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NAVIGATING THE LANDSCAPE FOR INNOVATIONS IN SOLUBILITY ENHANCEMENT FOR NEXT-GENERATION THERAPEUTICS: A RECENT REVIEW

Simran Chaurasia*, Shivam Bhadauria, Tirath Choudhary and Mansi

Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University, Badal Road, Bathinda, Punjab-151001.

***Corresponding Author: Simran Chaurasia**

Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University, Badal Road, Bathinda, Punjab-151001.

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ABSTRACT

The significance of solubility in pharmaceutical formulations cannot be overstated, as it profoundly shapes drug dissolution, absorption, and therapeutic efficacy. However, the limited solubility of numerous pharmaceutically active compounds poses a formidable obstacle in drug development, frequently resulting in suboptimal bioavailability and therapeutic outcomes. Addressing this challenge is paramount for fostering pharmaceutical innovation and fulfilling the medical needs of patients worldwide. This comprehensive review meticulously examines diverse strategies aimed at augmenting the solubility and bioavailability of poorly water-soluble drugs, with a special emphasis on their pivotal role in pharmaceutical research and development. Leveraging insights gleaned from a synthesis of scientific literature, this review provides an in-depth analysis of the contributions of nanotechnology, chemical methodologies, physical interventions, and miscellaneous techniques like particle size reduction, Hydrotropy, pH adjustment, Supercritical Fluid Process, Solid Dispersions, Inclusion Complexation, Lyophilization, Spray drying and many more to solubility enhancement. By elucidating the underlying mechanisms and practical applications of these methodologies, this review endeavors to furnish invaluable guidance to researchers and practitioners navigating the intricate landscape of drug development, with the ultimate goal of advancing patient care and therapeutic outcomes.

KEYWORDS: solubility, dissolution, absorption, bioavailability, water-soluble drugs.

INTRODUCTION

Solubility pertains to the process of dissolution of solute within a solvent, which is a critical step in establishing a uniform system. When viewed from numerical perspective, solubility can be described as the quantity of a solute that can be broken down into a solution under specific conditions of pH, temperature, and pressure.[1] Conversely, solubility refers to the capacity of a substance to dissolve in a fully saturated solution at a specified temperature.[2] Several terms such as molality, volume fraction, parts of solvent, percentage, molarity, mole fraction, and so on, are employed to express solubility.[3] As per the US Pharmacopoeias, solubility is quantified as the volume of solvent required to dissolve one gram of solute. Two primary approaches are employed in assessing solubility that is thermodynamic solubility and kinetic solubility.[4] The essential determinants governing the solubility of a drug, includes gastrointestinal permeability, solution, bioavailability, and absorption rate, are interconnected with the drug's solubility.[5] One of the crucial elements impacting absorption of a drug after oral ingestion is the aqueous solubility of therapeutic substances. The solubility of drug is the measurement of how fast the drug compound or formulation dissolves in the solution, when the dissolution time is constrained.[6] Nonetheless, solubility, dissolution rate, susceptibility to efflux mechanisms, water, first – pass metabolism all these factors affect the bioavailability.[7] The concept of solubility is operationally defined as the quantity of solute that can be dissolved in specific volume of solvent, where the amount represents the solute concentration in saturated solution at a specific temperature. Qualitatively, solubility may be explained as a unprompted interaction between two constituents to create a uniform dispersion at the molecular level. In a saturated solution, solute is considered to be at equilibrium with the solvent.[8] In the domain of pharmaceutical research, there has been a conspicuous surge in the amount of drug candidates that are insoluble, a trend that has been observed recently. Near about 70% of these novel drug preparations exhibit insufficient water solubility.[9] Subsequently, the sub optimal water solubility as well as limited dissolution within GIT fluids impose a significant obstacle to the bioavailability of drug candidates. Hence, the recognition of the invitro dissolution, as a critical aspect in drug advancement has been established. Therefore, the improvement of the dissolution rate of poorly water

soluble and the subsequent improvement in their bioavailability pose a significant obstacle for researchers of pharmaceutical field.[10]

Process of solubilization

The process of solubilization entails the interruption of intermolecular or interionic connections within the solute, (Tk and Jasti). It is the technique which results in formation of a gap for the solute molecule, initiating an intermolecular attraction among the two. The several steps of the solubilization process are depicted in the following figure 1. There is a destruction of bonds present within the solvent during the solubilization process, which forms an observable void as depicted in step 1. Solubilization process leads to a fracture of intermolecular bonds of the solute due to the impact of external kinetic energy, as explained in step 2. Unbound solute molecule (in its solid state) merges with solvent when there is external kinetic energy, as demonstrated in **figure 1**.[11]

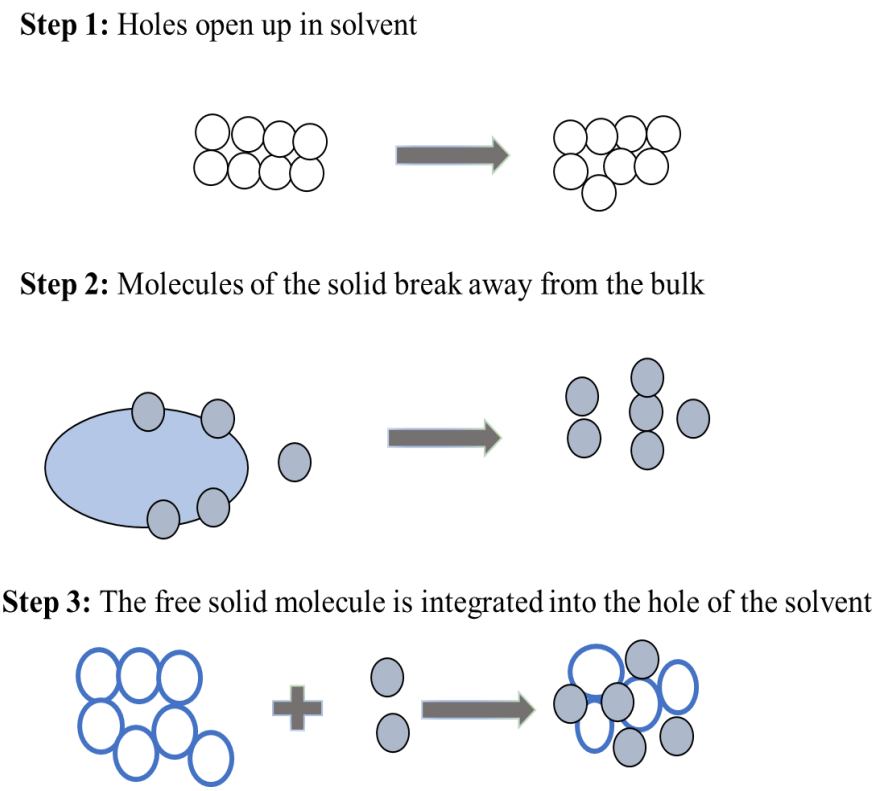

Figure 1: Process of Solubilization.

Importance of solubility in oral drug ingestion

Oral ingestion of drug is widely acknowledged as the leading and most appropriate method, mainly due to the multitude advantages associated with oral delivery of drugs. These advantages encompass raised levels of patient adherence, minimal risk of sterility concern, cost-effectiveness in manufacturing, as well as rapid evolution of dosage form.[7] Currently, almost 80% of pharmaceutical compounds are administered orally. The solubility characteristics of the active compound are closely interrelated with absorption, bioavailability, distribution as well as pharmacokinetic behaviour of orally delivered medications. Medication with limited solubility often requires heightened or frequent dosing schedules to achieve therapeutic plasma concentration post oral intake. Thus, augmenting solubility is a crucial aspect in the development procedure of these drugs. The chosen strategies to upsurge solubility are typically depending upon the fixed attributes of the medicine, which encompass the qualities of the selected additives, the intended method of delivery, as well as the pharmacokinetic profile necessary for optimal clinical efficacy. Fluctuations in insufficient bioavailability or drug accessibility are primarily attributed to the slow dissolution rates and limited solubility shown by drugs with poor water solubility, in Gastrointestinal tract.[11]

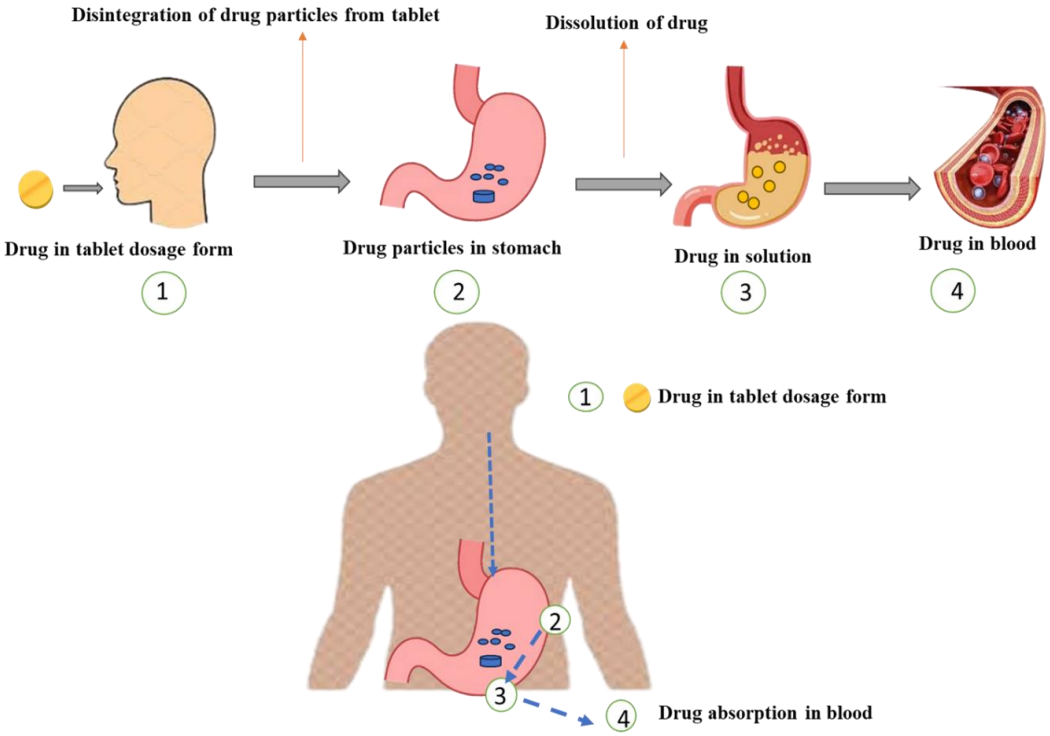

Figure 2: Fate of drug molecule after administration via oral route.

BCS classification

The biopharmaceutical classification system stands out as a widely employed scientific categorization system for pharmaceutical substances, focusing on their permeability and solubility characteristics.[12] Two major determinants govern the rate and amount of absorption of orally administered drugs, namely the solubility of drug in aqueous media and permeability through the intestine.[13]

Categorization of drug compound can be done into four classes, as per BCS. If a drug's maximum potency is dissolved in ≤250 mL of aqueous standard, it indicates raised solubility with a pH range of 1.0 to 7.5; or else, the components of drug are deemed to be less soluble. Efforts persist by biopharmaceutical researchers to obtain a system that exactly replicates the conditions of biological system, peristalsis, encompassing gut pH, food composition. The period from 1960 to 1970, was marked by significant advancements in the field of pharmaceutical research, with various inquires illuminating the connection between dissolution effect as well as formulation specifications that influences the bioavailability of drugs. Introduction of the first dissolution apparatus was done in 1970 which was named as USP apparatus I basket type. It played a crucial role in evaluating the rate of dissolution of formulation, later on which was followed by introduction of USP apparatus II paddle type.[14] By conducting the *in-vitro* tests, these apparatuses enable the estimation of formulation's in vivo performance. Nevertheless, due to impact of several factors on the in vivo functionality of formulations, there is continuous effort to enhance the in vivo functionality of formulations. Bioavailability of drugs falling under BCS class II classification is probably to be restricted by the rate of dissolution. Despite high permeability, medicines classified under BCS class II have captured substantial interest in recent years for investigations aimed at improving their solubility.[15][16] Several strategies for preparation of formulation have been devised for this classification of drugs. In BCS classification, the bioavailability of class Ⅲ drugs is mainly restricted by permeability rate, despite the quick anticipation of dissolution. Hence, the formulation of immediate- release solid dosage forms having absorption enhancers might serve as a feasible approach to upsurge the intestinal permeability of class III drugs. In contrast, class IV compounds of BCS encounter limited bioavailability of drug by both intestinal permeability and dissolution. Due to their poor intestinal membrane penetration ability, class IV drugs of BCS classification are frequently deemed unfit for development of drug, as enhancements in dissolution and solubility alone might not avail to upsurge their bioavailability. However, disregarding these compound classes purely based on permeability concerns would be imprudent. Thus, the techniques currently used for improving the bioavailability of medications in BCS class II, in conjunction with absorption enhancers, could be modified for developing class IV compounds.[9] A different approach for the development of class IV compounds involves choosing a more suitable pharmaceutical candidate with optimal physicochemical properties in the lead optimization stage.[17][18]

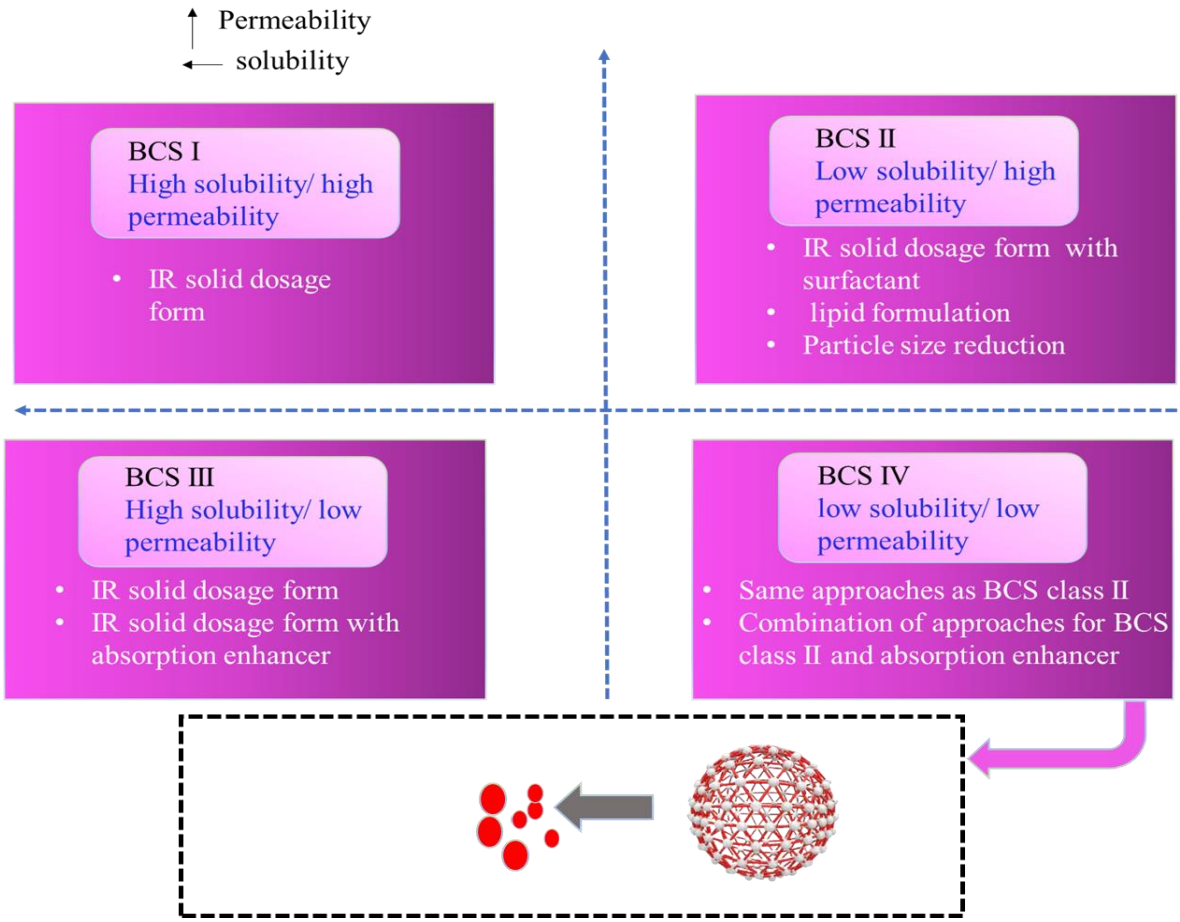

Figure 3: Biopharmaceutics Classification System (BCS) & feasible formulation choices based on the classification.

FACTORS AFFECTING SOLUBILUITY

Solubility of drug relies on synthesis, nature of solubility media, temperature, pressure as well as solid's physical form. Let us discuss the factors that influences the solubility alike:

Particle size

Dimensions of the solid particle have an impact on its solubility, as the reduced particle size leads to an upsurge in the volume ratio to surface area. This augmented surface area enables a more in-depth engagement with the solvent.

Temperature

On applying heat or temperature, the solution process experiences an energy absorption, resulting in surge in solubility. On the contrary, a drop in temperature occurred during dissolution process, leads to decrease in solubility due to the release of energy. Certain solid solutes exhibit reduced solubility in solutions at increased or elevated temperatures.

Pressure

For gaseous solutes, augmentation in pressure leads to solubility elevation whereas, reduction in pressure plays a significant role in solubility declination. On the other hand, modifications in pressure shows minimal impact on how much soluble solid and liquid solutes are.[19]

Polarity

Non-polar solute molecules typically demonstrate solubility in non-polar solvents, while polar solute molecules which are easily dissolved in polar solvents. The polarity of solute molecules is characterized by the presence of both a positive and a negative end within the molecular structure. In cases where solvent itself shows polarity, there is an electrostatic attraction between the two ends of solute molecules both positive and negative ends. These interactions are categorized as dipole-dipole forces, which represent a form of forces present within the molecule.[20]

Polymorphs

A solid is distinguished by a rigid structure and precisely distinct configuration. The distinctive characteristic of a crystal composed of a specific material may differ, nevertheless, the ratios between the surfaces remain steady. A crystal is arranged methodical geometric pattern or lattice constituted of atoms, ions, or molecules, that is reliable to recreate in three dimensions. This repeating configuration is commonly referred as unit cell. The capability of a material in which it undergoes

crystallization in multiple crystalline forms is known as polymorphism.[21]

Molecular size

The reduction in the solubility of a compound arises due to augmentation in the molecular weight or in the size of the molecule. More substantial molecules experience heightened challenges in their solvation due to impediments in being encircled by molecules of the solvent. In the case of organic substances, the solubility is influenced by the level of carbon branching, which leads to an improvement. This improvement is a result of diminished overall magnitude of the molecule that arises due to increased branching, thereby aiding in the process of solvation with solvent molecules.[20]

Nature of solute and solvent

Merely 1 gram of lead (II) chloride demonstrates solubility in 100 grams of water in contrast to the solubility of 200 grams of zinc chloride. The substantial variance in the solubility of these substances can be ascribed to variations in their intrinsic characteristics.[22]

Stirring

Solubility can be increased by stirring because it ensures that liquid and solid solutes come in contact with new solvent constituents.[23]

TECHNIQUES/APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS

Solubility of drug is referred to the maximum level of concentration of drug particles dispersed in solvent at room temperature, pressure and pH. There are several ways to express the solubility of drug like percentage, parts, molality, molarity, mole fraction and volume fraction. Various factors are responsible for the limited absorption of drug from GI tract, one of them is the poor solubility or the poor membrane permeability. Before permeation of drug through GI membrane to systemic circulation, it dissolves in gastric fluid and then in intestinal fluids.[24] Improvement of solubility and rate of dissolution of poorly soluble drugs are two major factors that can improve the oral bioavailability of the drug molecules. In Biological classification system, drugs are arranged on the according to their water solubility and intestinal permeability. In BCS classification, class Ⅱ and Ⅳ drugs have less solubility and rate limiting steps involves drug release from dosage form and gastric fluid solubility. Solubility enhancing techniques also increases bioavailability within the solubility of hydrophobic drugs.[25] About 40% of the drugs are practically insoluble among all the newly discovered drugs. Solubility of poorly water-soluble drugs can be enhanced by numerous physical, chemical and miscellaneous methods.[26]

PHYSICAL METHODS

Size reduction of particles: Solubility of drug is dependent on the particle size of the drug molecule; small size of molecule of drug provides larger surface area to come in contact with solvent, results in increase of surface area to volume ratio. Increased surface area provides better solubility by interacting with the solvent. Some prevalent methods of size reduction of drug particles are comminution and spray drying, which requires mechanical stress to separate active ingredients. Comminution involves mechanical forces like milling and grinding which could lead to degradation of drug product due to substantial physical stress production. Milling technique includes media milling and dry grinding processes for particle size reduction.[27]

Micronization: Micronization is the process in which physical methods are utilized to produce the drug particles in micron size. Milling is carried out by using rotor stator colloid mills and jet mills. Micronization has no effect on saturation solubility of drugs with high dosage number. Crystallization, milling, freeze drying and spray drying are commonly used methods to improve solubility of BCS class Ⅱ drugs.[28]

In conventional times, size reduction of larger particles was attained by mechanical methods such as milling, grinding, crushing by employing friction, attrition, pressure, impact and shearing. Techniques utilized for micronization includes ball mill, jet mill and high-pressure homogenizers. Dry milling is a highly recommended method for micronization that accelerates the rate of dissolution instead of enhancing equilibrium solubility of drugs.[29]

Table 1: Various methods of Particle Size Reduction.

Type of Method	Approximate particle size (in micro meter)	Examples
Compression	50-10,000	Roller mill Pestle – mortar
Attrition	1-50	Roller mill Colloidal mill
Cutting	100-80,000	Shears Scissors
Attrition and impact fluid energy mill	1-2000	Ball mill
Impact	50-8,000	Disintegrator Hammer mill

Microprecipitation: Microprecipitation technique is also known as High-Pressure Homogenization. This process is alliance of two processes, high-pressure homogenization and microprecipitation technique. In this technique, breakable elements that succeeds to pass through fragmentation are also precipitated.[30] It is based on the principle of particle collisions due to high pressure and high shear force.[31] Homogenization pressure and homogenization cycles are responsible for production of quality product i.e. size of the particle of drug.[32]

CARRIER BASED DRUG DISPERSION

Solid Dispersions: Any combination of solid products, constituted of two or more components, in which one(solvent) is hydrophilic in nature and other (drug) is hydrophobic in nature, is known as solid dispersion. The solid dispersion was first established by Sekiguchi and obi in early 1960s during their research on formation and dissolution of sulphonamides' eutectic melts.[33] Solid dispersions of hydrophobic drugs are prepared by various processes for their solubility enhancement. Some of them have been briefly discussed below:

- **Fusion process**: In this method, drug and a water-soluble carrier mixture was prepared by direct heating until they get melted. With vigorous stirring, the melted mixture was placed into ice bath for cooling and solidification so as to allow homogenous dispersion. During the drug dispersion process numerous mechanisms operate. Drugs which are very soluble in their carriers may stay dispersed in the solid-state, resultant is referred as solid solution.[34] Carrier selection and weight fraction of the drug are the elements on which melting point of this combination depends.
- **Solvent method**: In this process, carrier and drug are subjected to dissolution in organic solvent. Evaporation of solvent is carried out by applying high temperature or under vacuum.[35] Solid residue, obtained after solvent evaporation, is then dried by applying vacuum to remove the solvent which is freely adhered to particle surface. Majority of the solvents used are toxic and non-aqueous which possess challenge for pharmaceutical selection of the drug. Therefore, removal of the solvent even in trace amount becomes a necessity. Several techniques like Differential scanning calorimetry (DSC) and different spectroscopic techniques are utilized to authenticate the total removal of the solvent from the solid residue.
- **Fusion-solvent method**: In this method, drug is incorporated in the form of solution into the melted carrier material. This process is highly suitable for the thermosensitive drugs and drugs with high melting point. In this method, solvent removal is not necessary provided the liquid is non-toxic and carrier has the ability to retain certain proportion of liquid while keeping its solid characteristics.[36] For example, this method is appropriate for spironolactone and griseofulvin in PEG 6000.[26]

Table 2: Various commercialized products of poorly soluble drugs based on solid dispersion technique.

S.No	Trade name	Therapeutic agent	Manufacturer	Polymer employed in formulation	Indication
1.	Intelence	Etravirin	Tibotec	HPMC	Antiviral (HIV infection)
2.	Nivadil	Nivalidipine	Fujisawa Pharmaceutical Co., Ltd.	HPMC	Anti-Hypertensive
3.	Rezulin	Troglitazone	Pfizer, Inc.	PVP	Antihyperglycemic
4.	Certican	Everolimus	Novartis	HPMC	Anti-cancer
5.	Gris-PEG	Griseofulvin	Pedinol Pharmacal Inc	PEG6000	Antifungal
6.	Cesamet	Nabilone	Valeant Pharmaceuticals	PVP	Chemotherapy-induced nausea
7.	Sporanox	Itraconazole	Jansen Pharmaceuticals, Inc.	HPMC	Antifungal
8.	Isoptin SR-E	Verapami	Abbott	HPMC/HPC	Anti-Hypertensive
9.	Prograf	Tacrolimus	Fujisawa Pharmaceutical Co., Ltd.	HPMC	Immunosuppressant

Spray drying: Like solvent evaporation, spray drying employs the dispersion of carrier & drug with compatible organic solvent. Stream of heated air is passed over the dispersed solution to vaporize the solvent. Solvent immediately evaporates because droplets has large surface area and the solid dispersion is obtained instantly.[37]

Lyophilization: This process is a substitute for solvent-evaporation method in which process of molecular mixing of drug compounds and their carriers is carried out with universal solvents. The mixture is further frozen and dried afterwards at reduced pressure, to obtain a lyophilized dispersion.[38] This technique involves liquid spraying, having incorporated drug and its additives, directly into cryogenic liquid at room temperature. This is an effective approach for complex formation of thermolabile drugs.[35] This technique is widely used due to its advantages in comparison with the other conventional technologies for solid dispersion.[32]

Hot-melt extrusion: Hot-melt extrusion technique is highly usual technique utilized in the polymer industry. In the pharmaceutical industry, it was firstly utilized by Speiser[39] and Huttenrach.[40] This method consists of co-rotating twin-screw extruders. An opening section for feed material, heated barrel having extruder screws to pass and mix the feed materials. It also has exit port which contains an optical die to shape the extruding mass. Heated barrel of the extruder is fed with the active ingredients and carrier at constant rate. The mixture is when passed through the heated screws transformed into 'fluid like state'. Uniform and close mixing condition is enabled by extruder screws due to their high-shear force. The exit port shapes that melt form into pellets, films, powder or granules.[41] Significant benefit of this process is that the mixture of drug and carrier is only heated for only about one minute which makes it useful to process the slightly thermolabile drugs. Sustained release pellets are also formulated by this method.[26] This technique is similar to fusion process, the only difference is that the mixing of the components is carried out by the extruder based on principle of high shear force.[35]

Gel entrapment technique: In this process, an organic solvent is utilized in dissolution of HPMC and then drug is incorporated in liquid form by using sonicator for definite time. Removal of organic solvent is being done by applying vacuum, size of prepared dispersion is decreases by using mortar and pestle and finally separate out by using sieves.

Co-precipitation method: In this process, fixed quantity of drug is mixed with carrier solution with continuous stirring. Prepared solution is kept away from the sunlight. After precipitation, precipitates are separated by using vacuum. Due to formation of inclusion complexes, keep it for drying at room temperature to stop further the water loss.

Co-grinding method: Blender is used for preparation of carrier and drug combination, at a particular time and speed. Mixture is then transferred to ball mill in which balls of uniform size and surface are further added. The mixture is then pulverized by using ball mill and kept at room temperature. Mixture of mannitol and chlordiazepoxide, is prepared by co-grinding method.[42]

Melting method: In this method, drugs and carriers are merged by using mortar and pestle or high shear mixing. After mixing, homogeneous dispersion is obtained after heating the mixture up to the melting points of all components. After cooling the mixture, solidified mass obtained, is further crushed and sieved.[43] This process is not applicable for methanol like sublimable material.[44]

Solid Solutions: In a single homogeneous phase, when two components are mixed thoroughly, they get crystallized together, and are known as solid solutions. There are two types of solid solutions according to their position in the crystal lattice, like Substitutional & Interstitial.[45]

Eutectic mixtures: In this technique, one or more components do not exhibit phase compatibility to form a new entity when they combine with each other. But at certain concentrations they interfere each other's crystallization, which results in the lowering of melting point of new entity than both of the starting components.[46] Eutectic mixtures are prepared by the fusion method. They are different from solid solutions in which solute -solvent combined melt has complete miscibility but less solid-solid solubility.[47] For instance, these systems are essentially physically mixed combinations of two crystalline elements that are amalgamated together.[48]

SURFACTANT BASED SOLUBILIZATION

In this technique, surfactants are the major components which are utilized to improve the solubility of hydrophobic drugs.

- **Microemulsions**: A mixture of hydrophilic surfactant, oil and hydrophilic solvent that is used to dissolve poorly soluble drugs is known as Microemulsion. It is thermodynamically stable preconcentrate, isotropic, optically clear, translucent system in which mixture of oil, surfactant and solvent is incorporated.[49] Types of microemulsions are Oil-in-water microemulsions (o/w), Water-in-oil microemulsions (w/o) and Bi-continuous microemulsions. The commonly used methods of formulating microemulsions are: Phase titration method and Phase inversion method.[50] Microemulsions offer several merits like they are easy to prepare, exhibit Filtration ability, transparency, clarity and incorporation of variety of drugs having different solubility characteristics.[32]
- **Self-emulsifying drug delivery system (SEDDS):** It is optimally isotropic combination of drug, surfactant, co-surfactant and oil prepared without providing any energy or mechanical stress when mixed with water. Non-ionic surfactants and triglycerides are generally utilized for the preparation of SEDDS. When the dosage form upon administration reaches the Gastrointestinal tract, it draws water from surroundings and forms an oil in water emulsion which further gets diffused into small droplets.[51] These small droplets provide a large surface area for the drug molecules to disintegrate and absorb in the surrounding medium. SEDDS are generally prepared in liquid forms but in spite of that, if SEDDS are prepared in solid dosage form, then it favours the easy handling, transportation and increased stability.[52] Two processes for self-emulsification drug delivery systems are Self-nano emulsifying drug delivery system (SNEDDS) and Self-micro emulsifying drug delivery system (SMEDDS).[53]

Table 3: Marketed formulation using SEDDS drug delivery.

Trade name	Dosage form	Drug used	Company
Norvir	Soft gelatin capsule	Ritonavir	Abbott laboratories
Fortovase	Soft gelatin capsule	Saquinavir	Hoffmann roche
Neoral	Soft gelatin capsule	Cyclosporin	Novartis

CRYOGENIC TECHNIQUES

To produce an amorphous drug with a high degree of porosity at micro and nano scale, utilization of cryogenic techniques is favoured to boost up the drug breakdown. After cryogenic treatment, powder is dried by using spray, vacuum and lyophilization.

- **Spray freezing**: In this process, a drug is incorporated into an organic, aqueous or aqueous-organic cosolvent solution, emulsion or suspension. These formulated solution, suspension and emulsion are further subjected to atomization directly on the compressed gas like Nitrogen and Helium. Micronized powder is further obtained after lyophilization of the frozen particles.[54] Acetonitrile used as solvent, helps in improving drug loading and reduces drying time during lyophilization. This technique is also useful in formation of inulin based solid dispersions.[47] Cryogenic techniques involve multiple spray freezing processes such as Spray freezing onto cryogenic fluids in which water dispersed drug/carrier mixture atomized on boiling agitated fluorocarbon refrigerant's surface. Also, probe sonication of agitated refrigerant is carried out for improved dispersion of aqueous solution. Spray freezing into cryogenic liquids (SFL) is the process in which it uses direct liquid -liquid impingement to develop more intense atomization into nanodroplets from microdroplets and also fast freezing rates which are obtained by mixing atomized feed solution with cryogenic liquid. Lyophilization is carried out to get the frozen particles.[32] Spray freezing into vapour over Liquid (SFV/L) is the process in which drug solutions are firstly kept frozen in cryogenic fluid vapours by which highly wettable and fine drug particles are obtained after removing the frozen solvent from the frozen drug solution. The atomized droplets started getting freeze, before coming in contact with cryogenic fluid when in the vapour phase.[55]
- **Ultra-Rapid freezing (URF**): Nanostructured drug molecules with greater surface area and morphology of choice, both are obtained by this novel technique using solid cryogenic substance. Drug solution when applied on the surface of the cryogenic substrate, rapidly undergoes freezing followed by lyophilization that leads to the formulation of micronized drug powder exhibiting better solubility.[56]

CRYSTAL HABIT MODIFICATION

- **Crystal engineering**: It is the process which is applied to broad range of crystalline substances. It is a novel and potential method for improving dissolution rate and bioavailability of hydrophobic drugs. Crystal engineering is an technique for formulating effective and safe dosage forms of hydrophobic drugs. Crystal engineering is mainly based upon the methods to adjusting crystal size, shape and forms of the crystal. Crystal engineering is also referred to as the manipulation of the non-covalent interactions between the ionic and molecular elements of the solid-state structures that contains electrical, magnetic and optical characteristics.[57]
- **Hydrates & solvates**: Crystal modification technique involves the formation of hydrates and solvates, which enhances the rate of dissolution of the poorly water-soluble drugs. The solvent molecules are trapped within the lattice during the crystallization process. When the solvent used in crystallization process is water, then the crystal formed is hydrate. Whereas if the solvent used is not water, then the obtained crystal is named as solvate.[58] Rate of dissolution and drug solubility greatly varies for different solvates. For example, hydrate form of theophylline has better solubility and rate of dissolution. Formation of hydrates/solvates depends upon the crystallization process and molecular characteristics of the drug molecule.[27]
- **Polymorphs**: Polymorph is the compound having different crystal structure but similar chemical composition. Melting point varies for polymorphs showing direct relation to the solubility. Therefore, it is often observed that different polymorphs have different solubilities. Solubility difference ranges only 2-3 folds because of the low free energy difference between them.(35) Furthermore, drug having highest order of crystallinity, is more stable and is found in numerous polymorphic forms. Meta stable forms of drugs are also formed, which possesses high free energy. Different forms of polymorphs are prepared from almost all type of crystals.[59]

FORMATION OF COMPLEXES

- **Inclusion complexes**: These are generally obtained by incorporating guest molecule into the cavity of the host molecule or group of molecules. This approach is more flawlessly used than other techniques to improve the solubility of drug, rate of dissolution and bioavailability of the poorly water-soluble drugs. Tight fit between guest and host molecule's cavity is the primary structural requirement for inclusion complexation. The host have the precise cavity size to tackle the guest and arrange in such a way that it reduces the contact between non-polar regions of the host and guest or to eliminate the water.[60] Most common host

molecule for inclusion complex are cyclodextrins (CDs).[61] CDs have hollow lipophilic core cavity which attaches to the cavity of the disc by various intermolecular interactions. Processes involved in the preparation of inclusion complexes are Kneading method, Physical mixing, Solvent evaporation technique, Co-precipitation method, microwave irradiation method, Lyophilization and spray drying technique.[62][63]

- **Peptide complexation:** There are several benefits of using protein nanoparticles, because it is helpful in transporting peptide hormones, growth factors, genetic materials (DNA & RNA) and poorly soluble drugs. They are easy to prepare and show stability that makes it different from others. Due to the easy, environment friendly and cheap production process, proteins are obtained from multiple sources and prepared in the form of nanoparticles.[64] When the aqueous solubility of the protein nanoparticles is improved by complexation, it leads to better absorption of the bioactive substances accelerating increased bioavailability. This in turn increases the potency of the drug which may result in the reduction of side effects. For example, by encapsulating curcumin in egg white protein nanoparticles gave effective results by reducing the degradation ratio and also safeguard the antioxidant activity of curcumin.[65]

Table 4: Marketed formulation using complexation with cyclodextrins technique.

Trade name	Drug used	Dosage form	Company
Omebeta	Omeprazole/	Tablet	Betapharm
Nitropen	Nitroglycerine/	Sublingual tablets	Nippon kayaku
Nimedex	Nimesulid/βCD	Oral sachet	Novartis

CHEMICAL METHODS

pH Adjustment: By adjusting the pH, poorly soluble drugs are dissolved in water. Crucial factors to determine the solubility includes pH tolerance of the selected solution and buffer capacity. Soluble additives, which raise the surroundings' pH of the dosage form to a range greater than pKa of weakly acidic drugs, increases the solubility of that particular drug. Solubility of weakly basic drugs increased, when soluble additives function as alkalizing agents. Adjustment of pH offers several benefits like the ease of preparation, utilization of minute quantities of compounds and management of large number of evaluations in less time.[66] However, chances of precipitation might occur during dilution with the aqueous media of pH in which the particular drug exhibits lower solubility or no solubility at all. After pH adjustment, stable and soluble ionisable compounds are produced. Adjustment of pH is the principle which is used both for the oral and parenteral drugs administration.[35]

Co-crystallization: It is an alternative approach to optimize the properties of the drug by affecting the molecular interactions of crystal lattice. Co-crystals are the complex materials, which are having non-ionic supramolecular interactions. They are generally used to detect the issues related to physical properties such as drug stability, drug solubility and bioavailability without any effect on the chemical structure of the drugs. Prepared Co-crystals have two or more components which are linked together by weak intermolecular forces like π-π stacking and hydrogen bond interactions.[67] Various analysis techniques and physicochemical studies which includes investigation of solubility and stability are required to choose the suitable co- crystal. They generally have two major solid elements, the API and other one is co-crystal former. Several techniques used for this process are hot-melt extrusion and high throughput crystallization. Characterization parameters for the co-crystals are solubility, stability, melting, intrinsic dissolution and scanning calorimetry.[49]

Sono-crystallization: It is the process acts by utilizing the liquid solvents and antisolvents and results in decreasing particle size for recrystallization of poorly water-soluble drugs. It is the innovative approach for reduction in particle size which involves ultrasound waves in crystallization. Ultrasound waves of frequency 20-100 kHz are used for inducing crystallization. Mostly used ultrasound sound is limited between 20-5kHz. It not only raises the nucleation rate but also effectively reduces the size and also controls the distribution of size of drugs.[26]

Co-solvency: The process of obtaining a mixture of water and one or more water compatible solvents required for preparing a solution with enhanced solubility for hydrophobic drugs is known as co-solvency and the solvents which are used in combination for this process are known as co-solvents. They are generally used in multiple formulations like solids and liquids. PEG 300, propylene glycol and ethanol are commonly used solvents in the co-solvent mixture. Drug preparations of poorly soluble drugs formulated by co-solvency technique are ingested both orally and parenterally. Before administration of parenteral formulations, there is requirement of dilution with water and any other suitable aqueous media to reduce the concentration of solvent. Co-solvent system is utilized to reduce the interfacial tension between the aqueous solution and hydrophobic solute, is commonly known as solvent blending.[68] Hydrogen acceptor and donor groups are present in co-solvents within a small hydrocarbon region. Hydrogen bonding network of water is affected by the hydrophobic hydrocarbon region which results in the reduction of intermolecular interactions. Co-solvents enhance the solubility of drug by providing

nonpolar groups, resulting in increased aqueous solubility.[69]

Formation of salts: Original forms of various acidic and basic drugs have lesser solubility than their Salt form. Salt formation is the most favoured strategy for the preparation of various parenteral formulations. For example, sildenafil drug in form of glutarate salt enhances its solubility by 3.2 folds, furosemide drug in form of sodium salt enhanced its solubility by 20 folds.[70] Generally, rate of dissolution of salt form has different from its parent compound. Sodium and potassium salts forms of the weak acids dissolved more quickly than their pure form. Salt formation is only restricted because of the patient compliance. Commercialization of drugs in salt form also causes epigastric pain due to high alkalinity and precipitation of salt by carbon dioxide and atmospheric water reactivity.[48]

Hydrotropy: It is the solubilization improving technique in which second solute is mixed in large amount to enhance the solubility of the existing solute. Sodium benzoate, sodium salicylate, nicotinamide and sodium citrate are some concentrated aqueous hydrotropic solutions which are used to increase the aqueous solubilities of many poorly water-soluble drugs.[70] Regular self-agglomeration is usually observed in micellar solubilization due to the small hydrophobic tail. Hydrotropy is used to describe non-micelle-forming substances, they may be organic or inorganic, solid or liquid, which are capable to enhance the solubility of poorly soluble drugs.[71]

MISCELLANEOUS TECHNIQUES

Supercritical fluid (SCF) process: This technology was introduced industrially and in pharmaceutical sector in early 1980s.[72] During early 1980s, Supercritical fluid technology made its industrial debut in the pharmaceuticals, SCF technology is then employed for the manufacture of pharmaceutical formulations via precipitation and crystallization. This method, is renowned for its safety, cost efficiency, environmental friendliness, safety and thus, gained widespread acceptance. The appealing aspect of SCFs lies in their operational attributes, distinguished by minimal temperature and pressure level, which make them highly desirable for pharmaceutical research. A supercritical fluid assumes as a singular phase when subjected to pressures (Pc) and temperatures (Tc) beyond critical values.[95][96]

Now a days, the use of SCF technologies and applications expanded rapidly throughout the world. Due to its safety, eco-friendly and affordable characteristics carbon dioxide is used as most common SCF. Above its critical temperature and pressure, SCF exists in single phase. SCFs are generally used for product processing because of their dual properties of both liquids and gases. It contains liquid like density and diffusivity having gas like viscosity & compressibility. With small variations in the operating temperature and pressure or both, fluctuates significantly their density, transport properties and other physical properties like dielectric constant and polarity, therefore both temperature and pressure are critical parameters in this process. Due to its processing capabilities, they are applied to food industry and further incorporated in pharmaceutical industry. After recrystallization, particle size of the drug is reduced greatly when solubilized with the SCF. They have the potential to form nano-suspensions of particle size of diameter 5-2000nm in[73] SCF processing includes processes which are used for marking distinctive aspects such as processing with solution enhanced dispersion by SCF processes (SEDS) and aerosol supercritical extraction system (ASES).[74]

Micellar solubilization technique: Micellar solubilization entails the integration of a component onto or within the micelles. The primary attributes of micelles are focused on the capacity or ability to enhance the compound's solubility with solubility in water. In this context, solubilization may be referred as the spontaneous dissolution of a compound with surfactant micelles in water by reversible interactions, results in production of solubilized compound having reduced thermodynamic activity and thermodynamically stable isotropic solution.[97] When examining the solubility of a poorly water-soluble compound as a function of surfactant concentration, it is commonly observed that the solubility of the drug remains low until the surfactant concentration reaches the critical micelle concentration (CMC). Upon surpassing the critical micellar concentration, the solubility of the surfactant shows a linear surge with its concentration. This discovery highlights a direct relationship among micellization as well as solubilization. Multiple poorly water- soluble substances like glipizide, glyburide, rosiglitazone, glimepiride, pioglitazone, repaglinide depend on the micellar solubilization method to enhance their bioavailability as well as solubility.[98]

Electrostatic spinning method: It is the technique, which involves the formation of solid fibres by utilizing polymeric stream solution or melt which is passed by a millimetre-scale nozzle between potential of 5-30kV.[76] Electrostatic field is required in this process over a conductive capillary which is further attached to the reservoir containing polymeric solution. It also contains conductive collective screen. Submicron sized fibres are obtained, Electrostatic forces surmounts the surface tension of drug/polymer solution at air interface. For example, by using this technique Itraconazole/ HPMC mixture has been prepared easily.[77]

Direct capsule filling method: Francis and Jones suggested this technique in 1978, by filling the hard gelatin capsules with semi-solid materials as melts, which were solid at room temperature. This technique is potentially used for solid dispersions. Chatham proposed

the idea to fill the drug-PEG melts in hard gelatin capsules, but Serajuddin suggested that polyethylene glycol is not suitable as carrier for solid dispersion of poorly water-soluble drugs which are enclosed in hard gelatin capsules by direct filling method. For instance, they disperse hydrophobic drug REV5901 into melted PEG 1000, PEG 1450 and PEG 8000 and hot solutions are filled into 0 size gelatin capsules and each capsule containing 550mg of PEG and 100mg of drug. Solid plugs are prepared inside the capsule shell at room temperature when melted substance started getting solidified.[78] PEG based solid dispersion is incomplete because of the quick dissolution of the hydrophilic carriers. Solid plugs formed over the surface of the capsule shell helps prevent the dissolution of the drug from solid dispersions. At pH of less than 2, no dissolution occurs where surface of the solid plug is coated by drug layer until the capsule shell dissolves.[76]

Dropping technique: The dropping technique, was introduced by Ulrich et.al and was designed to upsurge the process of crystallization of several chemicals, characterizing an innovative method for preparing spherical particles from melted solid dispersion. This apptroach has a scope to address certain inherent difficulties encountered in different techniques. A molten mixture of carrier as well as drug in solid dispersion form is dispensed by employing a pipette and subsequently dripped on the surface, where it solidifies and changes into spherical particles.[101] Due to notable impact of temperature on viscosity, controlling temperature precisely is essential to ensure the solidification of molten substance into spherical shape when it encounters the surface. Furthermore, this technique evades challenges like pulverization, sifting, and compressibility that are frequently encountered with alternative methods involving melting. Whereas, there are few limitations to this method, including potential physical instability of solid dispersion.[102]

Role of Nanotechnology in solubility improvement of poorly soluble drugs

Nanotechnology is rising modern interdisciplinary scientific field that deals with materials and objects at the nanoscale. There is considerable growth in nano-medicines and nanotechnology in drug delivery by health care researchers due to its great potential. Various approaches based on nanotechnology are utilized these days to increase the solubility of hydrophobic drugs. Most commonly utilized nanocarriers for solubility enhancement are the formulations based on Nanosuspensions, Liposomes, Niosomes, Proniosomes, Transferosomes, Solid-Lipid Nanoparticles, Nano-emulsions and Nanocrystals.[70][79]

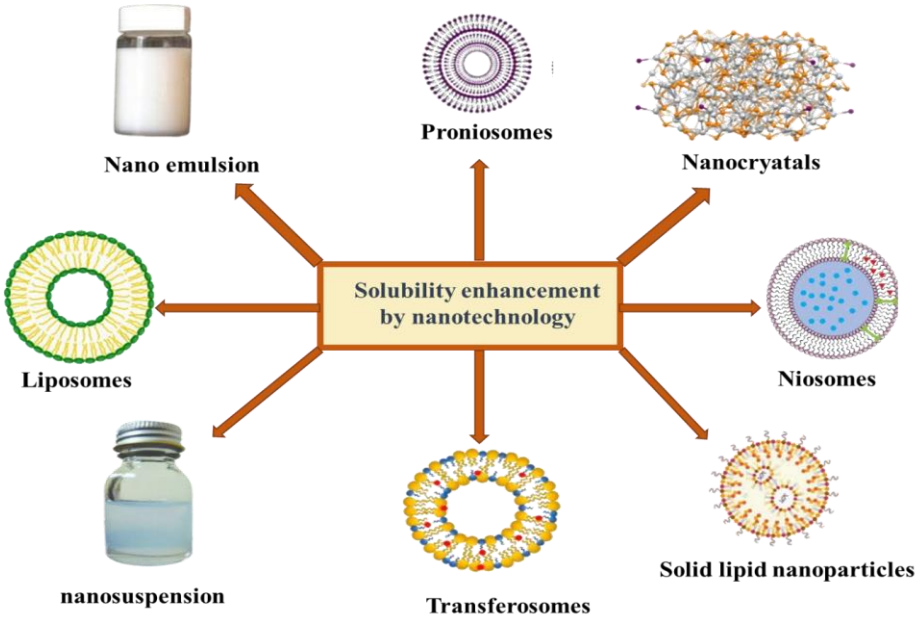

Figure 4: Various approaches of nanotechnology to enhance solubility of poorly soluble drugs.

Nanosuspensions: These are the colloidal dispersions containing drug particles of nano-size which are prepared by different processes and stabilized by using compatible stabilizer. Nanosuspensions have the unique ability to deliver the poorly water-soluble drugs for optimizing their therapy and improving their clinical efficacy. They are generally produced by the milling and high-pressure homogenization techniques. Nanosuspensions have a unique property that they are compatible with various drug delivery systems like hydrogels and mucoadhesive formulations. Rapid progress has been observed in delivery of nanosuspensions from previous decades. Nanosuspensions are delivered through different routes like parenteral, oral and pulmonary. Currently, researchers have attention on utilizing nanosuspensions for site specific drug delivery. Nanosuspensions increase

the dissolution velocity by increasing the surface area of the particles to nano scale about 2µm and it also increases the saturation solubility of the drug by disintegrating the ideal drug microcrystals to nanocrystals by creating high-energy surfaces.[80]

Liposomes: These are minute vesicles containing one or more lipid bilayer concentric spheres split up by water or an aqueous buffer compartment. They are employed as carriers, due to their versatility in structure, biphasic characteristics and composition to enhance the solubility, stability, therapeutic efficacy and site-specific drug targeting of poorly soluble drugs. Drugs like Amphotericin-B, artemisinin and dapsone are delivered to their desired sites through this drug nanocarrier. Central core of liposomes is suitable for water-soluble drugs, the membrane core favour lipid-soluble drugs and liquid-aqueous interface for peptide and small proteins. Generally, liposomes are prepared by thin film hydration technique. Lymphatic pathways are involved in the absorption of liposomes because it has lipid-based delivery system.[81]

Niosomes: Niosomes are the unilamellar and multilamellar vesicles based on non-ionic surfactants. These vesicles are prepared by the self-assembly of hydrated surfactant monomer. Non-ionic surfactants and additives are two major elements of niosomes. Surfactants form the vesicular layer, cholesterol and charged molecules act as additives. An aqueous solution of solute is enclosed inside the vesicles' bilayer. Niosomes possess similar physical characteristics like liposomes. Niosomes act as alternative tool to liposomes, because of their degenerative vulnerability and high cost of lipids. Both the hydrophilic and hydrophobic drugs are entrapped by the niosomes because they are of amphiphilic nature. Core cavity retains the hydrophilic drugs and non-polar region within bilayer retains hydrophobic drugs. No requirement of special conditions for surfactant storage. Stability or performance of the prepared niosomes is maintained by adjusting the concentration of excipients and surface charge of vesicles. By prolonging the elimination time of drug from circulation, solubility and drug absorption is enhanced. It also provides site-specific drug targeting. Methods used for formulation of niosomes are micro fluidization, thin film hydration and transmembrane pH gradient method. They are also prepared from the proniosomes.[82][83]

Proniosomes: Proniosomes are dried mixtures of liquid crystalline-compact hybrid niosomes with water soluble carrier coated with suitable surfactant. They are converted into niosomal dispersion rapidly by agitation immediately before use, when mixed in aqueous media. Uniform size of niosome has been observed in niosomal dispersion of proniosomes. They overcome the complications like agglomeration and leaking and also increase the shelf life of the drug. Two major forms of proniosomes which are utilized these days are dry granular type and liquid crystalline type. In dry granular proniosomes, coating of water-soluble carriers like sorbitol and maltodextrin is carried out by suitable surfactant and form a thin layer around each particle of water-soluble carrier. It is necessary to formulate vesicles at above temperature more than transition temperature of non-ionic surfactant, which is utilized in the formulation. In liquid crystalline type proniosomes, when surfactant surface is in contact with the aqueous media then its lipophilic chains get hydrated and became disarranged. Several factors like surfactant type, technique used in size reduction, nature of drug used, and hydration temperature, affects the physical nature of the proniosomes.[84]

Transferosomes: These are the liposomes of specific nature, containing an edge activator and phosphatidylcholine. Transferosomes act as carriers for targeted transdermal drug delivery. They can easily pass-through stratum corneum by generating osmotic gradient through intracellular route and transcellular pathways. Transferosomes have multiple benefits like better penetration through skin membranes, biocompatibility, biodegradability and solubilizing ability of variety of drugs. Alongside, transferosomes have some disadvantages that it can undergo oxidative degradation and is also expensive to formulate. Formulation of transferosomes is carried out by rotary evaporation and sonication method using surfactant, drug and phospholipids. Penetration ability, entrapment efficiency, vesicle size distribution and zeta potential are some parameters which are used for their evaluation. They are applicable for transdermal immunization, target delivery to peripheral subcutaneous tissues and drugs having high molecular weight.[85]

Solid-Lipid Nanoparticles (SLNPs): SLNs are the type of colloidal drug nanocarriers, in which the solid-lipids are stabilized by suitable surfactant at ambient temperature. They became preferable and alternative drug delivery approach because of their dominant features such as potential of controlled release, simple scale-up processing, drug stability, low toxicity and higher drug loading**.** They are delivered through the various routes like parenteral, oral, topical and also through the pulmonary route. Solubility of the hydrophobic drugs is improved by the lipophilic nature of the SLNPs, particularly the drugs of BCS class.[86] High pressure homogenization is the most common technique used for the preparation of quality nano-dispersions, because it provides uniform particle size distribution, easy scale-up processing and high particle content in dispersion. Bioavailability of the Apomorphon drug is enhanced by SLNPs approach by Limited liabilities companies, for US World Meds' marketed product. Mean particle diameter is between the range of 50-1000nm, because it is particulate system. Triglycerides, partial glycerides, fatty acids and steroids are commonly used lipids for SLNs. They are 10-100 folds less cytotoxic than their lead molecule. SLNPs

adhere to the gut wall due to their adhesive properties and are responsible for the proper absorption of drugs at the required site. It was observed that Piribedil, a dopaminergic drug with poor water solubility and shorter elimination half-life, when incorporated in SLNPs gave greater therapeutic efficacy and prolonged plasma levels in rabbits. Various techniques for preparation of SLNPs are ultrasonic solvent emulsification, breaking of o/w emulsions, solvent injection and solvent emulsification process.[59][87]

Nano-emulsions: Nano-emulsions are the dispersed combination of an oily phase and a dispersed phase with surfactant which forms the interfacial film for making the dispersion stable. Types of nanoemulsions are, oil in water (o/w) emulsion, water in oil (w/o) and Bi-continuous nanoemulsions. Nanoemulsions have an average droplet size between 5nm to 200 nm. Physical characteristics such as optical transparency and elasticity are altered during reduction in size to nanoscale. Nanoemulsions are utilized in various field of science like in pharmaceutical formulations and in food technology. They are transparent in nature and also have less interfacial tension due to nano size of the droplet.[88] Nanoemulsions can be given by various route to the patients but transdermal route shows better sustainability. Gel form of the drug formulations have less permeation through skin because of their viscosity but through nanoemulsions, drugs penetrate the skin easily. Nanoemulsions have better solubility of both hydrophilic and lipophilic drugs. Components of the nanoemulsions increase the skin permeation by changing the formation of the stratum corneum. For example, widely used permeation enhancer is short chain alkanol and Isopropyl myristate for transdermal formulations. Mainly non-ionic surfactants are used as solubilizing agents for nanoemulsions.[89]

Nanocrystals: Crystals with size in nano-meter range are known as nanocrystals. They are the nanoparticles having the crystalline properties. Nanocrystals contain only poorly soluble drugs with no carrier involved in it. They improve both solubility and bioavailability of the drug and can be administered by any route. Due to particle size reduction, solubility and dissolution of the nanocrystals is increased.[90] Surface modification of nanocrystals is the phenomenon by which targeting drug delivery can be achieved, when they are in suspension form. Nanocrystals also reduce the tissue irritation when given by intramuscular or subcutaneous routes. They also provide long term physical and chemical stability. Nanocrystals are prepared by several processes like antisolvent precipitation, nano-jet technology, NANOEDGE® Technology and Melt-emulsification. Poloxamer, lecithin, HPMC, polysorbate 80 and sodium lauryl sulphate are some nanocrystal stabilizers, which are generally used. Some marketed formulations of nanocrystals are Rapamune (Wyeth Pharmaceuticals,2000), Emend (Merck, 2001), Tricor (Abbott Laboratories) and Megace ES (Par Pharmaceutical Companies).[91][92][93][94]

CONCLUSION

In conclusion, this review provides comprehensive overview of cutting-edge technologies and strategies aimed at the solubility and bioavailability of poorly water-soluble drugs. The critical analysis of formulation design, solid particle techniques, prodrug strategies, crystal engineering, micronization, solid dispersions, particle size reduction technologies, nanosizing, cyclodextrins, solid lipid nanoparticles, drug conjugates, colloidal drug delivery systems, and various complexation methods underscores the multifaceted nature of this challenge in pharmaceutical formulation. Recognizing the pivotal role of solubility enhancement in achieving therapeutic efficacy and drug bioavailability, it is evident that addressing the hurdles posed by Class II and IV drugs is imperative for advancing pharmaceutical innovation. While molecular properties serve as a foundation for addressing these challenges, solid dispersions and lipid delivery emerge as particularly promising techniques, offering versatility across various dosage forms. The pursuit of novel processes and excipients to aid poorly soluble molecules reflects a dynamic landscape of innovation within the pharmaceutical industry. As researchers delve deeper into molecular modeling and understanding, the quest for an ideal solution, technique or polymer formulation capable of addressing 100% of solid molecules remains a compelling aspiration. While such a panacea remains elusive, advancements in molecular modeling hold promise for accelerating the identification of optimal formulations, thereby advancing the field towards enhanced drug solubility and therapeutic efficacy.

CHALLENGES AND FUTURE PERSPECTIVES

The escalating prevalence of insoluble Active Pharmaceutical Ingredients (APIs) has intensified the demand for scientists to pioneer innovative techniques enhancing bioavailability. In the pursuit of efficacious pharmaceutical products, researchers must explore a diverse array of formulation strategies to surmount these challenges. Despite the existence of conventional approaches capable of augmenting bioavailability, there remains a pressing need for further research to develop practical and efficient formulation methodologies. While recent research has spotlighted solid dispersion approaches and lipid-based nanotechnological techniques, the translation of these advancements into commercially available products has been hindered by challenges related to production scale-up, instability related to physicochemical properties, limited shelf life, and problem of reproducibility. Addressing the needs of poorly soluble molecules has spurred the emergence of various trends in solubility enhancement, including the exploration of novel methodologies and excipients. However, the adoption of entirely new techniques presents substantial financial investments for the pharmaceutical industry, often necessitating

infrastructural upgrades and skilled personnel. To streamline this process and identify optimal approaches, attention has increasingly turned to molecular modeling. While not yet fully realized, advancements in molecular dynamic simulations hold promise for predicting the efficacy of excipients or technologies with greater precision. For example, Fagerholm et al. proposed a pioneering approach wherein oral bioavailability in humans is predicted directly from chemical structure, employing an integrated technique comprising nine machine learning models, three sets of structural alerts, and two physiologically based pharmacokinetic models. With a successful predicted accuracy (Q2) of 0.50 on a benchmark dataset of 184 chemicals, this approach shows promise in applications such as predicting human exposure and dose, compound optimization, and decision-making in drug discovery and development. This methodology has the potential to rationalize drug development processes, mitigating failures and overexposures in early clinical trials with candidate drugs. Given that oral administration remains the most practical route for medication delivery, accurate determination of oral bioavailability is crucial during drug discovery and development. Quantitative structure-property relationship (QSPR), rule-of-thumb (RoT), and physiologically based pharmacokinetic (PBPK) approaches offer promising avenues for early oral bioavailability prediction. Harnessing the synergy of artificial intelligence and novel solubility enhancement technologies holds the potential to revolutionize the resolution of solubility challenges, while simultaneously reducing the costs associated with research and development.

REFERENCE

1. Rathi PB, Kale M, Soleymani J, Jouyban A. Solubility of etoricoxib in aqueous solutions of glycerin, methanol, polyethylene glycols 200, 400, 600, and propylene glycol at 298.2 K. Journal of Chemical & Engineering Data., 2018; 63(2): 321–30.
2. Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: II. Application of quantitative thermodynamic relationships for prediction of solubility enhancement in structurally diverse insoluble pharmaceuticals. Pharmaceutical research, 2010; 27: 2704–14.
3. Jain S, Patel N, Lin S. Solubility and dissolution enhancement strategies: current understanding and recent trends. Drug development and industrial pharmacy, 2015; 41(6): 875–87.
4. Kumari L, Choudhari Y, Patel P, Gupta G Das, Singh D, Rosenholm JM, et al. Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. Life., 2023; 13(5): 1099.
5. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research, 1995; 12: 413–20.
6. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to address low drug solubility in discovery and development. Pharmacological reviews, 2013; 65(1): 315–499.
7. Krishnaiah YSR. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequiv Availab, 2010; 2(2): 28–36.
8. Nidhi K, Indrajeet S, Khushboo M, Gauri K, Sen DJ. Hydrotropy: A promising tool for solubility enhancement: A review. Int J Drug Dev Res., 2011; 3(2): 26–33.
9. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International journal of pharmaceutics, 2011; 420(1): 1–10.
10. Hu J, Johnston KP, Williams III RO. Nanoparticle engineering processes for enhancing the dissolution rates of poorly water soluble drugs. Drug development and industrial pharmacy, 2004; 30(3): 233–45.
11. Shah P, Goodyear B, Michniak-Kohn BB. A review: Enhancement of solubility and oral bioavailability of poorly soluble drugs. Adv Pharm J., 2017; 2(5): 161–73.
12. Dahan A, Miller JM, Amidon GL. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. The AAPS journal, 2009; 11: 740–6.
13. Papich MG, Martinez MN. Applying biopharmaceutical classification system (BCS) criteria to predict oral absorption of drugs in dogs: challenges and pitfalls. The AAPS journal, 2015; 17: 948–64.
14. Bai GE, Armenante PM, Plank R V, Gentzler M, Ford K, Harmon P. Hydrodynamic investigation of USP dissolution test apparatus II. Journal of Pharmaceutical sciences, 2007; 96(9): 2327–49.
15. Kumar S, Bhargava D, Thakkar A, Arora S. Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2013; 30(3).
16. Onoue S, Kojo Y, Aoki Y, Kawabata Y, Yamauchi Y, Yamada S. Physicochemical and pharmacokinetic characterization of amorphous solid dispersion of tranilast with enhanced solubility in gastric fluid and improved oral bioavailability. Drug metabolism and pharmacokinetics, 2012; 27(4): 379–87.
17. Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. Expert opinion on drug delivery, 2007; 4(4): 403–16.
18. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation

classification system. European journal of pharmaceutical sciences, 2006; 29(3–4): 278–87.
19. Patel JN, Rathod DM, Patel NA, Modasiya MK. Techniques to improve the solubility of poorly soluble drugs. International Journal of Pharmacy & Life Sciences, 2012; 3(2).
20. Ain S, Ain Q, Parveen S. An overview on various approaches used for solubilization of poorly soluble drugs. The Pharma Research, 2009; 2: 84–104.
21. Singhal D, Curatolo W. Drug polymorphism and dosage form design: a practical perspective. Advanced drug delivery reviews, 2004; 56(3): 335–47.
22. Mahapatra AP, Patil V, Patil R. Solubility enhancement of poorly soluble drugs by using novel techniques: A comprehensive review. Int J Pharm Tech Res., 2020; 13(2): 80–93.
23. Martin A. Physical Pharmacy, 4th edi, BI Publication, Pvt. Ltd., 1993; 212-250.
24. Patil MS, Godse SZ, Saudagar RB. Solubility enhancement by various techniques: An overview. World J Pharm Pharm Sci., 2013; 2(6): 4558–72.
25. Pawar A. Novel techniques for solubility, dissolution rate and bioavailability enhancement of class II and IV drugs. Asian Journal of Biomedical and Pharmaceutical Sciences, 2012; 2(13): 9.
26. Kumar S, Singh P. Various techniques for solubility enhancement: An overview. Pharma Innov, 2016; 5(1, Part A): 23.
27. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. Int Sch Res Notices, 2012; 2012.
28. Leleux J, Williams RO. Recent advancements in mechanical reduction methods: Particulate systems. Drug Dev Ind Pharm., 2014; 40(3): 289–300.
29. Rasenack N, Müller BW. Micron-size drug particles: common and novel micronization techniques. Pharm Dev Technol, 2004; 9(1): 1–13.
30. Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly-water-soluble compounds. European journal of pharmaceutical sciences, 2003; 18(2): 113–20.
31. Venkatesh T, Reddy AK, Maheswari JU, Dalith MD, Kumar CKA. Nanosuspensions: ideal approach for the drug delivery of poorly water soluble drugs. Pharm Lett., 2011; 3(2): 203–13.
32. Bhalani D V, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines, 2022; 10(9): 2055.
33. Schiguchi K, Obi N. Studies on absorption of eutectic mixture. A comparis on of the behavior of eutectic mixture of sulfathiazole and that of oridinary sulfathiazole in man., 1961; 9(11): 866–72.
34. Habib MJ. Pharmaceutical solid dispersion technology. CRC Press; 2000.
35. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. Journal of Advanced Pharmacy Education and Research, 2012; 2(1–2012): 32–67.
36. Higuchi T, Ikeda M. Rapidly dissolving forms of digoxin: hydroquinone complex. J Pharm Sci., 1974; 63(5): 809–11.
37. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today., 2007; 12(23–24): 1068–75.
38. Tsinontides SC, Rajniak P, Pham D, Hunke WA, Placek J, Reynolds SD. Freeze drying—principles and practice for successful scale-up to manufacturing. Int J Pharm., 2004; 280(1–2): 1–16.
39. Adel EEM, Soliva M, Speiser P. Hot extruded dosage forms. Pharm Acta Helv., 1971; 46: 31–52.
40. Huttenrauch R. Spritzgieβverfahren zur Herstellung peroraler Retardpraperate. Pharmazie, 1974; 29: 297–302.
41. Kumar P, Singh C. A study on solubility enhancement methods for poorly water soluble drugs. Am J Pharmacol Sci., 2013; 1(4): 67–73.
42. Nokhodchi A, Talari R, Valizadeh H, Jalali MB. An investigation on the solid dispersions of chlordiazepoxide. Int J Biomed Sci., 2007; 3(3): 211.
43. Kalaiselvan R, Mohanta GP, Manna PK, Manavalan R. Studies on mechanism of enhanced dissolution of albendazole solid dispersions with crystalline carriers. Indian J Pharm Sci., 2006; 68(5): 599–607.
44. Devi NKD, Rani AP, Kumar KS, Kaushik J, Sowjanya V. Cyclodextrins in pharmacy-an overview. Pharmacophore, 2010; 1(3–2010): 155–66.
45. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I: Theoretical considerations and discussion of the literature. J Pharm Sci., 1965; 54(8): 1145–8.
46. Bhusnure OG, Kazi P, Gholve S, Ansari M, Kazi S. Solid Dispersion: An ever green method for solubility enhancement of poorly water soluble drugs. Int J Res Pharm Chem., 2014; 4(4): 906–18.
47. Jain P, Goel A, Sharma S, Parmar M. Solubility enhancement techniques with special emphasis on hydrotrophy. International Journal of Pharma Professional's Research (IJPPR), 2010; 1(1): 34–45.
48. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig, 2012; 2(1): 12.
49. Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research, 2018; 10(9): 2205–11.
50. Ghosh PK, Murthy RSR. Microemulsions: a potential drug delivery system. Curr Drug Deliv, 2006; 3(2): 167–80.
51. Katteboina S, Chandrasekhar P, Balaji S. Approaches for the development of solid self-

emulsifying drug delivery systems and dosage forms. Asian J Pharm Sci., 2009; 4(4): 240–53.
52. Sapra K, Sapra A, Singh SK, Kakkar S. Self emulsifying drug delivery system: A tool in solubility enhancement of poorly soluble drugs. Indo Global J Pharm Sci., 2012; 2(3): 313–32.
53. Rawat S, DV D, BS P, PR S. SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A METHOD FOR BIOAVAILABILITY ENHANCEMENT. International Journal of Pharmaceutical, Chemical & Biological Sciences, 2014; 4(3).
54. Wang W. Lyophilization and development of solid protein pharmaceuticals. Int J Pharm., 2000; 203(1–2): 1–60.
55. Buxton IR, Peach JM. Process and apparatus for freezing a liquid medium. Google Patents, 1984.
56. Purvis T, Mattucci ME, Crisp MT, Johnston KP, Williams RO. Rapidly dissolving repaglinide powders produced by the ultra-rapid freezing process. AAPS PharmSciTech., 2007; 8: E52–60.
57. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev., 2007; 59(7): 617–30.
58. Suleiman MS, Najib NM. Isolation and physicochemical characterization of solid forms of glibenclamide. Int J Pharm., 1989; 50(2): 103–9.
59. Shah P, Goodyear B, Michniak-Kohn BB. A review: Enhancement of solubility and oral bioavailability of poorly soluble drugs. Adv Pharm J., 2017; 2(5): 161–73.
60. Akhilesh D, Mehta H, Prabhakara P, Kamath J V. Enhancement of solubility by complexation with cyclodextrin and nanocrystallisation. International Research Journal of Pharmacy, 2012; 3(5): 100–5.
61. Sherje AP, Jadhav M. β-Cyclodextrin-based inclusion complexes and nanocomposites of rivaroxaban for solubility enhancement. J Mater Sci Mater Med., 2018; 29: 1–8.
62. Kumari L, Choudhari Y, Patel P, Gupta G Das, Singh D, Rosenholm JM, et al. Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. Life., 2023; 13(5): 1099.
63. Semcheddine F, Guissi NEI, Liu X, Wu Z, Wang B. Effects of the preparation method on the formation of true nimodipine SBE-β-CD/HP-β-CD inclusion complexes and their dissolution rates enhancement. AAPS PharmSciTech., 2015; 16: 704–15.
64. Hong S, Choi DW, Kim HN, Park CG, Lee W, Park HH. Protein-based nanoparticles as drug delivery systems. Pharmaceutics, 2020; 12(7): 604.
65. Chang C, Meikle TG, Su Y, Wang X, Dekiwadia C, Drummond CJ, et al. Encapsulation in egg white protein nanoparticles protects anti-oxidant activity of curcumin. Food Chem., 2019; 280: 65–72.
66. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement approaches. Int J Pharm Sci Rev Res Dev., 2010; 5(1): 41–51.
67. Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. Int J Pharm Sci Res., 2014; 5(9): 3566.
68. Rahman MM, Khalipha ABR, Azad MAK, Hossain S, Haque S. Methods of solubility and dissolution enhancement for poorly water soluble drugs: a review. World J Pharm Pharm Sci., 2014; 3(5): 107–30.
69. Millard JW, Alvarez-Nunez FA, Yalkowsky SH. Solubilization by cosolvents: Establishing useful constants for the log–linear model. Int J Pharm., 2002; 245(1–2): 153–66.
70. Ansari MJ. An overview of techniques for multifold enhancement in solubility of poorly soluble drugs. Current Issues in Pharmacy and Medical Sciences, 2019; 32(4): 203–9.
71. Rasool AA, Hussain AA, Dittert LW. Solubility enhancement of some water-insoluble drugs in the presence of nicotinamide and related compounds. J Pharm Sci., 1991; 80(4): 387–93.
72. Lipinski C. Poor aqueous solubility—an industry wide problem in drug discovery. Am Pharm Rev., 2002; 5(3): 82–5.
73. Manna L, Banchero M, Sola D, Ferri A, Ronchetti S, Sicardi S. Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO2. J Supercrit Fluids., 2007; 42(3): 378–84.
74. Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int J Pharm., 2005; 301(1–2): 199–208.
75. Liu C, Desai KGH, Liu C. Solubility of valdecoxib in the presence of ethanol and sodium lauryl sulfate at (298.15, 303.15, and 308.15) K. J Chem Eng Data., 2004; 49(6): 1847–50.
76. Karanth H, Shenoy VS, Murthy RR. Industrially feasible alternative approaches in the manufacture of solid dispersions: A technical report. AAPS PharmSciTech, 2006; 7(4): 87.
77. Bülau HC, Ulrich J. Parameters influencing the properties of drop-formed pastilles. Crystal Growth of Organic Materials, 1997; 87: 123–30.
78. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci., 1999; 88(10): 1058–66.
79. Inshakova E, Inshakov O. World market for nanomaterials: Structure and trends. In: MATEC web of conferences. EDP Sciences, 2017; 02013.
80. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. Journal of pharmacy and pharmacology, 2004; 56(7): 827–40.
81. Rao MRP, Babrekar LS. Liposomal Drug Delivery for Solubility and Bioavailability Enhancement of Efavirenz. Indian J Pharm Sci., 2018; 80(6).
82. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: a controlled and novel drug delivery system. Biol Pharm Bull., 2011; 34(7): 945–53.

83. Khan R, Irchhaiya R. Niosomes: a potential tool for novel drug delivery. J Pharm Investig, 2016; 46: 195–204.
84. Kumari R, Verma K, Verma A, Yadav GK, Maurya SD. Proniosomes: a key to improved drug delivery. Journal of Drug Delivery and Therapeutics, 2014; 56–65.
85. Solanki D, Kushwah L, Motiwale M, Chouhan V. Transferosomes-a review. World J Pharm Pharm Sci., 2016; 5(10): 435–49.
86. GL A. Theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res., 1995; 22: 11–23.
87. Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. Expert Opin Drug Deliv., 2007; 4(4): 403–16.
88. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst, 1999; 16(5).
89. Thakur A, Walia MK, Kumar SLH. Nanoemulsion in enhancement of bioavailability of poorly soluble drugs: a review. Pharmacophore, 2013; 4(1–2013): 15–25.
90. Junghanns JUAH, Müller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine, 2008; 3(3): 295–310.
91. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci., 1998; 1(1): 15–30.
92. Hanafy A, Spahn-Langguth H, Vergnault G, Grenier P, Grozdanis MT, Lenhardt T, et al. Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug. Adv Drug Deliv Rev., 2007; 59(6): 419–26.
93. Kipp JE. The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. Int J Pharm., 2004; 284(1–2): 109–22.
94. Müller RH, Benita S, Böhm BHL. Emulsions and nanosuspensions for the formulation of poorly soluble drugs. CRC Press, 1998.
95. Lenhardt T, Vergnault G, Grenier P, Scherer D, Langguth P. Evaluation of nanosuspensions for absorption enhancement of poorly soluble drugs: in vitro transport studies across intestinal epithelial monolayers. The aaps journal, 2008; 10: 435–8.
96. Lipinski C. Poor aqueous solubility—an industry wide problem in drug discovery. Am Pharm Rev., 2002; 5(3): 82–5.
97. Salager JL, Marquez R, Bullon J, Forgiarini A. Formulation in surfactant systems: from-Winsor-to-HLDN. Encyclopedia, 2022; 2(2): 778–839.
98. Liu C, Desai KGH, Liu C. Solubility of valdecoxib in the presence of ethanol and sodium lauryl sulfate at (298.15, 303.15, and 308.15) K. Journal of Chemical & Engineering Data., 2004; 49(6): 1847–50.
99. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. International journal of pharmaceutical investigation, 2012; 2(1): 12.
100. Bülau HC, Ulrich J. Parameters influencing the properties of drop-formed pastilles. Crystal Growth of Organic Materials, 1997; 87: 123–30.
101. Reneker DH, Chun I. Nanometre diameter fibres of polymer, produced by electrospinning. Nanotechnology, 1996; 7(3): 216.
102. Kamalakkannan V, Puratchikody A, Masilamani K, Senthilnathan B. Solubility enhancement of poorly soluble drugs by solid dispersion technique–A review. J Pharm Res., 2010; 3(9): 2314–21.