IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Methods Of Solubility And Permeability Of Drugs

[1]Karan Dnyanba Gavhane, [2]Dr. Harshal Anwane, [3]Dr. Shivshankar Mhaske, [4]Rushikesh Gajanan Navale, [5]Mayur Gulab Kharat, [6]Rahul Ganesh Wankhade.

[1]Student, [2]Professor, [3]Princilpe, [4] Student, [5]Student, [6]Student.
[1]Pharmacy,
[1]Satyajeet College of Pharmacy, Mehkar, India.

Abstract: The permeability and solubility of drugs plays crucial role in determining their bioavailability which affects patient's compliance and therapeutic outcomes. Drugs with low solubility and low permeability faced many challenges in reaching to their desired site of action. To overcome this problems various new techniques have been developed to enhance solubility and permeability of drugs. The approaches to improved solubility are polymeric micelles, nano-emulsion, dendrimers, liposomes, carbon nanotubes, nano-gels etc. while approaches to improved permeability are chemical modification, spray freeze drying, lipid technologies, self-emulsifying drug delivery system etc. often involve modifying drugs molecular structure. This review explores techniques to improve solubility and permeability with their mechanism of action and pharmaceutical application.

Index Terms - Bioavailability, Lipophilicity, Solubility, Solubility enhancement, self-emulsifying, and nanotubes.

I. INTRODUCTION

The physicochemical features of a pharmacological substance and its products, the physiological functions of the gastrointestinal tract, and the biochemical and physical properties of the epithelial barrier all have an impact on the complex process of intestinal drug absorption. Because oral delivery is the usual method of administration, effective therapy necessitates adequate intestinal absorption to guarantee that the medicine is available at the targeted target site.
Good oral bioavailability occurs when the medicine has the highest permeability and solubility at the absorption site. (3) Drug efficacy depends on its solubility. Without it, a drug substance cannot be absorbed, resulting in limited bioavailability. (2lutions and Solubility) A saturated solution is one in which the solute in solution is balanced with the solid phase.

Solubility is defined quantitatively as the concentration of solute in a saturated 333 solution at a specific temperature, and qualitatively as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. An unsaturated or sub-saturated solution contains the dissolved solute in a concentration lower than that required for complete saturation at a specific temperature. A supersaturated solution contains more of the dissolved solute than it would ordinarily hold at a given temperature. Was the undissolved solute present? (1)

Table 1: solubility definition in the united state pharmacopeia

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Range (mg/mL)	Solubility Assigned (mg/mL)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From1 to 10	100-1000	100
Soluble	From 10 to 30	30-100	33
Sparingly soluble (SPS)	From 30 to 100	10-33	10
Slightly soluble (SS)	From 100 to 1000	1-10	1
Very slightly soluble (VSS)	From 1000 to 10000	0.1-1	0.1
Practically insoluble (PI)	> 10000 -	<0.1	0.01

Table 2: biopharmaceutics classification system

Class	Solubility	Permeability	Iviv Correlation Expectation
Class 1	High	High	Absorption rate in high
Class 2	Low	High	The drug has the less solubility or limited solubility
Class 3	High	Low	The drug has limited permeability
Class 4	Low	Low	Limited absorption rate

The history of solubility includes the work of Joel H. Hildebrand, a US scientist and educator who set the groundwork for solubility theory. In 1916, Hildebrand released a seminal work on the solubility of nonelectrolytes.In 1924, Hildebrand published Solubility, which tried to construct a universal theory of solubility based on Raoult's Law of Vapour Pressures.In 1936, and Hildebrand introduced the square root of the cohesive energy density as a numerical value to represent a solvent's solvency behaviour. 1950 In the third edition of Hildebrand's book, the value indicated by the symbol ∂ was named the "solubility parameter". (6) William Thomson, 1st Baron Kelvin, created the term permeability in 1872, and Oliver Heaviside used it alongside permittivity in 1885. (7). In vitro techniques. Skin permeability research in the 1970s resulted in the development of in vitro models and forecasting approaches for transdermal absorption. Parallel artificial membrane permeation assay (PAMPA). The Roche team introduced the PAMPA in 1998, which uses artificial membranes in a 96-well microtiter plate configuration. The PAMPA barrier is a filter that contains phospholipids dissolved in an organic solvent. Variants of PAMPA. Following the PAMPA's launch, multiple revisions were published to account for the various lipid compositions of human tissues. A drug's permeability is strongly impacted by its physicochemical qualities, such as acid-base character, lipophilicity, and solubility.

Sonophoresis

Sonophoresis is a technology that utilizes ultrasound to improve medicine delivery through the skin. It can form small gaseous pockets within cells, potentially increasing pore size and facilitating drug diffusion. (7)

Solubility refers to a solid, liquid, or gaseous chemical substance's (referred to as the solute) capacity to dissolve in a solvent (typically a liquid) and produce a solution. (8) Drug permeability plays a crucial role in its absorption and distribution throughout the body. It's a measure of how rapidly a drug passes biological membranes and becomes bioavailable (9).

Problems face in the drug solubility

1. Particle size
2. Temperature
3. Molecular size
4. Nature of solute and solvent
5. Pressure
6. Polymorphs
7. Polarity
8. The shake-flask method was used to assess pH-dependent solubility and BCS classification of carvedilol, as previously described. The equilibrium solubility of carvedilol was examined at 37°C, pH 7.5 with phosphate buffer (potassium phosphate monobasic and sodium phosphate dibasic), pH 4.5 with acetate buffer (sodium acetate and acetic acid), and pH 1.0 with maleate buffer. Glass vials were filled with 500 microliters of buffer, then excess carvedilol was added until the solution was no longer clear. Equilibrium was determined by comparing 48- and 72-hour samples. The pH of each solution was determined after the medication was added to the buffer solution. Vial caps were tightly sealed, and vials were placed in a shaking incubator (100 rpm, 37°C). Before the drug concentration was determined, the vials were spun at 10,000 rpm for 10 minutes, the supernatant was collected, and the drug was quantified using UPLC. For dose number (D0) calculations, the maximum dose of carvedilol immediate-release (IR) oral medicinal product was set to 25 mg. (10)
9. In vitro permeability investigations were conducted using Millipore (Danvers, MA) 96-well Multiscreen-Permeability filter plates with 0.3 cm2 polycarbonate filter support (0.45 µm) for the hexadecane-based parallel artificial membrane permeability assay (PAMPA). The filter supports in each well were impregnated with 15 µL of a 5% (v/v) solution of hexadecane in hexanes and allowed to dry for 1 hour. This time limit allowed the hexanes to completely evaporate, resulting in a consistent hexadecane layer. The permeability investigations employing the hexadecane layer were carried out following the usual methodology, with minor alterations [13]. In brief, carvedilol and metoprolol solutions (n = 4) were produced in phosphate buffer solution (pH 6.5, 7.0, and 7.5) with comparable ionic strength and osmolality (290 mOsm/L). PAMPA sandwich plates included donor wells with 200 µL drug solutions and receiver wells with 300 µL blank buffers. The plate was incubated at room temperature for four hours, with samples obtained every hour from the receiving plates. The apparent permeability coefficient (Papp) was estimated using a linear plot of drug collected on the acceptor side vs. time using the following equation: Papp equals dQ/dT A multiplied by C0. where dQ/dt is the steady-state appearance rate of carvedilol/metoprolol from the receiver side, C0 is the starting drug concentration on the donor side (0.02 mm for carvedilol and 0.1 mm for metoprolol), and A is the membrane surface area (0.048 cm2). The drug's steady-state appearance rate on the receiver side was determined using linear regression. (10) Ensure drug solubility and permeability in the aqueous phase for optimal absorption and bioavailability, resulting in controlled pharmacological effects.

2. OBJECTIVES

1. To evaluate the impact of different formulation techniques to assess the influence of excipients.
2. To explore the use of nanotechnology.
3. To investigate the role of lipid-based systems.
4. To examine the effect of pH-dependent solubility modifiers.
5. To study the potential use of permeability enhancers
6. To perform in vitro and in vivo evaluations

7. To compare the performance of the enhanced drug formulations

3. REVIEW OF THE LITERATURE

S. Padma Ishwarya. At all Stapley present their work on the spray freeze drying technology. SFD principles, methodologies, key process parameters, particle shape, and quality aspects. Recent advances in this approach are discussed, including ultrasonic spray-freeze-drying, the use of computational fluid dynamics and mathematical modeling, and the incorporation of new technologies to improve product quality. Furthermore, the benefits, limitations, and future directions for SFD research are highlighted. (32)

Elien De Laet. At all Samples with similar particle size distributions but distinct microstructures were found. Acid pectin extraction was performed on these samples, and the extraction yield was equivalent and much higher than that of the non-treated sample, demonstrating that particle size reduction boosted extraction efficiency. However, the fracture mechanism had little consequence. Overall, the various particle size reduction strategies had no discernible effect on the structural properties of the extracted pectin, with the main distinction between the biomasses being the degree of protein and starch co-extraction during the pectin extraction process. (33)

Anton N. Bokatyi. At all Chemical modification of HA has opened up a wide range of possibilities for tailoring its properties, allowing the development of sophisticated drug delivery systems and biomaterials with better functions and specific applications. This review examines the methodologies and applications of chemically modified HA in drug delivery and biomaterials development. The first section of the paper focuses on the many methods and functional groups utilized to chemically modify HA, emphasizing how these alterations affect its physicochemical properties, degradation behavior, and interactions with medications. The second section of the paper examines the use of chemically modified HA in the development of sophisticated biomedical materials such as nano- and microparticles, hydrogels, and mucoadhesive materials with tailored drug release profiles, site-specific targeting, and stimuli-responsive behavior. Thus, the review brings together current developments and future possibilities in the field of chemical modification of HA, emphasizing its enormous potential to drive the development of new drug delivery systems and biomaterials with a wide range of biological uses. (34) Teófilo Vasconcelos, Bruno Sarmento and Paulo Costa. They are often given as amorphous materials, acquired primarily through two distinct techniques, such as melting and solvent evaporation. Surfactants have recently been added to formulations to help prevent medication recrystallization and increase solubility. New production procedures for solid dispersions have also been developed to address the shortcomings of the original technology. This paper is meant to explore recent advances in the field of solid dispersions. (35)

Yingying Ma. At allThe main technological difficulties encountered in nanosuspensions development, such as guidelines for stabilizer screening, the in vivo fate of intravenously administered nanosuspensions, and how to realize intravenously target delivery, were discussed. Furthermore, the challenges of using nanosuspensions to distribute natural compounds were explored and remarked on. As a result, it planned to provide guidance and support in the manufacturing of nanosuspensions, the use of stabilizers, the predictability of in vivo fate, and the controllability of targeting distribution of natural goods nanosuspensions. (36)

Kanchan Kohli. At all Provide an exhaustive account of various literature reports on various types of self-emulsifying formulations, with a focus on formulation, characterization, and in vitro analysis, as well as examples of currently marketed preparations. (37)

Sara Meirinho. At all These are isotropic mixes of oils, surfactants, and co-surfactants that, when diluted in water, produce micro or nanoemulsions containing high quantities of lipophilic medicines. SEDDS should prevent drug precipitation at absorption sites, boost permeability through absorptive membranes, and improve

the stability of labile medicines against enzyme activity. Thus, by combining the benefits of SEDDS and the intranasal route for brain delivery, medicines' brain targeting and bioavailability could be improved. (38)

4. METHODOLOGY

4.1. Methods For The Enhancement Of The Solubility Of The Drug

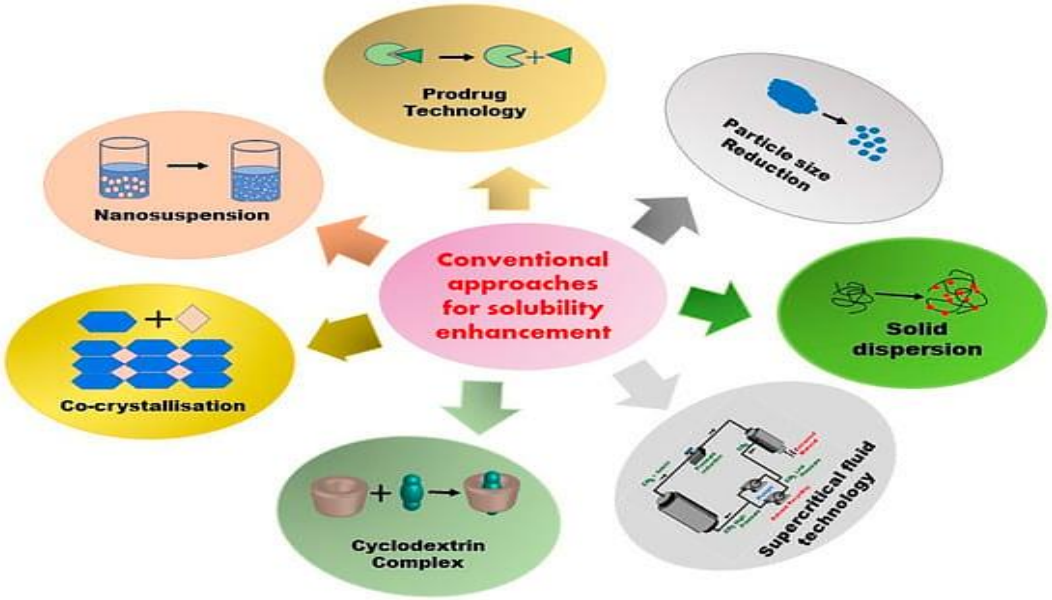


Fig1. Conventional methods for solubility enhancement. (27)

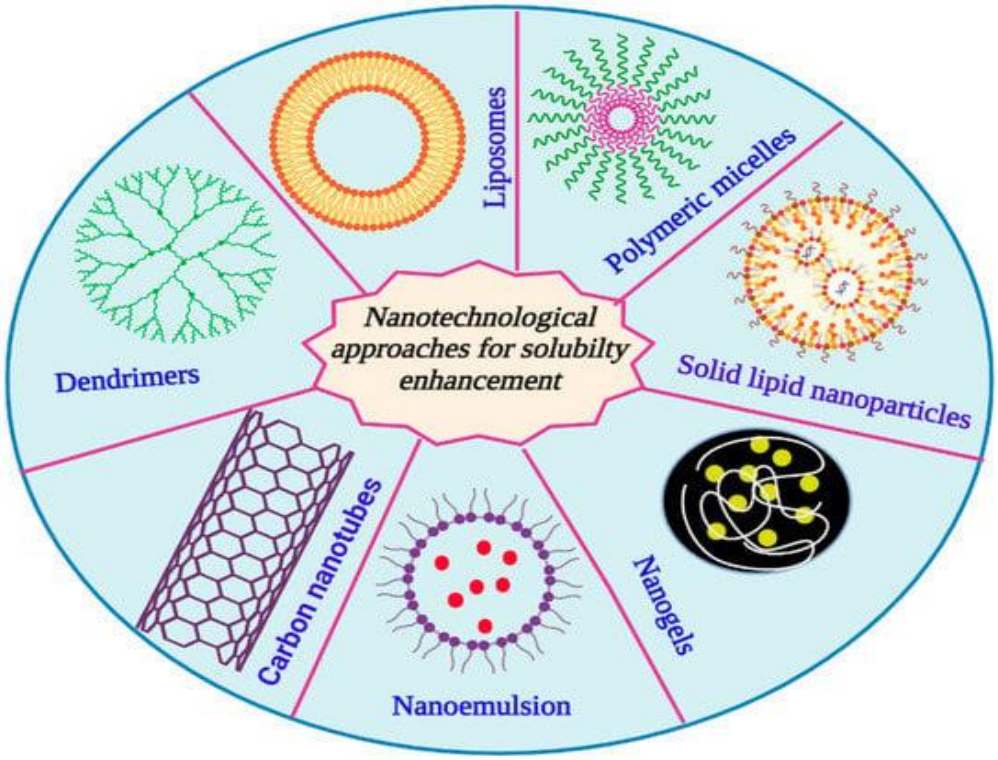
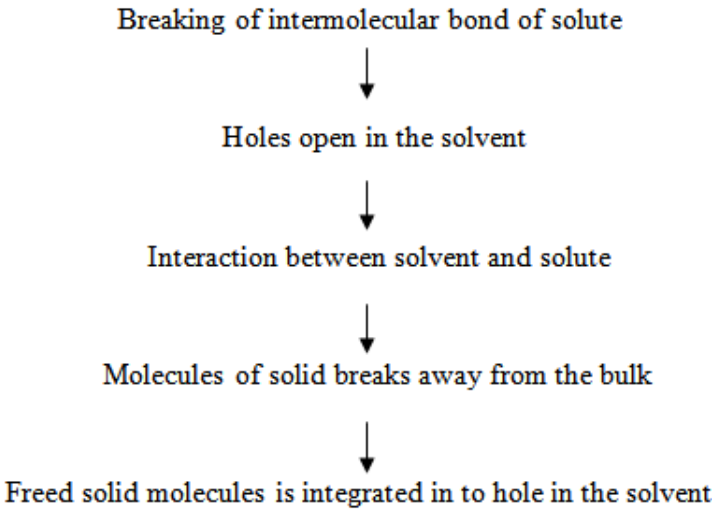


Fig2. Nano carrier-mediated solubility enhancement techniques (27)

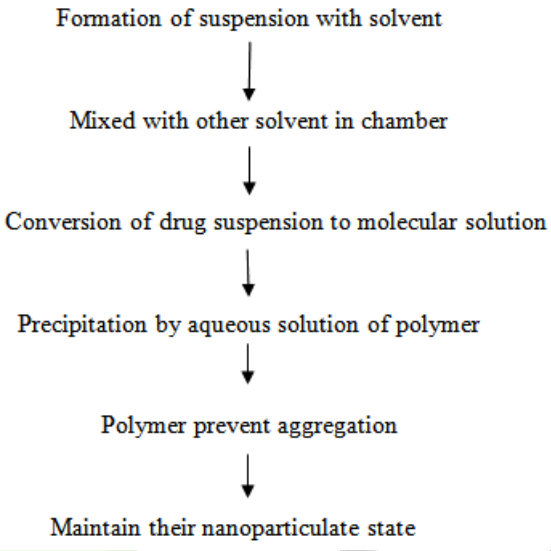
1. **Process of solubilisation**



(13)

2. **Nano morphs technique**

Technique for the solubility enhancement



3. **Particle size reduction**

As we all know, drug solubility is dependent on particle size. The grinding procedure reduces the drug's particle size. And, as the drug's surface area rises, so does its solubility due to the increased area of contact between the drug particle and the solute. Micronisation and nano suspension are now used to reduce particle size. Advantages: (3-4-5-6)

Advantages

Liquid forms can be quickly generated for early stage testing (pre-clinical) and then solidified for later clinical development. Typically, low excipient to medication ratios are necessary. Formulations are generally well tolerated as long as powerful surfactants are not used for stabilization. In general, crystals are more chemically and physically stable than amorphous particles. A approach to consider for recalcitrant chemicals that have resisted earlier attempts to boost solubility.

Disadvantages:

The high surface charge of discrete tiny particles causes a strong tendency for particle agglomeration. Creating a solid dosage form with a large payload while avoiding agglomeration may be technically difficult. Technically, developing sterile intravenous formulations is significantly more difficult. (3)

Instruments used for particle size reduction
1. Jet Mill.
2. Ball Mill.
3. High-pressure homogenizer.

1. Nanosuspensions

It's a colloidal dispersion of nano-sized medication particles. They developed an appropriate approach and used a special stabilizer. Nanosuspension technology keeps the medicine in a crystalline state with smaller particle sizes, which increases dissolving rate and thus bioavailability. Nano suspensions boost the drug's pharmacodynamic activity, hence improving its safety and efficacy. Nano suspension technology is also employed in medications that are soluble in both aqueous and aqueous solutions.

Advantages
Oral administration of Nano suspension provides faster onset, a lower fed/fasted ratio, and increased bioavailability. Increased the drug's dissolving velocity and saturation solubility. Enhanced biological metabolic performance.

Disadvantages
Uniform and effective doses cannot be achieved. Improper dosing or location. Special precautions must be taken when handling in a production plant and material transportation. (3-4-5-6)
It is done primarily through two processes.

1. Bottom-up.
2. Top-down approach 3. Water homogenization with high pressure
4. High pressure homogenization for non-aqueous medium.
5. Combined precipitation and high-pressure homogenization.

2. Sonocrystallization.

The crystallization procedure is carried out using the ultrasound technique to reduce particle size (11).

3. Micro emulsions

Micro emulsions are the isotropic and thermodynamically stable kind of emulsion for pharmaceuticals that are essentially insoluble in aqueous medium. The micro emulsion's droplets range in size from 20 to 200 nm. The media employed in this micro emulsion is low-viscosity, such as oil, water, and surfactants. Due to these reasons, micro emulsions have been utilized to enhance the solubility of essentially intractable medicines. (12)

4. Complexation

The aqueous solubility, dissolution rate, and bioavailability of drugs that are only slightly water-soluble have been enhanced more successfully than any other solubility augmentation strategy. These are formed when nonpolar molecules cannot dissolve in the presence of another molecule, most often cyclodextrin. Cyclodextrins are the most commonly employed host molecules. Inclusion complexes form when a nonpolar molecule or nonpolar component of a molecule is incorporated into the cavity of another molecule or set of molecules, known as the host. (14-15-16-17)

5. Soft Gel Technology:

A liquid formulation in a soft gelatin capsule can boost the solubility of an oil-soluble medication that is insoluble in water. (13)

6. Homogenization

The drug particle size is lowered in this procedure by using high pressure and high velocity, as well as shear force. In this process, medication particles are distributed. (18)

7. Hydro Trophy

In this method, the second solute is introduced in large quantities to increase the water solubility of the first solute. Hydrotrophy is the ionic salt of an organic molecule. Salts that improve solubility in a particular solvent are called to "salt in" the solute, while salts that reduce solubility "salt out" the solute. Several salts with large anions or cations that are particularly soluble in water cause the "salting in" of nonelectrolytes called "hydrotropic salts," a phenomena known as "hydrotropism." Hydrotropic solutions do not exhibit colloidal features and have a weak contact between the hydrotropic agent and the solute. (19)

8. Solid dispersion.

According to Chiou and Riegelman (1971), solid dispersion is a set of solid goods made up of at least two separate components, often a hydrophilic matrix and a hydrophobic medicament. The matrix could be either crystalline or amorphous. The medicine can be spread in molecular, amorphous, or crystalline particles. Solid dispersion is also defined as the solid dispersion of one or more active substances in an inert matrix created using the melting, solvent, or melting solvent methods.

9. pH correction

Drugs that are poorly soluble in water can become soluble if the pH is adjusted. Excipients that raise the pH of the environment within the dosage form above the pKa of weekly acidic medicines increase the drug's solubility; excipients that act as alkalizing agents may increase the solubility of weekly basic pharmaceuticals. It is also suitable for usage with crystalline and lipophilic poorly soluble compounds. (20)

10. Supercritical Fluid Recrystallization:

Supercritical fluids (e.g., carbon dioxide) have temperatures and pressures that exceed their critical temperature (Tc) and critical pressure, allowing them to behave as both liquids and gases. At near-critical temperatures, SCFs are highly compressible, allowing moderate pressure changes to significantly modify a fluid's density and mass transport properties, which essentially define its solvent power. Once the drugs are solubilized in SCF, they can be recrystallized at much smaller particle sizes. Carbon dioxide serves as the best example of this. SCF are highly compressible at critical temperatures, allowing for changes in density and mass transport properties, which dictate solvent power in response to mild pressure variations. As the medication becomes solubilized within SCF, it can be recrystallized with smaller particle size. Several pharmaceutical businesses, like Nektar Therapeutics and Lavipharm, specialize in particle engineering using sSCF technology for particle size reduction. (21)

11. Prodrug

The prodrug is an inactive, bioreversible by-product of active drug molecules that must be converted in vivo to release the active parent drug, resulting in the desired pharmacological impact in the body. Prodrug development can be difficult, but it represents a viable approach to improving the unpredictable features of medications in development or already on the market. (22)

4.2. Methods for Enhancement of the Permeability Of The Drugs

1. **Solid lipid nanoparticle**

These solid lipid nanoparticles have numerous advantages over traditional dosage forms, including improved physical and chemical stability, increased bioavailability, biocompatibility, sustained and prolonged drug release, enhanced uptake as particulates by Peyer's patches, and drug degradation protection. Solid lipid nanoparticles have the advantage of increasing lymphatic uptake while also reducing the activity of the enzyme cytochrome P450 on drugs. They also improve drug permeability through the intestinal wall by reducing P-glycoprotein efflux transport activity. Furthermore, the nano size of the solid lipid nanoparticles enhances the uptake of the substrate through the intestinal wall (23)

2. **Chemical Modifications**

Bare and naked oligonucleotides are the most susceptible to degradation and exhibit weak drug-like characteristics. Chemical modification is one of the most successful methods for improving the delivery of oligonucleotide medicines. Modifying the sugar motif or the phosphate backbone of an oligonucleotide can maintain it metabolically stable and functional, increase its protein-binding characteristics, and delay renal clearance. Each modification adds unique characteristics to the oligonucleotide, some of which may be a combination, difficult production, or impede its mode of action (Chen et al., 2005). The target determines the type of chemical alteration that will be put into the oligonucleotide. (25)

3. **Self-emulsifying drug delivery systems (SEDDS).**

Self-emulsifying drug delivery systems (SEDDS) have emerged as possible drug delivery systems for improving the solubility of poorly soluble medicines by enhancing drug particle surface area and membrane permeability. During the previous two decades, SEDDS-based registered pharmaceuticals have obtained a large market share in the United States, United Kingdom, and Japan.SEDDS have been defined as isotropic mixtures of natural or synthetic oil, surface active agents, or, alternatively, a single or many hydrophilic solvents and co-solvents with a medicine that produce oil-in-water nanoemulsions in aqueous media after gentle stirring. (26)

4. **Bile Salts**

Bile, which contains glycine and taurine conjugates of cholic acid and chenideoxycholic acid, emulsifies dietary fat and speeds up lipolysis and transfer of lipid products through the intestinal mucosa's unstirred water layer via micellar solubilization. The bacterial flora converts bile salts that escape active reabsorption in the ileum into secondary bile salts deoxycholic acid and lithocholic acid. The decreasing order of hydrophilicity is as follows. Taurine conjugates are followed by glycine conjugates, which then lead to free bile salts. Polarity rises with the number of hydroxyl groups. Bile salts are capable of binding calcium, however their binding capabilities decrease as hydrophilicity increases. There is no unambiguous data on how bile salts improve absorption. It may be carried out by impacts on the mucosal layer, as well as paracellular and transcellular absorption routes. They have been shown to impact the intestinal glycocalyx structure and reduce gastric and intestinal mucus. Unconjugated and conjugated bile salts' phospholipid disordering action suggests a transcellular absorption-enhancing impact. In rabbits and rats, bile salt concentrations of 5mM or less appear to alter colonic tight junction structure. This paracellular absorption-promoting impact is thought to be mediated by Ca2+ binding. Although bile salts have been shown to significantly improve drug uptake, their use as a safe absorption promoter in humans is fraught with problems, as mucosal injury appears to be associated with their uptake.On the other hand, two years of oral chenodeoxycholic acid (350-750 mg/day) therapy for gallstone dissolution was associated with modest adverse effects (an increase in serum amino transferase and cholesterol levels, diarrhoea). This observation suggests that long-term therapy with bile salt-containing formulations may be beneficial in humans. However, the potential co-carcinogenic and co-mutagenic effects of secondary bile salts inhibit the development of bile salt-containing medicinal formulations. (3)

5. **Spray-freeze drying.**

Another method for increasing permeability is spray freeze drying. For example, when oleonolic acid (OA), a BCS class 4 compound, is spray freeze dried with sodium caprate (CS) as a wetting agent and penetration enhancer and polyvinyl pyrolidone-40 (PVP-40) as a stabilizer, the result is an amorphous solid dispersion system that is kinetically stable, has better in vitro dissolution performance, and has better and more uniform absorption when compared to commercial OA tablets. The oral bioavailability of the SFD processed OA formulation and commercial OA tablet varies significantly amongst animals, which is consistent with the absorption properties of BCS class IV drugs. The addition of SC, combined with the replacement of OA with its sodium salt (OA-Na) in the formulation, significantly reduces the observed absorption inconsistency. The absorption inconsistencies of OA can be considerably reduced by using SC and using sodium salt, OA-Na, in the formulation. The above results indicate that improvement in both dissolution and intestinal permeability of BCS class IV drugs, as demonstrated by the SFD processed OA Na/PVP/SC system, is insufficient to reduce the significant interindividual inconsistency in oral absorption commonly observed with this class of compounds. (24-25)

6. LIPID TECHNOLOGIES:

As hydrophobic medications become more prevalent, lipid-based formulations have been developed to enhance bioavailability through a variety of processes. a) physicochemical: increased dissolution and solubility b) physiological: possible processes include. Increased effective luminal solubility by stimulating the release of bile salts, endogenous biliary lipids, including phospholipids and cholesterol, which form mixed micelles and enable. Drug solubility in the gastrointestinal tract. Reduced gastric emptying rate, allowing more time for breakdown and absorption.

Increased intestinal membrane permeability.

Increased intestinal blood flow.
Reduced luminal degradation.
Increased intestinal lumen uptake into the lymphatic system (and a decrease in first-pass hepatic and Gl metabolism)
the various lipid dose types are:

A. Lipid Solutions and Suspensions
B) Coarse, multiple, and micro emulsions (SMEDS) C) Solid lipid nanoparticles:

To solve the problems of oil droplet lipidation, the liquid lipid is replaced with a solid lipid, resulting in the creation of solid lipid nanoparticles. In contrast to emulsions, the particles are made up of a solid core of lipids. They are distinguished by a typical diameter of roughly 100–1000 nm. There are two fundamental methods for producing solid lipid nanoparticles: homogenization of melted lipids at extreme temperatures and homogenization of a solid lipid suspension at or below room temperature.
D) Nanostructured Lipid Carriers (NLC): Nanostructured lipid carriers are oil-loaded solid-lipid nanoparticles with the added benefit of increased drug loading.

E) Lipid Drug Conjugate (LDC) Nanoparticles: Covalent bonding or salt creation between a hydrophilic medication and a lipid to increase membrane permeability.

F) Liposomes are defined as lipid bilayers that enclose an aqueous phase. Lipo-soluble medications can be entrenched in the fatty areas, whereas hydrophilic compounds are kept in the watery internal spaces of these globular vesicles.

7. Ion Pairing:

The ion pairing strategy entails administering a hydrophilic or polar medication in conjunction with an appropriate lipophilic counter ion, which facilitates the partitioning of the resulting ion-pair (which is substantially more lipophilic) into the intestinal membrane. In fact, the technique appears to boost the oral

bioavailability of ionisable medicines such as atenolol by about twofold. However, it is crucial that a counter ion has high lipophilicity, enough aqueous solubility, and physiological compatibility & metabolic stability.

8. **Penetration Enhancers:**

Penetration/permeation enhancers or promoters are compounds that facilitate drug transport across the biomembrane. This approach is mostly employed for hydrophilic medications that are believed to have trouble entering the lipid structure of the bio membrane. Penetration enhancers work by interacting with the lipid polar components of membrane phospholipids. The penetration enhancers can be classified into three categories: Substances that work fast, have a powerful effect, and cause harm to the membrane (reversible) Examples include fatty acids such as oleic, linolic, and arachidonic acid, as well as their monoglycerides. Substances that act fast, inflict transient damage, and have average activity, For example, salicylates and some bile salts. Substances with moderate to strong activity that produce long-term histological alterations, For example, SLS, EDTA, and citric acid

4.3. Description

Particle size reduction

Jet mill

Jet mills are the most extensively used and acknowledged industrial method for reducing particle size. Jet mills work on the basis of impact and attrition, producing high viscosity collisions between particles suspended in nitrogen gas or compressed air. The resultant impacts lead the particles to disintegrate into smaller bits. The centrifugal forces in the jet mill separate large, heavy particles from smaller, lighter particles. The fluid stream carries the smaller particles to the milling chamber's centre, where they are emptied into a collection unit. Larger particles remain in the milling chamber and recirculate, causing them to break down, resulting in a homogeneous particle size distribution. Jet mills are widely used to reduce particle size because they eliminate the requirement for grinding media, which can have a negative impact on the formulation. (http://www.catalent.com/index.php/offerings/A-Z Offerings/Catalent Micron Technologies/Particle-Size Reduction-Services).
Advantages include: (1) the ability to produce very fine particles, (2) the need for relatively little equipment space, (3) grinding of hard products with decreased equipment wear, (4) a low working temperature, (5) a contamination-free operation, and (6) the absence of moving parts and a foundation. Disadvantages include: (1) limited process capacity, (2) high energy consumption, and (3) high maintenance expenses.

Within the grinding chamber of the mill, jet milling transforms the potential energy of compressed gas into high-velocity kinetic energy. This causes particles to collide and fracture, resulting in comminution. (26)

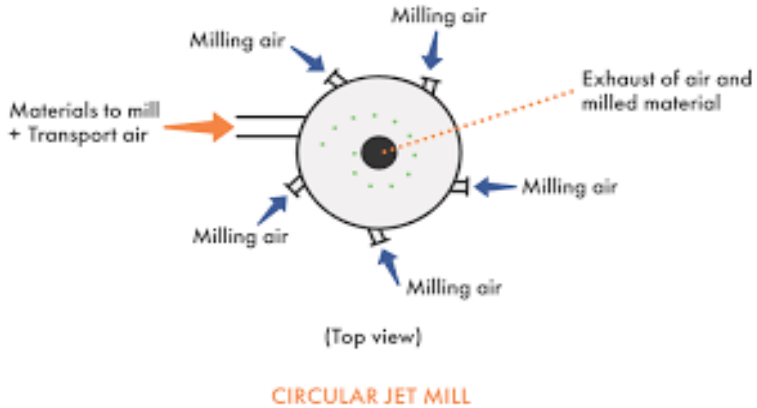


Fig 3. Circular Jet Mill

Solid dispersion.
Characterization of Solid Dispersions
A variety of techniques have been employed to characterize solid dispersions, including.

1. Differential Scanning Calorimetry (DSC) is a popular thermoanalytical technique that produces data on melting endotherms and glass transitions.Samples can be thermally analyzed using differential scanning calorimetry (DSC). 72. American Journal of Pharmacological Sciences
2. Powder X-ray Diffraction: Powder X-ray diffraction is a qualitative method for detecting material with long range order. Sharper diffraction peaks imply crystalline material. Newly designed X-ray technology is semiquantitative.

3. Microscopical Studies: The dynamics of nucleation and crystal growth were investigated using a polarized light microscope. Polarized light microscopy is more sensitive than DSC or XRD at detecting the transition from amorphous to crystalline pharmaceuticals in solid solutions. Typically, materials can be inspected via a polarized light microscope, and photos can be captured with a digital camera and processed using the Motic photos Plus 2.0 software.
4. Spectroscopic Methods, Specifically I.R.: FTIR spectra can be used to detect polymer-drug interactions by observing the shift in vibrational or stretching bands of important functional groups. This approach has been used to determine polymer-drug interactions in solid molecular dispersions.

5. Calculating the Dissolution Rate: Calorimetry quantifies the energy of dissolution, which is proportional to the crystallinity of the sample. Crystalline dissolution is often endothermic, whereas amorphous dissolution is exothermic.

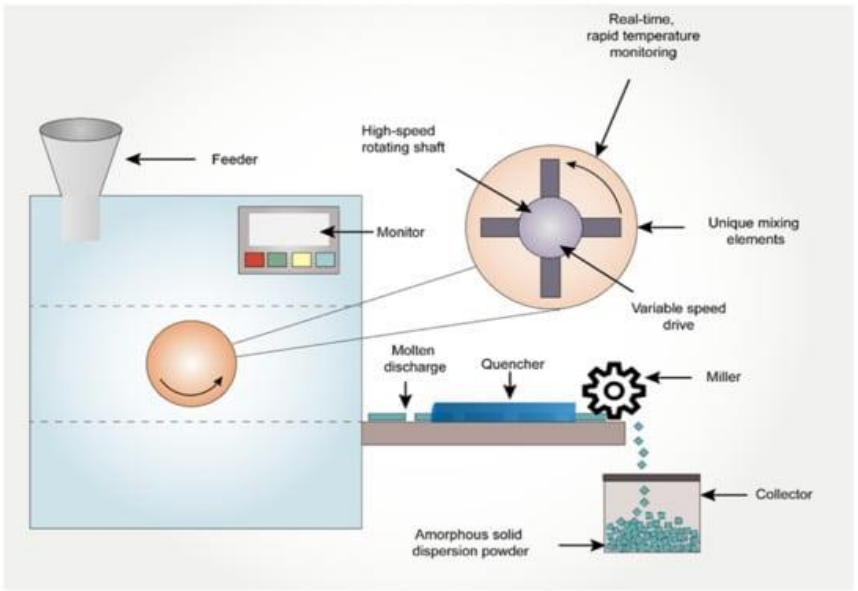


Figure 4. The schematic representation of Kinetisol® process in preparation of amorphous solid dispersions. (27)

Spray freeze drying

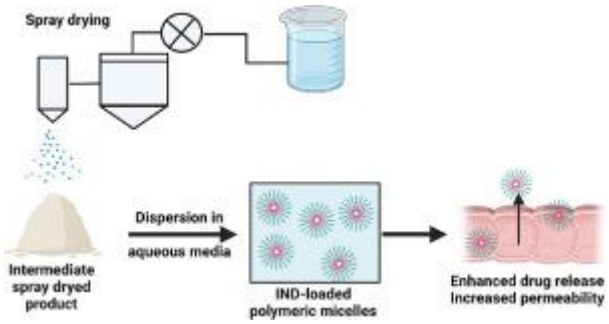


Fig5: spray drying method

Spray freeze drying is a novel and growing technique for turning liquid suspensions and solutions into solid powders. As a result, it combines two more popular and conventional methods, spray drying and freeze drying, into one for a more efficient procedure and higher-quality output. Here, the procedure can be utilized to dry pharmaceutical items. Furthermore, the porous particles formed have excellent aerodynamics and low water solubility encapsulation, making them ideal for direct drug delivery to the lungs. The spray freeze drying technique involves three steps: atomizing a liquid or solution into droplets, hardening them through contact with a cold fluid, and subliming those particles at a low temperature and pressure. There are numerous methods for achieving the desired effect at each of the three stages of spray freeze drying. Atomisation is the process of breaking up bulk liquids into minute droplets, which can be performed by spraying the liquid with a nozzle. These nozzles can be either one fluid, two fluids, or ultrasonic. The freezing stage is the second step in spray freeze drying. Rapid freezing is typically performed using a cryogen such as liquid or gas nitrogen, which helps to prevent phase separation of the biomolecular structure. In the final stage of the procedure, freeze drying techniques are used to sublime the particles. Here, the frozen powder is removed from the spray-freezing mechanism and dried. Droplets are often dried into particles using a vacuum. Spray freeze drying has the ability to improve operating efficiency as well as final product quality. This enhancement is the result of increased heat and mass transfer during the drying phase, which is attributed to the larger surface area of frozen particles. However, scaling up this method for commercial production is predicted to be a challenging task, owing to numerous restrictions at each stage. Addressing this difficulty may require the development of innovative technologies specialized for continuous manufacturing, which appears to be a viable option for adjusting to the changing industry landscape while taking into account the practical aspects of scaling up. (29)

Chemical Modification:

1. Adjusting pH

This is crucial to medication solubility. It can affect a drug's water solubility. The charge state of medication molecules can be changed by adjusting the pH of the solution. If the pH of the solution is such that a certain molecule has no net electric charge, the solute has low solubility and precipitates out of the solution. The pH at which the net charge is neutral is known as the isoelectric point (or IEP).

2. Hydrotrophy.

This is a solubility sensation; when used, the solute's water solubility can be increased by adding an excess amount of a second solute. Earlier publications used the word hydrotrophy to characterize non-micelle-forming compounds, whether solids or liquids, organic or inorganic, that are capable of increasing the solubility of insoluble molecules.

3. Cocrystallization

Non-ionic supramolecular materials form complexes known as co-crystals. They can be used to solve difficulties with physical qualities like as medication solubility, bioavailability, and stability without changing the chemical structure of APIs. Co-crystals are formed when two or more molecular units contact weakly, such as by π-π stacking or hydrogen bonding. Co-crystallization alters the composition and molecular interactions of medicinal substances, and it is widely acknowledged as a viable approach for optimizing therapeutic properties. Co-crystals will provide a variety of methods for crystallizing any API, regardless of whether it is acidic, basic, or ionizable. Due to their nonionizable functional groups, molecules with modest pharmacological profiles may benefit from this.

4. Co-solvency.

When the structural complexity of newly discovered entities increases, the drug's solubility in H2O drops dramatically. When a compound's water solubility is significantly lower than its therapeutic dose, a solvent blend is used to increase solubility. Co-solvents are utilized to improve the drug's solubility by giving numerous nonpolar groups, which increases its aqueous (water) solubility. Co-solvents are essential for pharmaceutical formulations and, in some cases, to improve drug solubility.

5. Salt formation

Acidic and basic medicines have lower solubility in water than their salts. The most popular technique for developing parenteral administration is to increase solubility through salt production.

6. Nanotechnology in Pharma

Nanotechnology can improve the solubility of medications with low water solubility. Nanotechnology entails considerable research and use of structures and materials at the nanoscale, which is up to 100 nm. Micronization is insufficient for several NCEs to improve solubility and oral bioavailability since the micronized material tends to agglomerate, resulting in a reduction in the effective surface area for dissolution. (30)

5. Result and Discussion

In the preceding article, we investigated the primary factors that influence medication bioavailability in the systemic circulation. The solubility and permeability of medicines. This page discusses some of their enhancing approaches. One of them is solid dispersion, which involves combining the drug with a highly soluble carrier to boost the drug's solubility and permeability. The second is the particle size reduction technique in which there is the chopping of the particle to the smaller size with the assistance of the mills in the jet mill, the particles are traveling in the circular motion by which they hit the wall of the jet mill and reduction of the. Third technique is the spray freeze drying in which there is atomizing a fluid or liquid into droplets, solidifying them by interaction by cooling water, and sublimation them at low temperature and pressure interaction with the liquid phase. And the last one is the chemical modification of the drug in which the drug has changed in the pH, Nanotechnology in Pharmaceuticals**,** Salt Formation, Co-Solvency**,** Co-Crystallization**,** hydrotropy of the particle nature to enhance their many properties. We have found that there are some the limitations this techniques to avoid them we need to calibrate the instruments very thoroughly to increase the drugs bioavailability. So, to increase the drugs stability there are many precautions are taken.

6. Conclusion

The physicochemical factors like solubility and permeability always affect the drugs stability in the body. So we studied about the four technique which enhance there solubility and permeability. Solid dispersion, particle size reduction, chemical modification and spray freeze drying are the most widely used techniques. Now a days for the increase in the solubility and permeability of the drug. . This technique allows the drugs which are taken orally to access the higher permeability and aqueous solubility of the drug. Due to this fours major technique the drugs is able to have the major improvement in the drugs dissolution and water soluble capacity. The more research is required on this techniques to minimise the limitations in this techniques.

7. REFERENCES

1. Martin physical pharmacy 6th edition 2011
2. Volpe, D. A. (2010). Application of Method Suitability for Drug Permeability Classification. The AAPS Journal, 12(4), 670–678. doi:10.1208/s12248-010-9227-8
3. Nicolazzo, J. A., Charman, S. A., & Charman, W. N. (2006). *Methods to assess drug permeability across the blood-brain barrier. Journal of Pharmacy and Pharmacology, 58(3), 281–293.* doi:10.1211/jpp.58.3.0001
4. Ting, J. M., Porter, W. W., Mecca, J. M., Bates, F. S., & Reineke, T. M. (2018). *Advances in Polymer Design for Enhancing Oral Drug Solubility and Delivery. Bioconjugate Chemistry, 29(4), 939–952.* doi:10.1021/acs.bioconjchem.7b00646 10.1021/acs.bioconjchem.7b00646
5. https://www.britannica.com/biography/Joel-H-Hildebrand - :~:text=Hildebrand,-American%20chemist&text=Chatbot%20a%20Question-,Joel%20H.,1881%2C%20Camden%2C%20N.J.%2C%20U.S.&text=Hildebrand%20spent%20the%20greater%20part,and%20the%20College%20of%20Chemistry.&text=Hildebrand%20was%20the%20author%20of,and%20updated%20by%20Encyclopaedia%20Britannica.
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8039394/ -:~:text=Mechanistically%2C%20sonophoresis%20creates%20various%20amendments,effective%20level%20of%20ultrasound%20application.
7. https://uen.pressbooks.pub/introductorychemistry/chapter/precipitation-reactions/ -:~:text=Solubility%20is%20the%20ability%20of,well%20as%20temperature%20and%20pressure.
8. https://www.creative-biolabs.com/drug-discovery/therapeutics/permeability-and-absorption.htm -:~:text=A%20drug's%20permeability%20across%20biological,several%20semipermeable%20cell%20membranes%20firstly.
9. Henderson, L.S.; Tenero, D.M.; Baidoo, C.A.; Campanile, A.M.; Harter, A.H.; Boyle, D.; Danoff, T.M. Pharmacokinetic and pharmacodynamic comparison of controlled-release carvedilol and immediate-release carvedilol at steady state in patients with hypertension. Am. J. Cardiol. 2006, 98, 17l–26l
10. Patel J, Patel N, Modasiya M. 2012. Techniques to improve the solubility of poorly soluble drugs. International Journal of Pharmacy and Life Sciences, 3:1459-1469
11. Solubility enhancement techniques https://globalresearchonline.net/journalcontents/volume5issue1/article-007.pdf
12. American Journal of Pharmacological Sciences, 2013, Vol. 1, No. 4, 67-73 Available online at http://pubs.sciepub.com/ajps/1/4/5 © Science and Education Publishing DOI:10.12691/ajps-1-4-5 A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs
13. SOLUBILITY ENHANCEMENT TECHNIQUES: UPDATES AND PROSPECTIVES. (2022). *Journal of Pharmaceutical Negative Results*, 2847-2855. https://doi.org/10.47750/pnr.2022.13.S08.353 (Original work published 2022)
14. Pawar SR, Barhate SD. Solubility enhancement (Solid Dispersions) novel boon to increase bioavailability. Journal of Drug Delivery and Therapeutics. 2019 Mar 22; 9 (2):583-90. http://jddtonline.info/index.php/jddt/article/view/2437
15. Alshora DH, Ibrahim MA, Alanazi FK. Nanotechnology from particle size reduction to enhancing aqueous solubility. In Surface chemistry nanobiomaterials 2016 Jan 1 https://www.sciencedirect.com/science/article/pii/S2589965121000933 (pp. 163-191). William Andrew Publishing.
16. Patel P. Formulation, development and evaluation of rivaroxaban tablets by using solubility enhancement technique. Int J Pharm SciSci Res. 2017; 3:51-5.
17. Juppo A.M., C. Boissier, C. Khoo. Evaluation of solid dispersion particles prepared by SEDS, Int. J. Pharm., 2003; 250/385-401.
18. Badwana A.A., Khordaguib L.K., Saleh A.M., Khalil, S.A. The solubility of benzodiazepines in sodium salicylate solution and a proposed mechanism for hydrotropic solubilization. International journal of Pharmaceutics, 1982; 13(1), 67-74

19. . Young OA, Zhang SX, Farouk MM, Podmore C. Effects of pH adjustment with phosphates on attributes and functionalities of normal and high pH beef. MeatScience, 2005; 70: 133-139.
20. B.A. Bhairav, J.K. Bachhav, R.B. Saudagar. Review on Solubility Enhancement Techniques. Asian J. Pharm. Res. 2016; 6(3): 147-152. doi: 10.5958/2231-5691.2016.00025.3
21. https://ascendiapharma.com/newsroom/2021/07/26/solubility-enhancement-techniques
22. Vishwakarma, N., Jain, A., Sharma, R., Mody, N., Vyas, S., & Vyas, S. P. (2019). *Lipid-Based Nanocarriers for Lymphatic Transportation. AAPS PharmSciTech, 20(2).* doi:10.1208/s12249-019-1293-3
23. Chen X., Dudgeon N., Shen L., Wang J. H. (2005). Chemical modification of gene silencing oligonucleotides for drug discovery and development. *Drug Discov. Today* 10, 587–593. 10.1016/S1359-6446(05)03426-4 [PubMed] [CrossRef] [Google Scholar]
24. Jianxian, C., Saleem, K., Ijaz, M., Ur-Rehman, M., Murtaza, G., & Asim, M. H. (2020).*Development and invitro Evaluation of Gastro-protective Aceclofenac-loaded Self-emulsifying Drug Delivery SystemInternational Journal of Nanomedicine, Volume 15, 5217–5226.* doi:10.2147/ijn.s250242 10.2147/ijn.s250242
25. MDPI and ACS Style
26. Kumari, L.; Choudhari, Y.; Patel, P.; Gupta, G.D.; Singh, D.; Rosenholm, J.M.; Bansal, K.K.; Kurmi, B.D. Advancement in Solubilization Approaches: A Step towards Bioavailability Enhancement of Poorly Soluble Drugs. *Life* 2023, *13*, 1099. https://doi.org/10.3390/life13051099
27. https://www.customprocessingservices.com/jet-milling
28. Recent Advances in Amorphous Solid Dispersions: Preformulation, Formulation Strategies, Technological Advancements and Characterization by Srushti Tambe,Divya Jain,Sai Kishore Meruva,Gopinath Rongala,Abhishek Juluri,Girish Nihalani,,Hemanth Kumar Mamidi,,Pavan Kumar Nukala andPradeep Kumar Boll
29. Spray-dried indomethacin-loaded polymeric micelles for the improvement of intestinal drug release and permeability
30. https://oxfordglobal.com/formulation/resources/what-is-spray-freeze-drying
31. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics (pubmed)
32. Maji, I., Mahajan, S., Sriram, A., Medtiya, P., Vasave, R., Khatri, D. K.Singh, P. K. (2021). *Solid selfemulsifying drug delivery system: Superior mode for oral delivery of hydrophobic cargos. Journal of Controlled Release, 337, 646–660.* doi:10.1016/j.jconrel.2021.08.013
33. Ishwarya, S. P., Anandharamakrishnan, C., & Stapley, A. G. F. (2015). *Spray-freeze-drying: A novel process for the drying of foods and bioproducts. Trends in Food Science & Technology, 41(2), 161–181.* doi:10.1016/j.tifs.2014.10.008
34. *The effect of different particle size reduction techniques on the biomass microstructure and the influence on the pectin extraction yield and structureElien* De Laet [a], Tom Bernaerts [a], Koen Dewettinck [b], Marc E. Hendrickx [a], Ann M. Van Loey
35. Anton N. Bokatyi, Natallia V. Dubashynskaya, Yury A. Skorik Chemical modification of hyaluronic acid as a strategy for the development of advanced drug delivery system
36. Teófilo Vasconcelos [1 2], Bruno Sarmento [1], Paulo Costa Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs
37. Yingying Ma [a b], Zhufeng Cong [a], Peng Gao [a], Yancai Wang. Nanosuspensions technology as a master key for nature products drug delivery and *In vivo* fate
38. Kanchan Kohli [1], Sunny Chopra [1], Deepika Dhar [2], Saurabh Arora [1], Roop K. Khar Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability
39. Sara Meirinho,[1,2] Márcio Rodrigues,[1,2,3] Adriana O. Santos,[1,2] Amílcar Falcão,[4,5] and Gilberto Alves[1] Self-Emulsifying Drug Delivery Systems: An Alternative Approach to Improve Brain Bioavailability of Poorly Water-Soluble Drugs through Intranasal Administration