducing, crystalline, and soluble in water. Cyclodextrins are synthesised from sugar monomers and have a toroidal structure resembling a donut. The three predominant cyclodextrins are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin[32]. The ternary inclusion complex system comprising curcumin extracts, hydroxypropyl-β-cyclodextrin, and polyvinylpyrrolidone K30 was synthesised using the solvent evaporation technique. The compound enhances the water solubility of curcuminoids (up to 70.3 µg/mL) and also enhances the separation rate and exhibits effects on human lung adenocarcinoma (A-549), human adenocarcinoma (HeLa), and human cancer cells. The activity was effectively executed in the HT-29 cell line[33]. The molecular dynamics analysis verified that the combination of domperidone and macrocyclic cyclodextrin resulted in their total encapsulation within the cavity, leading to the formation of a stable frozen state. The complexes enhance water solubility by a factor of three[34].

Engineered Particle Size Control

Cryogenic Technique:

The cryogenic spray technique is an innovative method for reducing the size of chemicals, which enhances their separation. This is achieved by generating a high-temperature nanostructured amorphous solution with significant porosity. Following the cryogenic procedure, the powder can be dried using many ways including spray freeze-drying, air freeze-drying, vacuum freeze-drying, and freeze-drying[35]. The co-amorphous system including atenolol and hydrochlorothiazide, which has low solubility in water, was created using cryogenic milling. Pharmacokinetic tests showed that this system exhibited enhanced separation of the medium and increased bioavailability compared to the clear form[i].

Crystal Engineering:

The extent to which a drug can disintegrate is determined by the surface area it occupies and its ability to be moistened by luminal liquids, which is influenced by the size of its molecules. The size of this molecule, which is crucial for the speed at which medicine breaks down, relies on either its crystallisation states or the methods used to break it down, such as agitation processing and liquid energy processing. Comminution processes possess the capacity to generate particles that are extremely heterogeneous, charged, and persistent. These particles have the ability to interfere with item execution and downstream management. To achieve the production of very pure powders with clear distribution of molecule size, crystal orientation, crystal structure (crystalline or amorphous), surface characteristics, and surface energy, techniques for crystal engineering have been developed. By modifying the crystallisation circumstances, such as employing various solvents, altering the mixing process, or introducing additional components, it is feasible to create gems with diverse pressing techniques in drug organisation. These precious stones are commonly referred to as polymorphs[37].

The physicochemical properties, such as solubility, rate of disintegration, melting point, and stability, might vary across different polymorphs of the same drugs. Many drugs have many forms, known as polymorphs. It is best to grow the most stable polymorph of the drug in order to maintain consistent bioavailability when used in various real-world storage conditions. Chloramphenicol palmitate solutions serve as a prominent illustration of how polymorphism affects bioavailability. It was shown that when the same amount of chloramphenicol palmitate was given, the stable polymorph resulted in lower levels of the drug in the blood, whereas the less stable polymorph resulted in much higher levels in the blood[38].

Another experiment demonstrated that tablets containing the oxytetracycline A polymorph structure had a higher rate of disintegration compared to tablets containing the B polymorph structure[39].Sublimation, crystallisation from arrangements, disappearance, heat treatment, desolvation, or crushing/processing are some commonly employed processes for crystallisation. These approaches, such as SCF advancements, are replacing traditional methods of gem designing[40].

Given these remarkable findings, it is imperative to utilise precious stone engineering methods more often in order to accelerate the dissolution of s with low solubility. Various methods employed to enhance the solubility of poorly water-soluble drugs encompass salt formation, alteration of the dissolvable dielectric constant, chemical modification of the, utilisation of hydrates or solvates, implementation of soluble prodrugs, application of ultrasonic waves, and spherical crystallisation. The solvent evaporation procedure utilised conformers of Imidazole and 5-fluorocytosine, both belonging to the BCS class IV, to generate solid crystallisation forms for furosemide, a potent loop diuretic. The structural characteristics of novel solid forms were investigated using single and powder X-ray diffraction (SCXRD, PXRD), Fourier Transform Infrared (FT-IR), proton Nuclear Magnetic Resonance (1H NMR), and thermal analysis (thermogravimetry, differential scanning calorimetry, and hot-stage microscopy). Compared to the pure form, notable enhancements were seen in permeability (increasing by 2.1 to 2.8 times), intrinsic dissolution (increasing by 1.3 to 2.6 times), and solubility (increasing up to 118 times)[41]. Through the use of different isoforms of crystals for co-crystallization, the solubility and physicochemical characteristics of the poorly soluble lornoxicam are enhanced, leading to enhanced in vitro dissolution. Utilising different variations of crystals to co-crystallize, enhances the solubility and physicochemical characteristics of the poorly soluble lornoxicam, leading to enhanced dissolution in laboratory settings[42].

Quinine (QUN), a drug used to treat malaria, has low water solubility. QUN's adoption of a specific conformation in complexes implies that the structure class has a greater statistical probability[43]. Vanillin (VAN) is extensively utilised in the fields of food, medicine, and optoelectronics. However, its limited solubility hampers its bioavailability and increases its application costs. Three active pharmaceutical ingredients (APIs), namely nicotinamide (NIC), isonicotinamide (INM), and isoniazide (INH), were employed to generate cocrystals with VAN. The present work establishes a foundation for developing cocrystals of natural goods and drugs, which will enhance the solubility and dissolution rate of natural products[44].

2. ChemicalMethod

pH Adjustment:

Merely having liquid chemicals is insufficient; certain compounds have the ability to undergo protonation (primarily) or deprotonation (corrosively), leading to their dissociation in water through pH alteration. At first, there are pH alterations in both oral and parenteral tissues. The injection of drugs may promote negative drug usage as it results in the blood having a pH level of 7.2-7.4. In order to assess the credibility of this strategy, it is necessary to establish the boundaries and acceptable variations of the selected pH value. The pH in the stomach ranges from 1 to 2, whereas in the duodenum it ranges from 5 to 7.5. Consequently, the drug's solubility in oral tissues is influenced by its entry into the digestive system. The most suited chemicals are those that are both stable and soluble during changes in pH and may undergo ionisation. The chemical can be classified as an acid, base, or zwitterion. It is

suitable for glass-like solvent combinations that lack sufficient lipophilicity[44-48]. When excipients are dissolved, they can increase the pH of the sample (such as tablets or containers) to a level that is higher than the pKa of weakly acidic pharmaceuticals. This, in turn, enhances the solubility of these s. Enhances the solubility of important drugs[49-50].

By using Neusilin S2, a pH adjuster, with telmisartan powder, a remarkable five-fold increase in isolation was found, achieving the desired microenvironment pH[51].Soybean meal is a protein-rich byproduct of agriculture that has the potential to be utilised as a protein isolate. The thermal stability of the soybean protein isolate formula was enhanced when changed to a pH of 10. Additionally, this adjustment resulted in a decrease in size, an increase in solubility, and improved emulsification, foaming, water, and oil binding capabilities. Hence, altering the pH level might potentially enhance the quality of the juice and render it suitable for a diverse range of culinary applications[52].

Co-Solvency

The solubility of chemicals that are not easily soluble in water can be increased by using a cosolvent, which is a water-miscible substance that can dissolve the material[53]. The co-solvent consists of water and at least one chemical. An aqueous solvent employed to induce a reaction that enhances the solubility of the inert solvent. This programme might be regarded as the most often utilised software due to its simplicity in distribution and assessment. Some solvents that can be used for mixing include PEG 300, propylene glycol, and ethanol. Co-dissolution refers to the ability to give drugs that have low solubility through both oral and parenteral routes. To minimise the concentration of dissociation in front of the tissue, injection schemes may necessitate the inclusion of water or the dilution with aqueous medium. Co-solvents have the ability to significantly enhance the solubility of a combined solvent in water, increasing it by thousands of times compared to the solubility of a single solvent. Cosolvents can enhance the solubility of insoluble solvents by combining them with other solubilization procedures and adjusting the pH. Utilising cosolvents is a very efficient approach to enhance the solubility of drugs that have low solubility[54-56].

To enhance the water solubility of etoricoxib, three distinct cosolvents, such as PEG 400, PG, and glycerol, were employed. This investigation also yielded data on the solubility of etoricoxib in different pharmaceutical solvents, which will facilitate the development and manufacturing of liquid products containing etoricoxib[57].

3. Other Methods

Superficial Fluids Methods: -

Supercritical fluids (SCFs) are nanosized and soluble liquids that are viscous and non-condensable, representing a recent breakthrough. The SCF cycle enables the reduction of chemical particle size to the submicron scale. Supercritical fluids are characterised by having temperatures that exceed both their critical temperature (Tc) and critical pressure (Tp). At temperatures close to the lowest possible level, supercritical fluids (SCFs) exhibit a high degree of compressibility and can undergo small changes in shape. This property effectively controls the viscosity and dimensions of the resulting liquid, which ultimately influences its ability to dissolve substances. When the drug substance is dissolved in a supercritical fluid (SCF), it has the ability to form various molecule sizes upon reproduction. Carbon dioxide and water are ubiquitous liquids. The SCF cycle enables the manipulation of nanoparticle spacing ranging from 5 to 2000 nm[58-62]. Several principles have been formulated and ensured in the measurement of SCF. The SCF technique is employed to purify non-reactive water for the purpose of isolating test samples and enhancing the solubility of low-quality solvents. The use of carbamazepine in polyethylene glycol (PEG) 4000 enhances the force of compression, resulting in an accelerated disintegration rate and prolonged disintegration duration of carbamazepine e. In this method, a mixture of carbamazepine and PEG-4000 in acetone (CH3)2CO is introduced into a container designed for sedimentation. By using supercritical CO2, soluble solids are extracted from the bottom of the container. Simple dispersion (SD) technology is a very efficient method for addressing issues such as limited bioavailability and low water solubility. Supercritical fluids (SCF) that include carbon dioxide have the capacity to enhance solubility and bioavailability. They are non-toxic, cost-effective, environmentally friendly, and highly efficient[63]. Conducted an experiment to determine the solubility of metoclopramide hydrochloride in supercritical carbon dioxide (SC-CO2) and obtained an accurate estimation of its solubility[64].

Micellar Solubilization: -

Employing supplementary surfactants to produce a product devoid of solvents would be a crucial, indispensable, and effective approach. Surfactants decrease the surface area and facilitate the segregation of lipophilic compounds in liquids. Additionally, they are employed for the purpose of stabilising suspensions. Micelle production takes place when the concentration of the surfactant exceeds the critical micelle concentration (CMC), typically ranging from 0.05% to 0.10% for most surfactants. This concentration threshold allows the surfactant to capture and enclose the within the micelles. This process is known as micellization and often enhances the solubility of soluble medicines in an inefficient manner. Surfactants enhance the ability of wastes to be wetted and accelerate the pace at which goods break down[65].Non-ionic surfactants that are often employed include polysorbates, poly-oxyethylene castor oil, poly-oxyethylene glycerides, lauryl macroglycerides, and monounsaturated and saturated fatty esters of lower molecular weight polyethylene glycol. Surfactants are frequently employed to solubilize microemulsions and eliminate contaminants[66-68].

Limited aqueous solubility frequently poses a significant challenge in the process of clinical advancement. Micellar solubilization is a commonly employed technique for enhancing the solubility of poorly regulated pharmaceuticals. The study focuses on the synthesis of seven antidiabetic s, namely gliclazide, glibenclamide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone. These pharmaceuticals are developed employing cationic, anionic, and non-ionic surfactants, as well as solubility combinations. The synergistic action of surfactants and buffers in ionic–nonionic mixed surfactant systems enhance solubilization and can serve as very effective solubilization devices[69].

Hydrotrophy: -

Hydrolysis is a chemical process in which the solubility of a substance in water is significantly increased by the addition of another substance, leading to an enhanced ability of the first substance to dissolve in water. Hydrotropes are ionic compounds made up of acid-resistant metal salts derived from various acids. The act of introducing chemicals or salts that enhance the solubility of a certain solute is referred to as "salting up" the solvent, whilst those that reduce the solubility are referred to as "salting out" the liquid. Salts that include several water-soluble anions or cations can create non-electrolyte "salts" and are referred to as "water-soluble salts". This occurrence is known as "hydrotropism". The presence of additives in food items enhances their solubility in water, leading to enhanced dissolution. Methods to enhance solubility are associated with the use of several compounds, such as sodium benzoate, sodium acetate derivatives, sodium alginate, urea, and weight loss s, which can be combined in a manner that is not very successful[70-72].

It enhances solubility, which is strongly linked to complexation with little collaboration between drinking water and solvent specialists. The solutes consist of several naturally occurring acids' soluble salts of base metals. Hydrotropes are naturally occurring ionic salts. Some specific examples of compounds are ethanol, resorcinol, urea, sodium ascorbate, pyrogallol, catechol, aromatic alcohols such as a- and b-naphthols and salicylates, alkaloids such as caffeine and nicotine, acid plasma surfactant, SDS (sodium dodecyl lauphenylsulphate), and dodecylatedoxidibenzene. Hydrotropes are employed to enhance the solubility of several s, including anti-tumour drugs, anti-inflammatory drugs, palliative drugs, antipyretic drugs, analgesic drugs, and xanthine pharmaceuticals[73-75]. The solubility of cefpodoxime proxetil is increased by using urea as a hydrotrope, which can be used as a solubilizer[76-78].

Lyophilization/Freeze-Drying Technique: -

The use of a lyophilization/freeze-drying technique was deemed essential in order to achieve a powder with permeability, which does not adhere to the hard structure of the and the CD. By appropriately freezing and drying the drug and CD-containing device, the stress on the soluble framework of the device is diminished. These approaches enable the creation of thermally unstable materials into intricate architectures. The drawbacks of this technique include the reliance on specialised equipment, potential unpleasant responses, and the generation of undesirable outcomes in equipment manufacture. Lyophilization, also known as freeze-drying, is a method that may be used as an alternative to soluble administration. It involves the process of atomically mixing and conveying the into a normal soluble distribution. Piroxicam (PX) is utilised as an antibiotic because of its limited aqueous solubility, dispersion, and mobility. A mixture of dimethylformamide (DMF), chloroform, and water was employed to enhance the solubility and separation of (PX) by freeze-drying[79].

4. Particles Technologies for Improved Bio-availability

Solid self-emulsifying drug delivery systems (SEDDS): -

Self-emulsifying drug delivery systems have become more popular as novel substances that can enhance the solubility characteristics of lipophilic and water-insoluble s. Their innovation is in providing a substitute for liquid self-emulsifying drug delivery systems (SEDDS) in the manufacturing of pharmaceuticals that are not soluble in water. Solid self-emulsifying drug delivery systems (S-SEDDS) are created by incorporating liquid or semi-solid self-emulsifying (SE) agents into powders or nanoparticles using various purification techniques. (For instance, techniques such as cargo adsorption, spray drying, melt granulation, and melt extrusion technology)[80].

The use of SEDDS has been researched to enhance the solubility and dissolution of several insoluble substances, as well as to develop additional techniques for preparing S-SEDDS. utilises a carrier. Utilise the spray dryer apparatus and employ the carrier substance. Gliclazide (GCZ) is a commonly prescribed for diabetes, although it has limited effectiveness when taken orally and is prone to degradation since it does not dissolve well in water. The objective of this study is to create a self-emulsifying drug delivery system (Solid-SEDD) that enhances the oral absorption of poorly water-soluble medicines (GCZ) by using fluoride R[81].

Complexation with Cyclodextrins: -

Cyclodextrins are a kind of cyclic oligosaccharides derived from starch. They consist of α-D-glucopyranose units joined by (α-1,4) linkages. Cyclodextrins have a hydrophilic outer surface and a lipophilic central chamber. There are different types of cyclodextrins based on the number of (α-1,4)-linked α-D-glucopyranose units, namely α, β, γ, δ, and ε cyclodextrins, which have six, seven, eight, nine, and (at least ten) (α-1,4)-linked α-D-glucopyranose units, respectively[82]. Cyclodextrins are large molecules with several hydrogen donors and acceptors, and they are unable to penetrate lipophilic layers. Cyclodextrins are versatile and transparent complexing agents used in the field of pharmaceuticals. They have the potential to enhance the solubility, bioavailability, and stability of active pharmaceutical ingredients (APIs). Additionally, they can mask the colour and taste of drugs and also prevent gastrointestinal and visual disturbance[83].

Cyclodextrins are extensively examined for their extensive uses in the drug formulation design, particularly their crucial role as a solubilizer for poorly soluble drugs[84-86]. Extensive investigations have been conducted on cyclodextrin as a solubilizer for poorly soluble medicines. An inquiry was conducted to examine the solubility of praziquantel in water. The drug complexes with α, β, and γ cyclodextrins were prepared using freeze drying technology and subsequently evaluated for their capacity to enhance solubility. Although the breakdown of praziquantel was more noticeable in each of the three buildings compared to the pure, the complex with β-cyclodextrin exhibited optimal stability, suggesting that the β-cyclodextrin complex may be the preferred choice for various formulations as well[87].

The results of these tests indicate that cyclodextrins, namely β-cyclodextrin, have the potential to be a beneficial additive in the development of therapeutic molecules, enhancing the solubility characteristics of drugs with low liquid solubility. Resveratrol, a naturally occurring stilbene, exhibits anticancer effects; yet, it is characterised by limited water solubility, chemical stability, and bioavailability. The aqueous solubility and stability of RES (Resveratrol) can be

enhanced by complexing it with sulfobutylether-β-cyclodextrin (SBECD)[88].

Polymeric micelles: -

Polymeric micelles have emerged as effective carriers for poorly soluble drugs by solubilizing them in their inner core and possessing desirable characteristics such as a relatively small size (100 nm) and a tendency to evade recognition by the mononuclear phagocyte system[89-90]. Polymeric micelles are small particles, less than 100 nm in width, that are formed by amphiphilic polymers dispersed in a liquid medium. These micelles have a core-shell structure, which can be either a di-block structure (with a hydrophilic polymer shell and a hydrophobic polymer centre), a multi-block structure with alternating hydrophilic and hydrophobic segments, or a copolymer with a hydrophilic backbone and hydrophobic segments[91].There are primarily two distinct methods for incorporating drugs into polymeric micelles: the primary approach involves quick disintegration, while the secondary approach involves the design of drug-loaded micelles by solvent removal[92-93].

The immediate disintegration procedure is a direct approach commonly employed for moderately hydrophobic copolymers. The process involves dissolving the square copolymers and the drug together in a water-soluble solution, which may need heating to initiate micellization. The second categorization of medicine stacking approach is utilised for amphiphilic co-polymers that are not readily soluble in water and necessitate an organic solvent that is compatible with both the co-polymer and the micelle formation is dependent on the dissolvable expulsion process, which is one of several methods including dialysis, oil-in-water emulsion, solution casting, and freeze-drying[94-96]. Polymeric micelle frameworks are innovative drug delivery systems that not only enhance the solubility of hydrophobic drugs in water, but also have applications in drug targeting, formulation of unstable drugs, and reduction of adverse effects. Due to its broad applicability to a large range of therapeutic compounds, the incorporation of drugs into polymeric micelles is a viable molecular strategy for formulating poorly soluble drugs in the future. Polymeric micelles have been employed as innovative drug delivery methods for the treatment and diagnostics of cancer[97].

Freeze-dried liposomes: -

Liposomes are spherical structures made up of phospholipids, with a double layer of phospholipids surrounding a watery interior. They have the ability to break down drugs that are soluble in lipids inside their lipid-filled area. Due to their biphasic nature and diverse plan and arrangement, they provide a dynamic and adaptable innovation for enhancing solubility[98].Encapsulation or incorporation of medicine into liposomes induces certain alterations in the pharmacokinetic and pharmacodynamic characteristics of the unbound drugs, therefore reducing toxicity and enhancing therapeutic efficacy in some cases[99].

The freeze-dried liposomal formulation of sirolimus (rapamycin) demonstrated enhanced stability after reconstitution compared to the traditional suspension form of the same drug. Furthermore, the stability of the formulation was further improved when dextrose was employed as a lyoprotectant during the freeze-drying process[98].Freeze-drying is suggested as a possible method to address the stability concerns of liposomal formulations. Various sugars such as dextrose, sucrose, and trehalose can be employed as lyoprotectants. This method has been reported to be used for the liposomal formulation of paclitaxel, with sucrose being employed as a lyoprotectant[97-98].

The use of freeze-dried liposome framework shows great potential in formulating pharmaceuticals with low aqueous solubility and enhancing the stability of liposomal design. The combination of liposomal fusion and freeze-drying can produce a powdered form of poorly soluble drugs that can easily dissolve in water. This molecular innovation can also be exploited to construct a wide range of medicinal agents that are not soluble in water. Estragole is utilised as a food preservative due to its antioxidant and antibacterial characteristics. However, because to its susceptibility to light and oxygen, its volatility and hydrophobic nature hinder its widespread usage. In order to enhance the stability of estragole, conventional liposomes (CL) and drug-in-cyclodextrin-in-liposomes (DCL) were synthesised using the ethanol injection technique. The study demonstrated that freeze-dried CL and DCL effectively preserved estragole[99].

Solid-liquid Nanoparticles: -

Solid lipid nanoparticles (SLNs) are colloidal drug delivery systems that mimic nanoemulsions. However, they differ in terms of lipid composition, since the liquid lipid component of emulsions is replaced by a solid lipid at room temperature, such as glycerides or waxes with a high dissolving point[100]. The interest in SLN as a novel molecule innovation is growing due to its potential as an alternative carrier system to conventional colloidal carriers, such as emulsions, liposomes, and polymeric micro and nanoparticles. Additionally, SLNs are being explored for their potential use in various methods of drug delivery. In their assessment, Mehnert and Mader have delineated both the benefits and drawbacks of SLN technology. SLN innovation is more advantageous than other colloidal transporter frameworks due to its potential for being developed as controlled drug release delivery systems. Additionally, it offers improved drug targeting, increased drug stability, absence of carrier toxicity, and the possibility of incorporating both lipophilic and hydrophilic drugs into the carrier. However, several challenges associated with solid lipid nanoparticles (SLN), such as poor drug loading capacity and concerns related to storage or administration (gelation, increase in molecule size, drug release from SLN), cannot be overlooked. Several studies have been conducted to investigate the efficacy of SLN in improving the solubility of poorly water-soluble drugs. During a study investigating the oral bioavailability of a poorly soluble called all-trans-retinoic acid (ATRA), it was discovered that incorporating ATRA into solid lipid nanoparticles (SLNs) significantly improved its absorption. This suggests that SLNs could be a promising approach to enhance the oral bioavailability of poorly soluble drugs.

This signifies a novel epoch of SLN in the formulation of models that facilitate and prolong drug testing for hydrophobic s. SLN innovation involves the preparation of s in various dosage forms to enhance their bioavailability, particularly for pharmaceuticals that are insoluble in water.

The study focused on the development and assessment of lipid nanoparticles coated with a polymer called 2-ethyl-2-oxazoline and chitosan for delivering ciprofloxacin to the eyes. The results indicated that chitosan-coated lipid nanoparticles (CSLN) had the ability to adhere to mucus and retain in the eye tissues[ii].

CONCLUSIONS

This review is focused on the methods enhancing the solubility of poorly water-soluble drug to deal with maintaining the bioavailability problem that elicited the pharmacological response. There is different type of conventional methods to reduce the particle size like particle size reduction, micronization, etc, but these methods have some limitations to the various drug leading to the thermal and chemical degradation of drug. The novel particle techniques can overcome the limitations of the methods and are more efficient methods of formulating poorly soluble drugs. The novel methods are developed from conventional methods where the basic principle remains the size reduction for solubility improvement. The use of polymers, cyclodextrins and liposomes for formulating poorly soluble drugs has been discussed, providing wide applications in improving the solubility as well as stability of the drug formulations. Each particle technology has its own importance and applicability in enhancing water solubility of poorly aqueous soluble drugs. The different methods mentioned in the article used alone or in combination to increase the solubility of the drug. Appropriate selection of solution-enhancing technology is one way to ensure that effective therapeutic goals such as oral bioavailability, reduced dose recovery, and improved quality are achieved at low construction costs.

List of abbreviations

API Active Pharmaceutical Ingredient

BCS Biopharmaceutical Classification System

CMC Critical Micellar Concentration

DSC Differential Scanning Colorimetry

SEDDS Solid self-emulsifying drug delivery systems

SLN Solid-liquid Nanoparticles

XRD X-ray Diffraction

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