Review on Solubility Enhancement Methods Use in BCS Class II Drug

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Abstract— **In the review paper discuses about solubility enhancement method of biopharmaceutical classification (Bcs) class two that is high permeability and low solubility. In that review paper discus of method complexation/solubilization (conjugation to dendrimers and co-solvent addition, and use of cyclodextrins or surfactants); reduction of particle size (micronization, nanonization. Drug nanocrystals are parent compound nanoscopic crystals that are less than 1 mm in size. They are usually stable and made entirely of the medication without any carriers. Recently, the the purpose of the self-emulsifying drug delivery system (SEDDS) technique is to improve the bioavailability and solubility of drugs that are not very soluble in water. Cyclodextrin complexes In1891, Villiers published the first description of cyclodextrin complexes. Between 1903 and 1911, Schardinger identified both α- and β-cyclodextrin and established the fundamentals of cyclodextrin chemistry. Freudenberg discovered γ-cyclodextrin in the 1930s and proposed that There may be larger cyclodextrins. Nanocarrier based on lipids the purpose of loading drugs into drug delivery systems is to raise the solubility of weakly water-soluble (and poorly permeable) pharmaceuticals in order to boost their bioavailability. Hydrotropy A technique for increasing solubility called hydrotropy entails adding a substantial amount of a second solute to make another substance more soluble in water. When the final particle size is fewer than 10 microns, the process is referred to as "micronization." In order for grinding to occur through interaction between particles or impact against a solid surface, micronization size reduction entails acceleration of particles**

Index Terms—**Biopharmaceutical classification (Bcs), micronization, self-emulsifying drug delivery system (SEDDS), Cyclodextrin, Lipid, Hydrotropy**

I. INTRODUCTION

Regarding pharmaceutical technology, improving the medication dissolving performance of active compoundsare still a major issue. The goal of improving therapeutic potency through better receptor binding mediated by hydrophobic interactions, as well as numerous push-throughput screening in non-aqueous solutions, have all resulted in the arrival of new drug candidates with poor water solubility[1]In the past ten years, solid dispersions made of sugar or polymer-based solids have been created using sophisticated manufacturing techniques such electrospinning and centrifugal spinning (melt and solution).based micro- and nanofibers[2]the methods for physical modification include the following: complexation/solubilization (via conjugation to dendrimers, the inclusion of co-solvents, and the use of surfactants or cyclodextrins); reduction of particle size (micronization, nanonization); production of drug dispersions in carriers (eutectic mixtures, non-molecular solid dispersions, and solid solutions); and production of polymorphs and pseudo polymorphs, including solvates).[3] Drug nanocrystals are parent compound nanoscopic crystals that are less than 1 mm in size. They are usually stable and made entirely of the medication without any carriers. [4] The characteristics of nanocrystals are as follows. (i) The surface area of the nanocrystals increases as the particle size decreases. According to the Noyes-Whitney equation, the rate at which nanocrystals dissolve increases with surface area. (ii) Ostwald-Freundlich According to the equation, shrinking the size to a more manageable range [5] Recently, the self-emulsifying drug delivery system (SEDDS) approach was created to improve the solubility and bioavailability of medications that are not particularly

soluble in water. SEDDS is a potential substitute for conventional oral lipophilic chemical formulations. When exposed to the fluids and motility of the gastrointestinal tract, isotropic solutions of oil, surfactant, cosurfactant, and medication create oil–water (o/w) emulsions. The drug is presented in a soluble form via this spontaneous emulsion formation, Despite the little size of the resulting droplet. offers A large surface area of the interfacial layer for drug absorption.[6] For drugs that are not very soluble in water, self-emulsifying drug delivery systems (SEDDS) are a crucial method with a lot of promise for increasing their oral bioavailability.[7] In 1891, Villiers published the first description of cyclodextrin complexes. Between 1903 and 1911, Schardinger identified both α- and β-cyclodextrin and established the fundamentals of cyclodextrin chemistry. Freudenberg discovered γ-cyclodextrin in the 1930s and proposed the possibility of bigger cyclodextrins.[8]Without requiring structural changes, A type of oligosaccharide composed of glucose units linked in a ring, cyclodextrins (CDs) show promise in combining with pharmaceutical compounds to improve their physical properties.[9] As transporters, lipids have the capacity to enhance oral pharmaceutical delivery by enhancing gastrointestinal solubilization and absorption because they can selectively absorb poorly bioavailable medications through lymphatics[10] The need to create appropriate drug-carrier systems to regulate, localize, and enhance medication delivery is growing. LBDDS can lessen the intrinsic restriction of slowly and incompletely dissolving poorly soluble medications and help the gastrointestinal tract (GIT) create solubilized structures following digestion, which may lead to absorption.[11] The majority of recently created medications are hydrophobic and hence poorly soluble in water, making it challenging to choose the best delivery method to ensure adequate bioavailability of these medications. In terms of absorption rate and bioavailability, Restrictive factors include low water solubility and dissolution rate certainly.[12] Even while it has been known During the 1960s, when hydrophilic charges medications, such the majority of class 3 medications, penetrate membranes significantly more deeply in the form of hydrophobic ion pairs [13]

II. PREPARATION METHOD

Small-particle nanocrystals (NCs) are thought to be a practical way to improve the insoluble drugs' oral bioavailability. NCs are distinguished by their high drug loading and low requirement for carrier materials when compared to the other nano-formulations previously described.[14] The creation of nanocrystals involves two fundamental methods: top-down technologies, such as nanonizing, and bottom-up technologies, such as controlled precipitation/crystallization. (the reduction of big medication powder in size, for example, through mechanical attrition). Nevertheless, combination approaches are also being used, which combine a pretreatment followed by a size-reduction operation[15] Quasi-crystalline alloys can be created using a variety of procedures, including quick quenching methods (such as gas atomization and melt spinning), solidification of molten alloys, and atomization) [23] The top-down and bottom-up synthesis procedures are the two techniques used to create ceramic composite powders. Bottom-up synthesis involves creating nanostructures in the material, layer by layer and atom by atom, ranging in size from tiny too big. Examples of bottom-up synthesis processes include sol-gel, melt spinning, melt quenching (MQ), chemical and physical vapour deposition (CVD and PVD), heat treatments, and others. Researchers typically use a specific bottom-up synthesis technique with controlled parameters to investigate changes in the properties of materials in order to develop a regulated microstructure and a fully dense polycrystalline material. [24]

2.1 Bottom–up precipitation methods

Wet bead milling and high-pressure homogenization are the two primary components of top-down technology, which is readily industrialized. Shear and impact forces produced mechanically cause drug particles to shrink. [16] followed by crystalline species breaking apart and the development of secondary nucleation centres. Supersaturation has no effect on the rate of top-down technology formation. Most previously documented anticancer medications have been produced using this method since it eliminates the need for organic solvents and makes production scaling up comparatively simple. [17] In conclusiondrugs that don't dissolve in either the phases

that are aqueous and organic can be treated using top-down technology. It works fast and is frequently applied to commercially available drug nanocrystals.[18] To precipitate the crystals in the bottom-up method utilizing solvent antisolvent precipitation approach, the drug must first dissolve in a solvent before being exposed to a non-solvent. The addition of polymer and/or surfactant controls the following development of the crystals to generate fine particle [21]

2.2 Top-down method (breaking large particles)

The necessary material is usually shielded by a mask in classic lithography, and the exposed material is then etched away. Chemical etching with an acid base or mechanical etching with an ultraviolet base the employment of light, X-ray, or electron beams determines the feature resolutions of the final result. Additional top-down strategies include techniques like block co-polymer lithography, nanoimprint lithography, and scanning probe lithography. [19] In short, impaction caused by milling balls breaks down the drug particles during in milling. The drug particles can be ground to reduce the amount of amorphous material. while suspended in an appropriate non-solvent, typically water for medications that are hydrophobic. This promotes any amorphous areas created during milling to recrystallize. For example, polyvinylpyrrolidone K-15-containing water was used to grind the drug particles.to create a danazol nanosuspension. [20] Top-down methods are by far the most important and practically applicable particle size reduction technology. Wet ball milling and high-pressure homogenization are typical top-down procedures. In these methods, a micronized powdered drug is first suspended in an aqueous or non-aqueous dispersion media that contains polymeric stabilizers. or surfactants.[22] Special Notes on Drug Indication Procedure Aprepitant Fenofibrate Sirolimus Acetate megestrol Sulphate of morphine HCl dexmethylphenidate HCl methylphenidate Tizanidine hydrochloride Phosphorus calcium Palmitate paliperidone Antiemetic Elevated cholesterol levels Immunosuppressive Drug Anti-anorexic A psychostimulant Relaxant for muscles Bone replacement Schizophrenia Increased bioavailability and quicker absorption Easy administration and increased bioavailability Increased bioavailability Lower dosage Extended release, increased medication loading and bioavailability Increased bioavailability and loading of drugs Increased bioavailability and loading of drugs Increased bioavailability and loading of drugs allows for cell attachment and development by mimicking the structure of bones. permits the delayed release of a medication with low solubility that can be injected. Grinding HPH and Nanosat Milling

Examples of commercially available nanocrystalline goods that have received FDA approval

Drug	Indication	Special Note	process
sirolimus	immunosuppressant	enhance bioavailability	Grinding
aprepitant	Antiemetic	to improve its solubility and absorption	Milling
fenofibrate	Hyperlipidemia	to enhance the drug's bioavailability	Milling
Paliperidone palmitate	Schizophrenia	permits the delayed release of a medication with low solubility that can be injected.	Milling, HPH
Calcium phosphate	Bone substitute	allows for cell attachment and development by mimicking the structure of bones.	NanOssTM
Tizanidine HCl	Muscle relaxant	Increased bioavailability and loading of drugs	Milling
Megestrol acetate	Anti-anorexic	Reduced dosing	Milling
Morphine sulfate	Psychostimulant	Increased drug loading, bioavailability, and prolonged release	Milling
Dexmethylphenidate HCl	Psychostimulant	Enhanced medication loading and bioavailability	Milling
Methylphenidate HCl	Psychostimulant	Enhanced medication loading and bioavailability	Milling

III. SELF EMULSIFYING DRUG DELIVERY SYSTEM

To increase the drug's solubility, a brand-new technique known as the Self Emulsifying Drug Delivery System (SEEDS) was developed recently. Isotropic blends of liquid or solid surfactants, natural or synthetic oils, and occasionally one or more hydrophilic solvents and co-solvents/co-surfactants make up SEDDS. [25] A summary of the novel excipients employed in SEDDS as well as the biopharmaceutical features of SEDDS are provided in this article. The utilization of Additionally presented are SEDDS and closely similar medication delivery methods based on lipids, with a focus on how SEDDS can be used in traditional Chinese medicine (TCM). [26] SEDDS, or Drug delivery systems that self-emulsify have become popularity due to their ability to increase the bioavailability and solubility of poorly soluble drugs [27] The process has been shown to be influenced by the type of oil/surfactant mixture, the ratio and concentration of the surfactant, and the temperature at which self-emulsification takes place. [28] For lipophilic pharmaceutical compounds that exhibit dissolution, SEDDS can boost the pace and scope of absorption. -absorption rate limitation, leading to reproducible profiles of blood time. However, it makes sense that all four pharmaceutical categorization system (BCS) class pharmaceutical categories can be classified using SEDDS.[29] SMEDDS creates clear microemulsions with a droplet size of 100–300 nm, whereas SEDDS usually creates emulsions with a droplet size of less than 50 nm. Unlike emulsions, which are fragile and metastable dispersed forms, SEDDS are easily generated, physically stable compositions. Consequently, these methods may boost the rate and volume of absorption and result in more consistent blood-time profiles for lipophilic medicinal molecules that show dissolution rate-limited absorption. [28] In addition to solubilization, intestinal lymphatic transport is promoted to increase oral bioavailability. and as a result, the added surfactants like polysorbate 80 decrease metabolism and P-glycoprotein-mediated efflux, increase intestinal permeability, and decrease first pass metabolism. [30]

SEDDS use in a variety of BCS category medications

Bcs class	Aqueous solubility	Membrane permeability	Hurdles overcome bySEDDS
I.	High	High	Breakdown by enzymes and outflow from the gut wall
II.	Low	High	Bioavailability and solubilization
III.	High	Low	Bioavailability, gut wall efflux, and enzymatic degradation
IV	Low	Low	Gut wall efflux, enzymatic breakdown, solubilization, and bioavailability

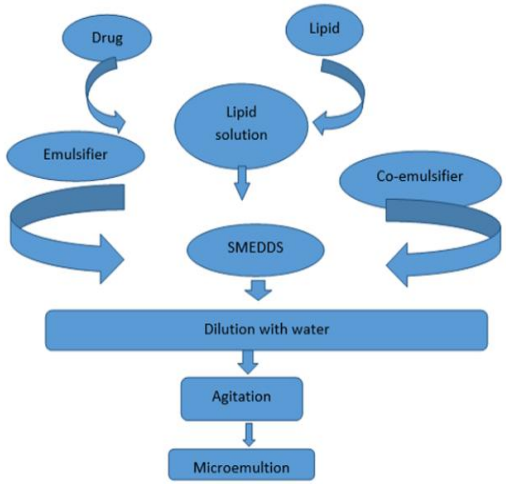
IV. SELF-EMULSIFICATION MECHANISM

According to Reiss, when the energy needed to increase the material's surface area is less than the entropy change that promotes dispersion, self-emulsification takes place. Spread out. The following equation describes the traditional emulsion's free energy, which is a direct function of the energy needed to form a new interface between the water and oil phases:[32] The free energy of the self-emulsifying processes, ΔG, is determined by

$\Delta G = \sum N \pi r2 \sigma$ where N is the number of droplets with r as their radius.

σ = Interfacial energy

It is evident from the above equation that spontaneous interface formation between the water and oil phases is unfavorable due to the elevated energy level. The system often known as SEDDS has not yet been shown to emulsify spontaneously in a true thermodynamic sense. [31]



The overall process of creating SMEDDS and then turning them into micro-emulsion

Advantages associated with SMEDDS [33]

- It is possible to shield drugs from the gastrointestinal environment.
- It is possible to protect sensitive medications.
- Selective medication delivery to a particular window of gastrointestinal absorption.
- It is possible to attain a consistent medication absorption profile.
- It is possible to improve oral bioavailability
- It is possible to enhance drug delivery profiles
- A wide range of dose forms, both liquid and solid, can be produced
- Predictable therapy is aided by less variability, including food effects.
- Drug payloads are heavy.

Disadvantages [34]

- Low solvent capacity (unless the medication has a high lipophilia)
- Turbidity of o/w dispersion
- A potential decrease in solvent capacity during dispersion. Less readily absorbed
- A probable decrease in solvent capability upon dispersion
- Dispersion-related loss of solvent capacity; perhaps indigestible
- Before the in vitro model's strength can be assessed, it requires more development and validation
- GIT irritation may result from chemical instability of medications and a high surfactant content.
- Precipitation medicines can be produced when Co solvents move into the firm or soft gelatine capsule shells.
- The dilution action of the hydrophilic solvent may cause a significant precipitation propensity of the medication upon dilution.
- It gets harder to validate formulations with several excipients [35].

V. CYCLODEXTRIN COMPLEXES

In 1891, Villiers published the first description of cyclodextrin complexes. Between 1903 and 1911, Schardinger identified both α- and β-cyclodextrin and established the fundamentals of cyclodextrin chemistry. Freudenberg discovered γ-cyclodextrin in the 1930s and proposed that There may be larger cyclodextrins.[36] A centre chamber that is lipophilic and an outside that is hydrophilic characterize cyclic oligosaccharides called cyclodextrins (CD), which are made up of 1,4-linked glucose units Natural substances called cyclodextrin (CD), cyclodextrin (CD), and cyclodextrin (CD) are found in trace quantities in beer and other fermented consumer products. In spite of the fact that the natural Despite being hydrophilic, CD, and the solubility of their complexes, especially CD, in aqueous solutions is limited. Therefore, even though both CD and CD can be present in parenteral drug formulations at low concentrations, the more soluble CD derivatives, such as 2-hydroxypropyl-CD (HPCD) and sulfobutylether CD sodium salt (SBECD), are advised for use in aqueous pharmaceutical solutions, such as parenteral drug formulations[37] Typical host molecules, cyclodextrins can tarp a wide range of molecules with one or two benzene rings or even larger ones with a side chain of similar size, to create complexes of crystalline inclusions. When water is present, hydrophobic molecules or portions of molecules that have the ability to fit into the cyclodextrin cavity are added.[38] Cyclodextrins can create dynamic molecular inclusion complexes with a range of medications by integrating the drug molecule into the central cavity, or more commonly, a lipophilic region of the molecule. No covalent bonds are formed or broken during the formation of the drug/cyclodextrin combination. The creation of the inclusion complex is primarily caused by electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, conformational strain release, charge-transfer interaction, and the release of enthalpy-rich water molecules from the cavity.[42] Because of this shape, cyclodextrin has a lipophilic core chamber lined by hydrophilic glucose residues, skeletal carbons, and ethereal oxygen. external surface [43] Bioavailability These days, for poorly soluble medications, physiologically based pharmacokinetics using computers (PBPK) modeling can predict increases in solubility and dissolution augmentation. For example, in vitro dissolution experiments and in silico modeling have been used to predict the pharmacokinetics of several formulations of a BCS class II chemical.[44] When low solubility cyclodextrins like β-cyclodextrin are utilized, hydroxy

acids demonstrated a synergistic mutual increase in both host and cyclodextrin solubility. This can be clarified by the way that hydroxy acids specifically interact with the host's hydrogen bond system or by the way the surrounding water molecules' hydrogen bond network varies.[45] The use of cyclodextrins (CDs) as carriers in the formulation of poorly soluble medications has enormous promise. CDs can create inclusion and non-inclusion complexes, which can change the physicochemical characteristics of guest molecules[46] Depending on their substitution, cyclodextrin derivatives can be hydrophilic or somewhat lipophilic; these characteristics can help explain how well they function as permeability enhancers.[47] When hydrophilic circumstances are present, cyclodextrins molecules having a polar hydrophilic exterior and an apolar hydrophobic cavity offer hydrophobic drugs known as the "inclusion complex."[48] Cyclodextrin (CD) complexation is one of the main methods to increase the solubility and bioavailability of medications. When medications are delivered as CD inclusion complexes, a number of pharmacokinetic characteristics may change in addition to the bioavailability. There may also be an increase in efficacy, which could lead to a decrease in the therapeutic dosage.[49] This includes inorganic materials like silicon, carbon, gold, and silica as well as organic materials including polymers, liposomes, and micelles. Because of their solid character and potential for porous structures that can encapsulate pharmaceuticals in their amorphous state through spatial confinement that limits the loaded drug's crystal development, inorganic materials can have advantages [50]

Some examples of marketed products containing cyclodextrin

Drug	Use	formulation	Trade name	company
-β-cyclodextrin (SBE-β-CD)				
Voriconazole	Improves solubility of antifungal drug	Intravenous injection	VFEND®	Pfizer
Midazolam	Improves solubility for sedative/anesthetic use	Intravenous injection	Dormicum®	Roche
Nicardipine	Enhances solubility for IV antihypertensive drug	Intravenous injection (IV solution)	Cardene IV®	Chiesi
Phenytoin	Improves solubility for anticonvulsant therapy	Intravenous injection (IV solution)	Solfoton®	Pfizer
Diazepam	Improves solubility for emergency benzodiazepine administration	Intravenous injection (IV solution)	Valium Injectable®	Roche
Ropivacaine	Improves solubility of local anesthetic	Injectable solution (IV/epidural use)	Naropin®	AstraZeneca
Esomeprazole	Enhances solubility of proton pump inhibitor for IV administration	Intravenous injection (IV solution)	Nexium IV®	AstraZeneca
Melphalan	Improves solubility for chemotherapy in multiple myeloma treatment	Intravenous injection (IV solution)	Evomela®	Spectrum Pharmaceuticals
γ-Cyclodextrin				
Sugammadex	Reverses neuromuscular blockade caused by rocuronium and vecuronium	Intravenous injection (IV solution)	Bridion®	Merck
Itraconazole [Hydroxypropyl-γ-cyclodextrin (HP-γ-CD)]	Enhances solubility and bioavailability of antifungal agen	Oral solution	Sporanox®	Janssen
Coenzyme Q10	Improves solubility and absorption of Coenzyme Q10 for cardiovascular health	Oral capsules/tablets	Q-Sorb® CoQ10	Various Manufacturers
Curcumin	Enhances solubility and bioavailability of curcumin for anti-inflammatory benefits	Oral powder/capsules	CAVACURMIN®	Wacker Chemie

Omega-3 Fatty Acids	Improves stability and bioavailability of Omega-3 fatty acids	Oral powder	CAVAMAX® Omega-3	Wacker Chemie
Resveratrol	Enhances solubility and absorption of resveratrol for antioxidant and cardiovascular benefits	Oral powder/capsules	CAVAMAX® Resveratrol	Wacker Chemie
Hydroxypropyl-β-cyclodextrin (HP-β-CD)				
Aripiprazole	Long-acting injectable antipsychotic	Intramuscular (IM) injection	Abilify Maintena®	Otsuka/Bristol-Myers Squibb
Diclofenac	Improves solubility for ocular anti-inflammatory use	Ophthalmic eye drops	Voltaren Ophtha®	Novartis
Progesterone	Hormone therapy for progesterone deficiency	Soft gelatin oral capsules	Utrogestan®	Besins Healthcare
Ibuprofen	Improves solubility for pediatric use	Oral suspension (liquid formulation)	Nurofen®	Reckitt Benckiser
Raloxifene	Enhances bioavailability for osteoporosis treatment	Oral tablets	Evista®	Eli Lilly
Alprostadil	Enhances drug solubility for erectile dysfunction treatment	Topical cream	Vitaros®	Ferring Pharmaceuticals
Budesonide	Improves solubility and absorption for nasal corticosteroid treatment	Nasal spray	Rhinocort®	AstraZeneca
Furosemide	Enhances solubility for diuretic therapy	Intravenous injection (IV solution)	Lasix Injection®	Sanofi
Mitomycin-C	Improves solubility for anticancer chemotherapy	Intravenous injection (IV solution)	MitoExtra®	MediCure
Tacrolimus	Enhances solubility for immunosuppressive therapy in organ transplants	Oral extended-release capsules	Advagraf®	Astellas Pharma
Bortezomib	Improves solubility for multiple myeloma treatment	Intravenous injection (IV solution)	Velcade®	Takeda
Candesartan	Improves solubility of antihypertensive drug	Oral tablets	Atacand®	AstraZeneca
Salbutamol	Enhances solubility for better lung absorption in asthma treatment	Nebulizer solution	Ventolin Nebules®	GlaxoSmithKline
Nitroglycerin	Enhances drug stability in angina treatment	Sublingual tablets	Nitrostat®	Pfizer
Erythromycin	Enhances solubility of macrolide antibiotic	Intravenous injection (IV solution)	Erythrocin IV®	Abbott
Levocetirizine	Enhances solubility for antihistamine therapy	Oral solution (liquid formulation)	Xyzal®	UCB
β-Cyclodextrin				
Piroxicam	Improves solubility and absorption of piroxicam (NSAID) for pain relief	Oral tablets	Brexin®	Chiesi
Nifedipine	Enhances solubility of nifedipine for hypertension and angina treatment	Oral tablets	Nifedicor®	Recordati
Hydrochlorothiazide	Improves water solubility of the diuretic hydrochlorothiazide	Oral tablets	Cyclo-HCTZ	Experimental Formulation
Clotrimazole	Improves solubility and stability of the antifungal clotrimazole	Topical cream	Canesten® Cream	Bayer

Dexamethasone	Improves solubility and stability of miconazole for oral antifungal treatment	Oral solution	Dexsol®	Martindale Pharma
Omeprazole	Enhances solubility and stability of omeprazole for gastric acid control	Oral tablets	Omebeta®	S.A.L.F.
Risperidone	Improves solubility and bioavailability of risperidone for schizophrenia treatment	Oral solution	Risperdal®	Janssen

VI. COORDINATION COMPLEXES

Coordinate bonds are what create coordination complexes, in which two interactants partially transfer a pair of electrons. The metal-ion coordination complexes between bases and metal ions are the most significant examples. [39]

Complexes Of Molecules

Molecular complexes are produced by noncovalent interactions between the ligand and substrate. Among the numerous complex species in this class are dimers, ion pairs, inclusion complexes, small molecule-macromolecule species, and small molecule-small molecule complexes. One of the molecules in these complexes, referred to as the "host," creates or has a hole that it can allow a "guest" molecule to enter.[39]

Cyclodextrin Synthesis

The microorganism that produces cyclodextrins is called macerals. Using Bacillus macerals amylase to treat starch is one way to create cyclodextrins. The resulting raw material contains around 60% cyclodextrin, 20% βCD, and 20% ϒ CD. Small amounts of additional substances, such as proteins, are also present in the result.[40] cyclodextrins, are naturally occurring as cyclic oligosaccharides that dissolve in water and are made up of d-glucopyranose units that are -1,4-linked. Hydroxypropyl-cyclodextrin (HP CD), one of the most notable classes of modified CDs, has a higher solubility in water than the parent CD (CD).[41]

VII. LIPID BASED NANOCARRIER

The goal of loading pharmaceuticals into drug delivery systems is to increase the solubility of medications that are weakly water soluble and poorly permeable in order to increase their bioavailability. These requirements are satisfied by delivery systems that are based on lipid raw materials and are designed for a a range of delivery methods, including parenteral, pulmonary, oral, and topical. Toxicological incidents are less likely when generally recognized as safe (GRAS) products are used. [51] Delivery via lipids Drug delivery systems is growing in popularity due to their capacity to get around some of the Poorly absorbed medications are linked to more resilient chemical and physical barriers.[54] Additionally, lipid nanoparticles solid lipid nanoparticles, for example, or Leading the way in the quickly evolving field of nanotechnology, SLNs have a number of potential uses in drug delivery, clinical treatment, research, and other fields Lipid nanoparticles can be created to target novel treatments at the second and third levels of medication targeting because of their small size characteristics. [52] By mimicking the synthesis of chylomicrons, lipid carriers may improve the lymphatic transport of lipophilic substances. Lipophilic medications attach to the chylomicrons' triglyceride core to enter the lymphatic system.[53] The need to create appropriate drug-carrier systems to regulate, localize, and enhance medication delivery is growing. Lipid-based drug delivery systems [LBDDS] can lessen the intrinsic restriction of slowly and incompletely dissolving poorly soluble medications and help the gastrointestinal tract (GIT) create solubilized structures following digestion, which may lead to absorption.[55] Oil-in-water nano emulsions are isotropic, thermodynamically stable emulsions at the nanoscale. These systems typically consist of two immiscible phases: an exterior aqueous phase and an inner oil phase.[56] For increasing oral bioavailability, one of the most promising methods is a drug delivery system based on phospholipids (PL). When immersed in water, PLs' amphiphilic nature, biocompatibility, and biodegradability allow them to form lipid bilayers. Because their hydrophilic head groups face the water on both sides and their hydrophobic tails align with one another, PLs are thought to be suitable excipients for medications that are poorly soluble in water. [57].

In connection with LBDDS, chemicals that correspond to BCS classes II and IV or have low aqueous solubility are commonly discussed. For a number of physical and chemical reasons, compounds may fall between BCS II and IV, making it useful to identify the origin of the low solubility.[58] In 1986, Dior released the first liposomes onto the cosmetics industry. After a few years, pharmaceutical items containing liposomes made their debut on the market.[62] The methodical procedure involves pre-selection of excipients based on their melting point, fatty acid content, digestibility, disposability, and HLB value. Next, specific excipients are tested. for compatibility, stability, solubility, and characteristics of dissolution and dispersion; choosing a formulation method that works well for the intended dosage form; and creating suitable animal models to forecast the formulation's effectiveness in vivo; For improving the recipe while considering drug solubility and loading profiles into account.[63] Microemulsions (MEs) are formulations based on lipids. These are water, oil, and surfactant systems that are commonly mixed with a cosurfactant. Their droplet size is typically between 20 and 200 nm, and they are transparent, isotropic, and thermodynamically stable.[64]

VIII. ORAL LIPID-BASED MEDICATION DELIVERY METHOD

Lipid-based drug administration increases oral bioavailability while decreasing chemical and enzymatic drug degradation. One more crucial the high surface area of lipid-based formulations enables them to exhibit robust resistance to intestinal lipase enzyme attack and protects the medication from the unfavorable conditions of the gastric system. [59] Lipids include things like waxes, fatty acids, steroids, triglycerides, and partial glycerides. Mixtures of mono-, di-, and fatty acids with different chain lengths and degrees of unsaturation make up natural ring oils and fats make up triglycerides. [60] Bioactive chemicals originating from plants are continually in demand since they are thought to be safer and more natural. The secondary metabolites of plants are called polyphenols, and they comprise around 10,000 distinct molecules having hydroxyl groups and one or more aromatic rings.[61] This study primarily aims to improve the permeability of fenofibrate through the formulation of a microemulsion for oral use. The choice of excipients was founded on fenofibrate's ability to be solubilized and its enhanced permeability through the GI membrane. Together with the factorial design, ternary phase diagrams were made. The experimental design's goal is to use a low concentration of surfactant to decreaseenhance the zeta potential and droplet size. Two methods were used to examine the optimized microemulsion's permeability over the GI membrane, and the outcomes were contrasted with those of the free drug powder.[64] Drugs with low water solubility or other biologic restrictionsor stability, can benefit from the therapeutic potential of lipid-based nanocarriers, which can also offer substitutes for the parent route. [65] Oil droplets carrying hydrophobic medications form Nano emulsions, which are isotopic and kinetically stable emulsions supported by a tiny emulsifier layer.[66] The nanocarrier technique has received a lot of interest lately because the surface area of smaller particles is greater., which speeds up dissolving and improves oral bioavailability. If a solubility increase of more than a few orders of magnitude is required, methods such as complexation, salt generation, or polymeric micelle can be used to develop a drug delivery system. [67] There are two main categories of lipid-based nanocarriers.To overcome the shortcomings of traditional colloidal carriers such emulsions, liposomes, and polymeric nanoparticles, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were developed.[68] Solid lipid nanoparticles were used to introduce the articles. (SLN), whereas the second generation of SLN is commonly referred to as nanostructured lipid carriers (NLC). Combinational advantages from various systems of carriers, including liposomes and polymeric NP, are the primary drivers for the development of SLN. They are made of medically recognized like liposomes and nano emulsions, Lipids and fatty acids are examples of biocompatible excipients. Like polymeric nanoparticles, they can successfully shield the loaded active medicinal substances from chemical deterioration in a harsh biological environment, and their solid matrix offers the greatest flexibility in altering the drug's release patterns. High pressure homogenization is another industrial method of producing them. Due of all these favorable attributes, SLN [69] The solid matrix of the lipid can control the release of encapsulated compounds. An o/w emulsion,

or oil phase distributed throughout the water phase of the emulsion, is created in SLN by a solid lipid or mixture of solid lipids with particle sizes ranging from 80 to 1000 nm.[70] The low toxicity of lipid-based nanocarriers makes them more significant.[71] Compared to other more traditional colloidal carrier systems, lipid particles with a solid lipid core have a number many advantages, such as a simple and expandable manufacturing technique, reduced toxicity from their organic solvent-free natural lipid components, and enhanced cellular absorption. [72]

Some marketed lipid-based drug delivery formulations

Company	Drug	Indication	Mechanism
Johnson & Johnson (Janssen Pharmaceuticals)	Doxorubicin (liposomal formulation)	Cancer (such as multiple myeloma, Kaposi's sarcoma, breast cancer, and ovarian cancer)	Liposomal formulation of doxorubicin that improves the drug's pharmacokinetics and reduces its toxicity to healthy tissues.
Celgene (Bristol Myers Squibb)	Paclitaxel (albumin-bound formulation)	Cancer (such as non-small cell lung cancer, breast cancer, and pancreatic cancer)	Albumin-bound nanoparticle formulation that enhances the solubility and delivery of paclitaxel, improving bioavailability and reducing side effects.
Celator Pharmaceuticals (Acquired by Jazz Pharmaceuticals)	Daunorubicin and Cytarabine (liposomal formulation)	Acute Myeloid Leukemia (AML)	A liposomal combination of daunorubicin and cytarabine, providing controlled release and improving the pharmacokinetics and tumor targeting of both drugs.
Pacira Pharmaceuticals	Morphine sulfate (liposomal formulation)	Postoperative Pain	Liposomal formulation of morphine, providing extended-release delivery for long-lasting pain relief after surgery.
Spectrum Pharmaceuticals	Vincristine sulfate (liposomal formulation)	Examples of lymphomas include non-Hodgkin lymphoma and acute lymphoblastic leukemia.	Liposomal formulation of vincristine to improve its pharmacokinetics, reduce neurotoxicity, and enhance drug delivery to tumor cells.
Ipsen	Irinotecan (liposomal formulation)	Cancer(e.g., metastatic pancreatic cancer)	Liposomal formulation of irinotecan that improves drug delivery and enhances the therapeutic effect of the chemotherapy agent.
Gilead Sciences	Amphotericin B (liposomal formulation)	Fungal infections (e.g., systemic fungal infections, aspergillosis)	Liposomal formulation of amphotericin B designed to reduce nephrotoxicity while improving the efficacy of the antifungal treatment.
Samyang Biopharmaceuticals	Paclitaxel (micellar formulation)	Cancer (e.g., breast cancer, non-small cell lung cancer, ovarian cancer)	Micelle-based formulation of paclitaxel that improves solubility and allows for targeted drug delivery.
Fresenius Kabi	Lipid emulsion (contains soybean oil, egg yolk phospholipids, and glycerin)	Parenteral nutrition, lipid replacement therapy	Oil-in-water emulsion providing a source of calories and essential fatty acids to patients unable to consume oral nutrition.
Chimerix (formerly owned by Neutec Group)	Calcium phosphate (lipid-based delivery system for oral rinse)	Oral mucositis (especially for cancer patients undergoing chemotherapy or radiation therapy)	A lipid-based formulation of calcium phosphate that helps to restore normal tissue hydration and reduce pain in patients with mucositis.
Insmed Incorporated	Amikacin (liposomal formulation)	Mycobacterium avium complex (MAC) lung disease	Liposomal formulation of amikacin, designed for aerosol delivery to improve drug targeting to the lungs.

Santen Pharmaceutical Co.	Unoprostone (lipid-based ophthalmic formulation)	Glaucoma and ocular hypertension	Lipid-based emulsion that improves the delivery of unoprostone to the eye to reduce intraocular pressure.
Amgen	Panitumumab (lipid-conjugated antibody)	Cancer of the colorectal region (with treatment)	monoclonal antibody that is lipid-conjugated and targets the cancer cells' epidermal growth factor receptor (EGFR).
Eli Lilly and Company	Duloxetine (lipid-based formulation)	Depression, generalized anxiety disorder, diabetic neuropathy	Lipid-based formulation of duloxetine used for improved absorption and bioavailability in treating mood and nerve disorders.
Spectrum Pharmaceuticals	Leucovorin Calcium (lipid-based formulation)	Cancer (e.g., colorectal cancer, methotrexate rescue)	Lipid-based formulation of leucovorin that enhances the bioavailability and stability of the drug to prevent or treat methotrexate toxicity.
NovaDel Pharma	Liposomal platinum complex (liposomal formulation)	Cancer (such as non-small cell lung cancer and ovarian cancer)	Liposomal formulation of platinum-based chemotherapy drug that enhances the delivery to tumor cells, improving efficacy and reducing systemic toxicity.
Sandoz (Novartis)	Etanercept (lipid-based formulation)	Rheumatoid arthritis, psoriasis, ankylosing spondylitis	Lipid-conjugated biological drug that targets tumor necrosis factor (TNF) to reduce inflammation in autoimmune diseases.
Novartis	Octreotide acetate (lipid-based extended-release formulation)	Acromegaly, neuroendocrine tumors, gastrointestinal disorders	Lipid-based extended-release formulation of octreotide acetate for controlled, long-acting release in the body, reducing the frequency of injections.
Acorda Therapeutics	Capsaicin (lipid-based patch formulation)	Postherpetic neuralgia, neuropathic pain	Lipid-based patch formulation of capsaicin for localized pain relief. Capsaicin desensitizes nerve endings, providing long-term pain relief.
Pfizer	Gemtuzumab Ozogamicin (liposomal formulation)	Acute Myeloid Leukemia (AML)	Liposomal conjugate of gemtuzumab, an anti-CD33 monoclonal antibody linked to the chemotherapy drug calicheamicin. The liposomal formulation improves the delivery of the chemotherapy agent directly to leukemia cells.
Fresenius Kabi	Lipid emulsion (soybean oil and egg yolk phospholipids)	Parenteral nutrition and lipid replacement therapy	For individuals who are unable to receive oral nutrition, an oil-in-water emulsion is utilized as a source of calories and vital fatty acids.
Baxter International	Lipid emulsion (soybean oil, olive oil, fish oil)	Parenteral nutrition	A mixture of soybean oil, olive oil, and fish oil, used to provide essential fatty acids and energy in patients who require intravenous nutrition.
Akcea Therapeutics (a subsidiary of Ionis Pharmaceuticals)	Mipomersen (lipid-based formulation)	Homozygous familial hypercholesterolemia (HoFH)	Lipid-conjugated antisense oligonucleotide that inhibits the synthesis of apolipoprotein B-100, reducing low-density lipoprotein (LDL) cholesterol levels.
Pfizer	estosterone Cypionate (lipid-based injectable formulation)	Male hypogonadism, gender dysphoria	Lipid-based injectable testosterone formulation used for hormone replacement therapy in males with low testosterone levels.
Amarin Corporation	Icosapent ethyl (lipid-based formulation)	Hypertriglyceridemia, cardiovascular risk reduction	Omega-3 fatty acid formulation derived from fish oil, used to lower triglyceride levels and reduce cardiovascular events in patients with elevated triglycerides.
Alcon (a division of Novartis)	Ciprofloxacin (lipid-based ophthalmic formulation)	bacterial infections of the eyes, such as corneal ulcers and conjunctivitis	Lipid-based ophthalmic ointment for the targeted delivery of ciprofloxacin, improving the stability and the antibiotic's bioavailability at the infection site.

Allergan (AbbVie)	Cyclosporine A (lipid-based ophthalmic emulsion)	Dry eye disease	Lipid-based emulsion formulation of cyclosporine A that enhances the drug's absorption in the eye and helps reduce inflammation in patients with dry eye disease.
Pacira Biosciences	Bupivacaine (liposomal formulation)	Postoperative pain management	Liposome-encapsulated bupivacaine for extended-release delivery at the surgical site, providing prolonged local anesthesia and reducing the need for opioids.
Sanofi	Zolpidem Tartrate (lipid-based controlled-release formulation)	Insomnia	Controlled-release formulation of zolpidem that helps patients fall asleep quickly and maintain sleep throughout the night by releasing the drug in phases.
Johnson & Johnson (Janssen Pharmaceuticals)	Risperidone (liposomal formulation for long-acting injectable)	Schizophrenia, bipolar disorder	Lipid-based long-acting injectable formulation of risperidone for sustained drug release, reducing the frequency of injections for patients with schizophrenia and bipolar disorder.

IX. HYDROTROPY

The term hydrotropy was originally used in 1916 by the scientist Carl A. Neuberg Hydrotropy is a method of boosting solubility that involves making another material more soluble in water by adding a sizable amount of a second solute. Alkali metal salts, usually ionic organic salts, of different organic acids, make up the second solute. These salts or additions are referred to as "salt in" the solute if they make it more soluble in a certain solvent, and vice versa. The purpose of these is to "salt out" the solute. These salts cause "salting in" non-electrolytes, possess sizable cationic or anionic groups and are easily dissolved in water. Known as "hydrotropism," this property is what makes them "hydrotropic salts."[73] Traditional The hydrotropic salt of Neuberg is composed of two groups. The first is an anionic group, which gives it its great solubility in water. The mechanism of hydrotropic solubilization is attributed to a hydrophobic ring structure. The type of metal ion or anion has a slight influence on solubilization.[74] The drugs' solubility with low water solubility can be significantly improved by combining two hydrotropic chemicals. The mixed hydrotropy will additionally be used to create aqueous formulations for medications with poor solubility in water Hydrotropic agents in nature can be either organic or inorganic, cationic, neutral, or anionic, and they can be liquids or solids. Compared to hydrotropes made from cationic headgroups, tehydrotropes with anionic hydrophilic groups have drawn more interest. Numerous research investigations have focused on the mechanics of hydrotropes. Tree diagrams can be used to summarize the available recommendations. [75] Lactose and acetate are extensively researched in order to improve the solubility of drugs that are not particularly soluble in water, such as urea, sodium benzoate, sodium ascorbate, and salt.[77] The majority of formulation techniques for these medications aim to achieve their fine dispersion at the absorption level in order to increase their rate of dissolution and/or solubility in vivo [83].

Hydrotrope Mode Of Action

Since this matter is still up for debate and needs to be resolved, the mechanism of action of hydrotropes needs to be defined. Many scholars have conjectured about the probable functioning of a hydrotrope. The following are the three theories put forth to explain hydrotropic activity

a) The solute and the hydrotrope combine to produce a complex.

b) the disintegration or breakup of a tetrahedral complex based on water

c) the formation of hydrotrope connections on their own.[76]

It has been demonstrated that hydrotropy, a recently developed potent drug solubilization technique, greatly increases the solubility of numerous medications.[78] An organic solvent-free solubilizing method is hydrotropy. This is essentially a chemical phenomenon whereby a significant amount of hydrotrope is mixed with weakly soluble solutes to increase the solutes' water solubility. It is asserted that the solubilization of poorly soluble solutes is caused

by the weak interaction between hydrotropic agents such sodium alginate, sodium benzoate, sodium acetate, and urea.[79] In basic systems, micellar solubilization requires micelle production. The differences between flexible chain surfactants' solubilizing patterns and those of other surfactants, including sodium cholate, the bile salt, which shows less self-association cooperation, excellent cosolvents like ethanol, and hydrotropic agents, are clearly visible in these diagrams.s [80] in hydrotropic solutions of sodium benzoate, sodium aciculate, urea, and, many medications that do not dissolve well in water dissolve more readily. sodium acetate, sodium citrate, and otinamide. They lack a threshold concentration at which self-aggregation occurs simultaneously. Instead, when a solubilizer is applied, self-aggregation occurs gradually. In the industrial sector, hydrotropes are utilized to create highly concentrated surfactants. They are utilized, for instance, in the production of detergents.[81] Through complexation, which involves a mild interaction between the solute and hydrophobic substances (such urea, sodium alginate, sodium benzoate, etc.), it increases solubility. For instance, theophylline sublimation using sodium acetate and sodium alginate [82]

Some Marketed Formulation of Hydrotropy

Company	Drug	Indication	Hydrotropic Agent	Mechanism
Genentech (Roche)	Ketorolac tromethamine (injectable formulation)	Pain management (e.g., postoperative pain, moderate to severe pain)	Trometha mine	romethamine is employed in this formulation to increase the solubility of ketorolac, which is barely soluble in water. The drug's injectable form is made possible by the hydrotropic agent's assistance in increasing the drug's aqueous solubility.
Mallinckrodt Pharmaceuticals	Acetaminophen (oral liquid formulation)	Pain relief, fever reduction	Sodium benzoate	Sodium benzoate is used as a hydrotropic agent to improve the solubility of acetaminophen in aqueous solutions. This formulation is useful for pediatric or oral administration where solid tablets may not be suitable.
Pfizer	Ibuprofen (oral suspension)	Pain relief, fever reduction, inflammation	Propylene glycol and sodium chloride	These hydrotropic agents help improve the solubility and dissolution rate of ibuprofen, making it more suitable for liquid formulations such as syrups and suspensions.
Roche	Diazepam (injectable formulation)	Anxiety, seizures, muscle spasms	Propylene glycol	Propylene glycol serves as a hydrotropic agent to increase the solubility of diazepam, which is poorly soluble in water. This allows the drug to be administered intravenously.
AstraZeneca	Lidocaine (injectable formulation)	Local anesthesia, arrhythmia treatment	Sodium chloride	Sodium chloride is often used to increase the solubility of lidocaine, which is typically poorly soluble in water. The hydrotropic agent ensures the formulation is suitable for intravenous or subcutaneous injection.
Pfizer	Promethazine (injectable formulation)	Nausea and vomiting, sedation	Sodium chloride	Sodium chloride is used to solubilize promethazine for injection by enhancing its water solubility.
American Pharmaceutical Partners	Theophylline (oral liquid formulation)	Long-term obstructive pulmonary disease (COPD) and asthma	Propylene glycol	As a hydrotropic agent, propylene glycol enhances theophylline's solubility and rate of dissolution, making it appropriate for oral liquid formulations.
Sigma-Tau Pharmaceuticals (a part of Astellas)	Caffeine and sodium benzoate (injectable formulation)	Apnea of prematurity (used to stimulate respiratory function in premature infants)	Sodium benzoate	Sodium benzoate increases the solubility of caffeine, allowing it to be used in injectable forms for critical care situations, particularly in neonatal care.

Revive Therapeutics	Dantrolene sodium (injectable formulation)	Malignant hyperthermia, spasticity	Sodium hydroxide	Sodium hydroxide enhances the solubility of dantrolene sodium, enabling its use in an injectable form for conditions like malignant hyperthermia.
Pfizer	Lorazepam (injectable formulation)	Anxiety, seizures, sedation	Propylene glycol	Propylene glycol is used in the formulation of lorazepam to enhance its solubility, making it suitable for intravenous administration, as lorazepam is poorly soluble in water.
Pfizer	Phenytoin sodium (injectable formulation)	seizures, status epilepticus	Propylene glycol	Propylene glycol helps to solubilize phenytoin, a drug with limited water solubility, allowing for intravenous injection in the treatment of acute seizures and status epilepticus.
Hospira (Pfizer)	Morphine sulfate (injectable formulation)	Severe pain management, postoperative pain	Sodium chloride and citric acid	Sodium chloride and citric acid are used to improve the solubility of morphine sulfate, allowing for its parenteral administration and ensuring stability in solution.
Pfizer	Diphenhydramine (injectable formulation)	Allergic reactions, motion sickness, insomnia	Sodium chloride	In order to increase diphenhydramine's solubility and facilitate its administration in intravenous or intramuscular injections for quick symptom alleviation, sodium chloride is employed as a hydrotropic agent
Lundbeck	Pentobarbital sodium (injectable formulation)	Severe insomnia, preoperative sedation, seizure management	Propylene glycol	Propylene glycol is employed to increase the solubility of pentobarbital sodium, which is typically poorly soluble in water. The formulation allows for intravenous or intramuscular administration.
Bayer	Ciprofloxacin (injectable formulation)	Bacterial infections (e.g., urinary tract infections, respiratory infections)	Sodium chloride	Sodium chloride enhances the solubility of ciprofloxacin, which helps in the intravenous formulation of this broad-spectrum antibiotic, enabling effective treatment of systemic infections.
Adapt Pharma (now part of Emergent BioSolutions)	Naloxone (injectable formulation)	Opioid overdose	Sodium chloride	The naloxone formulation contains sodium chloride to increase the drug's solubility for injectable delivery in emergency scenarios, such as opioid overdose.
Various manufacturers (e.g., Pfizer, Hospira)	Sodium bicarbonate (injectable solution)	Acid-base imbalance, metabolic acidosis	Sodium chloride	Sodium chloride helps in the solubilization and stability of sodium bicarbonate in an injectable formulation used to correct metabolic acidosis and alkalosis.
Revive Therapeutics	Dantrolene sodium (injectable formulation)	Malignant hyperthermia, muscle spasticity	Sodium hydroxide	Sodium hydroxide is used to improve the solubility of dantrolene sodium in water, allowing for its administration via intravenous injection in emergency conditions like malignant hyperthermia.
Abbott Laboratories	Valproate sodium (injectable formulation)	Seizures, bipolar disorder, migraine prophylaxis	Sodium chloride	Sodium chloride is used to increase the solubility of valproate sodium in its injectable formulation, enabling effective treatment of acute seizures and other conditions that require intravenous administration

Various manufacturers	Aminophylline (injectable formulation)	Chronic obstructive pulmonary disease (COPD), asthma	Sodium chloride	Sodium chloride is used to improve the solubility of aminophylline, a theophylline salt, making it suitable for intravenous administration in emergency respiratory conditions like asthma or COPD exacerbations.
Janssen Pharmaceuticals (Johnson & Johnson)	Fentanyl (injectable formulation)	management of pain (e.g., during surgery, cancer-related pain)	Citrate and propylene glycol	Citrate and propylene glycol are added to injections to increase solubility and facilitate effective intravenous or epidural pain management because fentanyl is poorly soluble in wate
Merck & Co.	Vincristine sulfate (injectable formulation)	Cancer treatment (e.g., leukemia, lymphoma, breast cancer)	Dextrose and sodium chloride	Vincristine sulphate is a poorly water-soluble chemotherapeutic drug that is made more soluble by dextrose and sodium chloride for intravenous delivery to cancer patients.
Pfizer	Hydrocortisone sodium succinate (injectable formulation)	Adrenal insufficiency, inflammation, allergic reactions	Sodium succinate	Sodium succinate acts as a hydrotropic agent in hydrocortisone formulations, enhancing the solubility of hydrocortisone for intravenous use in conditions requiring corticosteroid therapy.
Bayer	Loratadine (oral syrup formulation)	Allergic rhinitis, urticaria (hives)	Propylene glycol	Because loratadine is weakly soluble in water, propylene glycol is added to loratadine syrup to increase its solubility, making it appropriate for oral and paediatric usage.
Roche	Ceftriaxone (injectable formulation)	Bacterial infections (e.g., pneumonia, meningitis)	Sodium chloride	Ceftriaxone's solubility and stability for intravenous and intramuscular injection are enhanced by sodium chloride, guaranteeing efficient antibiotic treatment for severe infections
Pfizer	Nalbuphine hydrochloride (injectable formulation)	Pain management, analgesia	Propylene glycol	Propylene glycol is used to increase the solubility of nalbuphine hydrochloride, a synthetic opioid, in this injectable form, enabling pain relief through intravenous administration.
Pfizer	Tetracycline hydrochloride (injectable formulation)	Bacterial infections	Sodium chloride	Sodium chloride enhances the solubility of tetracycline hydrochloride, which is poorly soluble in water, for intravenous administration in treating various bacterial infections.
Bristol Myers Squibb	Cyclophosphamide (injectable formulation)	Cancer treatment (e.g., breast cancer, leukemia)	Propylene glycol and sodium chloride	These hydrotropic agents are used in the formulation to enhance the solubility of cyclophosphamide, a chemotherapeutic drug, for intravenous use in the treatment of cancers.
Pfizer	Tramadol hydrochloride (injectable formulation)	Moderate to severe pain	Propylene glycol	Propylene glycol is used to solubilize tramadol, a pain medication, in its injectable form, allowing for intravenous administration in patients with severe pain.
Purdue Pharma	Docusate sodium (oral liquid formulation)	Constipation (laxative)	Sodium benzoate	sodium benzoate is used to solubilize docusate sodium in the oral liquid formulation to help relieve constipation by softening stools.

Micronization Processes with Supercritical Fluids

The size, particle sized distribution (PSD), and shape of the particles have a significant impact on the bioavailability of medications when they are provided in a solid formulation. As a result, the creation of effective micronization technologies is gaining attention [84] When the final particle size is fewer than 10 microns, the process is referred to as "micronization." In order for grinding to occur through interaction between particles or impact against a solid

surface, micronization size reduction entails acceleration of particles. [85] Given that when particle size lowers, particle micronization greatly increases the contact surface area, it is a good substitute for increasing the rate of dissolution of weakly soluble substances. According to the Prandtl boundary layer equation, when the particle size is reduced, particularly below 5 μm, a rapid dissolving takes place, reducing the diffusion layer's thickness[86] The precipitation of particles Additionally, methods based on SCF technology have been used to create microencapsulated pharmaceutical formulations to enhance formulation qualities including taste and shield APIs against deterioration[87] Supercritical fluids (SCFs) are becoming more and more important in the pharmaceutical sector. Along with their chromatographic, extractive, Considering uses in biological processes, SCFs have intriguing uses in the processing of materials. Pharmacological processing using SCFs, particularly with supercritical carbon dioxide, has drawn more attention in recent years. [88] The most often used technique for processing medicinal chemicals is jet milling. however, the generated particles may be jagged and contain electrostatic charges that hinder their dispersion in the administration systems. In addition, the temperatures attained during this process cause biological compounds to lose their activity. [89] Over the past 20 years, supercritical fluid-based particle creation technology has taken many distinct forms. Numerous types of materials, both inorganic and organic, have been processed using supercritical fluids as solvents or anti-solvents to create particles, fibres, films, and foams. For instance, a supercritical fluid-soluble chemical was crystallized using supercritical fluids as solvents. [90] The foundation of this technique is fluids used as solvents at pressures and temperatures above their critical values When the sol is in this supercritical state, Vent densities are similar to liquids, but they have diffusivity that is about more than two orders of magnitude than liquids and viscosity that is close to that of typical gases.[91] The rapid expansion of supercritical fluids (RESS) process is comprised of the extraction and precipitation units. A substance dissolves in a supercritical fluid (SCF) at the extraction unit before dissolving in a supercritical solution. is rapidly nucleated and tiny particles are created when it is suddenly depressurized in a nozzle. The SCF solvating power decreases as a result of the supercritical solution's quick expansion via a nozzle and the resulting significant density drop. After being supersaturated, the solute precipitates. Supersaturation is what propels the nucleation process. Increased supersaturation tends to reduce particle size and increases the nucleation rate (J, particles/cm3 s).[92] Through experiment design, the YNS3107 and polymeric excipients (PEG4000, PEG400, and poloxamer 407) are being investigated, along with the effects of different experimental settings on the supercritical micronization of solid dispersion. The appropriate mathematical model defining the particle from the Gas Saturated Solutions approach was created and used during the optimization phase in order to identify the optimal micronization settings that would produce the smallest SD microparticles. The dissolving profiles of the produced microparticles, the matching physical combination, and the pure active component were then compared.[93] Traditional micronization techniques like spray drying and jet milling can cause significant surface roughness or change, heat denaturing, wide size dispersion, and consequently, restrict effective control of the particle material properties. It has been demonstrated that supercritical fluid (SCF) technology is a successful method for pulmonary medication delivery by particle creation.[94] In order to create microparticles for pulmonary medication administration with mean diameters ranging from 1 to 5 ml, a methodical investigation into the micronization of fluticasone propionate was conducted. Comparisons and discussions were held about the impact of process factors on particle size characteristics.[95] In this study, the p-Toluenesulfonamide (p-TSA) p-TSA particles were micronized using the RESS technique. Supercritical CO2 was saturated with p-TSA as part of the RESS process, and the solution was then depressurized by entering a low-pressure chamber via a heated nozzle. The quick breakdown of the nucleation and particle production were driven by supercritical CO2 containing the p-TSA. The ideal operating conditions were ascertained by applying Taguchi's experimental design method. The experimental data were used to assess the results of four control variables: temperature before, during, and after expansion; extraction temperature; and extraction pressure. The form and particle size of the produced samples were examined using scanning electron microscopy (SEM). Additionally, X-ray diffraction

(XRD), differential scanning calorimetry (DSC), and the Fourier transform infrared spectrometer (FTIR) were used to examine the samples before and after recrystallization.[96]

Some Marketed Formulation of Microinozation

Company name	Drug	Formulation	Drug Mechanism	How Micronization Helps	Micronization Technology
Celgene (now part of Bristol Myers Squibb)	Paclitaxel	Nanoparticle Albumin-Bound Injectable	By stabilizing microtubules and inhibiting their disintegration, the chemotherapeutic medication paclitaxel disrupts cell division. By interfering with the mitotic spindle's regular function, this action causes cell cycle arrest, which in turn kills cancer cells.	Paclitaxel is poorly soluble in water, limiting its intravenous administration. By micronizing the drug and binding it to albumin nanoparticles, it becomes more soluble, improving its bioavailability and enabling it to target tumors more efficiently. This improves its therapeutic index, meaning more of the drug reaches the cancer cells, and less is wasted in healthy tissue.	High-pressure Homogenization and Nanoparticle Formulation.
Gilead Sciences	Cidofovir	Injectable Solution	Cidofovir is an antiviral drug used to treat cytomegalovirus (CMV) retinitis in patients with AIDS. It works by inhibiting viral DNA polymerase, preventing the replication of viral DNA, thereby halting the spread of the virus.	Cidofovir has low solubility in water, and micronization increases the surface area for better dissolution and faster absorption into the bloodstream. This ensures effective treatment of CMV infections.	High-Pressure Homogenization or Wet Milling.
Pfizer	Piperacillin,	Injectable Powder for Reconstitution	A beta-lactam antibiotic called piperacillin kills bacteria by preventing the formation of their cell walls. The beta-lactamase inhibitor tazobactam prevents resistant bacteria's beta-lactamase enzymes from breaking down piperacillin.	Both piperacillin and tazobactam have poor solubility in water. Micronization improves the solubility of both drugs, ensuring that they are dissolved more efficiently in the body after intravenous administration, thus increasing their bioavailability and effectiveness in treating infections.	pray Drying, Wet Milling, and Ball Milling.
Pfizer	Amlodipine	Oral Tablets	Amlodipine functions as a calcium channel blocker by preventing calcium ions from entering smooth muscle and cardiac cells. Blood arteries dilate as a result, improving blood flow and lowering blood pressure.	Amlodipine has low solubility and poor bioavailability due to its crystalline form. Micronization increases the surface area, which enhances dissolution and absorption. This allows for more efficient blood pressure management with improved therapeutic outcomes.	Jet Milling.
GlaxoSmithKline	Fluticasone	Inhalation Aerosol	Fluticasone propionate is a steroidal anti-inflammatory that works by inhibiting the release of inflammatory mediators like prostaglandins and leukotrienes, thereby reducing inflammation in the airways and improving symptoms in asthma and COPD.	Fluticasone propionate is micronized into fine particles to ensure that the drug can be delivered deep into the lungs via an inhaler. This allows for better local delivery to the airways, maximizing the drug's anti-inflammatory effects while minimizing systemic side effects.	Jet Milling or Supercritical Fluid Expansion (RESS).
Pfizer	Methylprednisolone	Injectable Solution	Methylprednisolone is a synthetic corticosteroid that mimics the action of cortisol, binding to glucocorticoid receptors in the body to suppress inflammation. It reduces the activity of the immune system and inhibits the release of pro-inflammatory cytokines.	Methylprednisolone's low solubility can lead to poor dissolution in body fluids, limiting its effectiveness. By increasing the drug's surface area, micronization ensures quicker breakdown.and higher bioavailability. This enhances the drug’s efficacy in treating inflammatory conditions.	Spray Drying or Wet Milling.
Novartis	Cyclosporine	Oral Solution and Capsules	Cyclosporine is an immunosuppressant that inhibits calcineurin, an enzyme required for activating T-cells in the immune system. By blocking calcineurin, cyclosporine prevents the production of interleukin-2 (IL-2), a cytokine that promotes T-cell proliferation,	Cyclosporine has low solubility in water, which limits its absorption in the gastrointestinal tract. By micronizing the drug, the surface area is increased, allowing for better dissolution and more efficient absorption into the	Liquid Antisolvent Precipitation or Micronized Capsules.

			which is crucial in organ transplant rejection and autoimmune diseases.	bloodstream. This enhances its bioavailability, ensuring sufficient immunosuppressive levels for organ transplant patients.	
Pfizer	Tigecycline	Injectable Powder for Reconstitution	Tigecycline is a broad-spectrum antibiotic that attaches itself to the 30S ribosomal subunit of bacteria to prevent protein synthesis. This inhibition of bacterial development prevents the germs from multiplying, leading to bacteriostatic effects.	Tigecycline is poorly soluble, so micronization enhances its solubility and improves its absorption in the bloodstream after intravenous administration. This helps ensure that the antibiotic reaches effective concentrations at the site of infection, especially for multi-drug-resistant bacteria.	Wet Milling and Ball Milling.
AbbVie	Kaletra	Oral Tablets and Oral Solution	Kaletra is a combination of two protease inhibitors, lopinavir and ritonavir:Lopinavir inhibits the HIV protease enzyme, which is necessary for the maturation of new viral particles.Ritonavir boosts lopinavir's levels by inhibiting enzymes in the liver (specifically CYP3A4), preventing its metabolism and prolonging its effects.	Both lopinavir and ritonavir have low solubility, so micronization increases their surface area for faster dissolution and absorption. This ensures that the drugs are available in the bloodstream in higher concentrations to more effectively suppress HIV replication.	Jet Milling or Wet Milling.
AstraZeneca	Gefitinib	Oral Tablets	Tyrosine kinase inhibitors like gefitinib are used to treat non-small cell lung cancer (NSCLC). It functions by blocking the epidermal growth factor receptor (EGFR), a protein involved in cancer cell growth and survival. Gefitinib stops downstream signalling pathways that encourage the growth of tumour cells by inhibiting EGFR.	Gefitinib has poor solubility, which limits its absorption and effectiveness. Micronization of the drug increases its surface area for faster dissolution and absorption in the gastrointestinal tract, leading to higher plasma concentrations and better efficacy in inhibiting cancer cell growth.	Wet Milling or Spray Drying.
Apreciа Pharmaceuticals	Levetiracetam	Orally Disintegrating Tablets (ODT)	Levetiracetam is an anticonvulsant used to treat seizures in patients with epilepsy. It binds to the SV2A protein on synaptic vesicles, modulating neurotransmitter release and preventing abnormal electrical activity in the brain that leads to seizures.	The drug is micronized into fine particles, which are then formulated into rapidly disintegrating tablets. This increases the surface area, improving dissolution and ensuring fast absorption. The drug's fast onset of action helps control seizures more quickly.	Spray Drying and Direct Compression for ODT formulations
Johnson & Johnson	Cetirizine	Oral Tablets and Syrups	A second-generation antihistamine, cetirizine functions by preventing the body's histamine receptors (H1 receptors) from functioning. One substance that contributes to allergic responses is histamine. Cetirizine lessens allergy symptoms like itching, runny nose, and watery eyes by preventing its activity.	In order to increase its rate of dissolution and facilitate faster absorption in the digestive system, cetirizine is micronized. As a result, allergy symptoms are relieved more quickly	Jet Milling or Ball Milling.
AstraZeneca	Budesonide	Inhalation Powder	One type of corticosteroid that reduces lung inflammation is budesonide. It initiates a series of anti-inflammatory actions by attaching itself to the glucocorticoid receptor within target cells. This aids in the management of asthma and COPD by lowering the synthesis of pro-inflammatory cytokines and chemokines.	Budesonide is micronized into fine particles that can be inhaled deep into the lungs, where it exerts its local anti-inflammatory effects. The micronization increases the surface area, improving dissolution and absorption, making the drug more effective in treating respiratory conditions.	Jet Milling or Supercritical Fluid Expansion.

X. CONCLUSION

In that article, different methods for improving the solubility of drugs of the biopharmaceutical categorization (Bcs) class II are studied. The qualities of the medicine, the formulation's objective, and the planned dose form all influence the best way to increase the solubility of class II medications. In that acritical each method use best for the particular type of drug that is solid dispersions methos is use for thermally stable drug, nanocrystal/ nanonization method is best for poorly soluble drug with crystalline

nature, cyclodextrin complex method is best for small molecules with suitable size, lipid-based drug delivery system is best for lipophilic drug with high log p, amorphous form of drug is best for drug stable in amorphous state. best overall in that lipid-based formulation are often considered among the best for Bcs class II drug Due to their dramatic bioavailability enhancement, especially for oral drug

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