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TECHNIQUES FOR SOLUBILITY ENHANCEMENT OF HYDROPHOBIC DRUGS: A REVIEW

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ABSTRACT
Dissolution of solute in solvent to give a homogeneous system to achieve desired concentration of drug in systematic circulation called solubility. Low aqueous solubility is excessively big problem for development of new synthetic drug formulation as well as generic development. Approximately 40% of all novel chemical substances are lipophilic in nature and neglect to have a broad therapeutic range due to poor aqueous solubility, resulting in limited bioavailability and poor water solubility. The main point of survey article is introduction of various techniques for solubility enhancement of low aqueous soluble drug and selection of solubility improving methods depends on drug property, site of absorption and required dosage form characteristics.

KEYWORD: Enhancement of Solubility, Solid Dispersion, Bioavailability, BCS Classification System.

INTRODUCTION

Quantitative term of solubility - solubility is defined as the concentration of solute in a saturated solution at definite temperature. And Qualitative term of solubility – solubility is defined as spontaneous Interaction of two or more substances to form an analogous dispersion. Drug solubility is the extreme concentration of solute is break down in solvent under condition of temperature, pressure, and ph. The solubility of drug may be intimate as percentages, parts, molality, molarity, mole fraction and volume fraction. The drug solubility is related in many descriptive terms which is based on the number of drug Particle's dissolve in solvent. (Surawase et al., 2020).

Table 1: Expression of solubility.

Definition of solubility	***Nominally volume of solvent in millilitres per gram solute as per British pharmacopeia***
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Insoluble	More than 10000

Importance of solubility Importance of solubility

Over 40% of NCEs (new chemical entities) developed in the pharmaceutical sector are water insoluble. The absence of and varied bioavailability of these ineffectively water-soluble drugs, as well as their gastrointestinal mucosal toxicity, is a result of their sluggish pharmaceutical retention. Solvency is the key rate limiting boundary for orally directed medications to achieve their optimal fixation in fundamental dissemination for pharmacological reaction issue of solubility in tough for definition researcher. (Kumar et al.)

Biopharmaceutical classification system

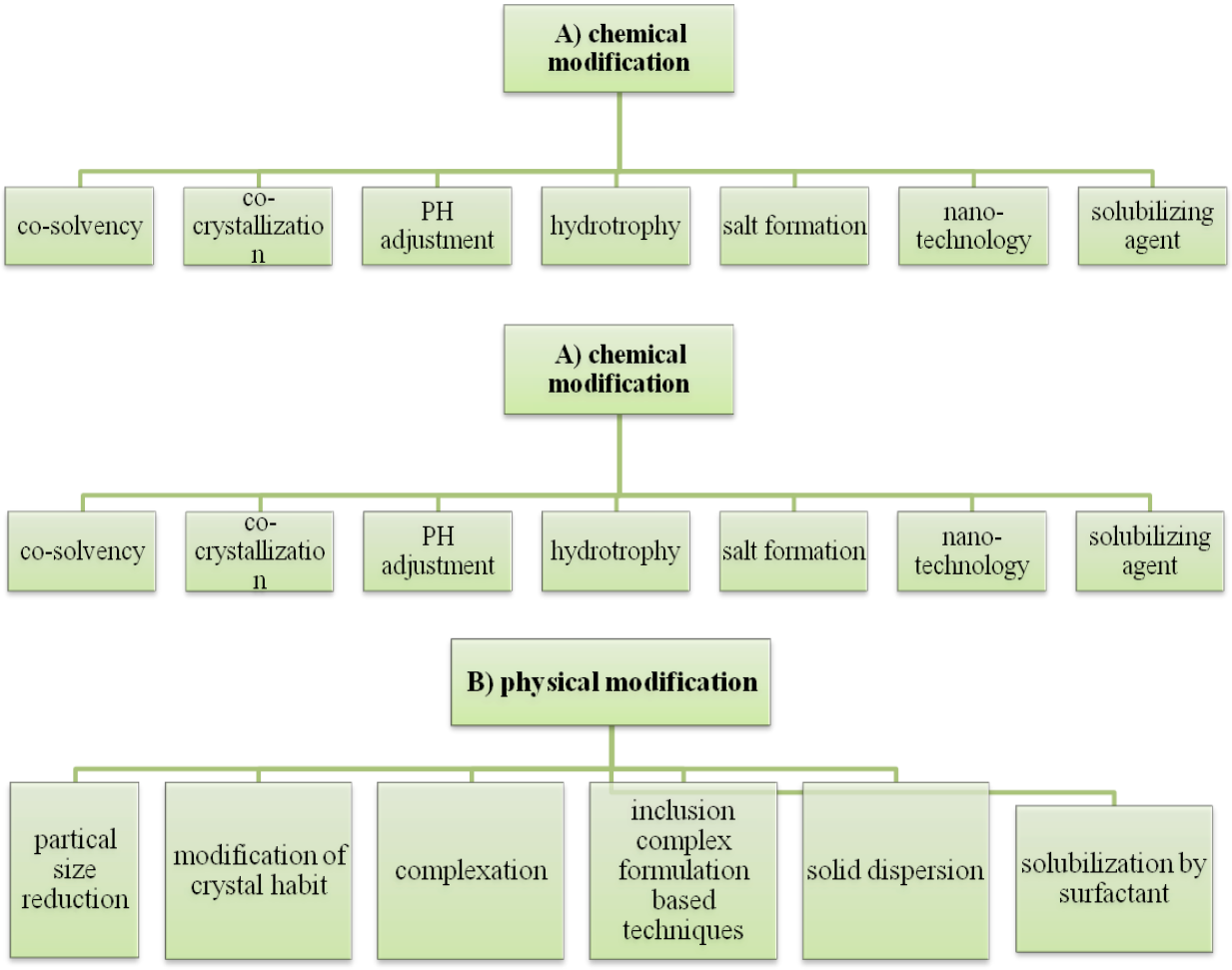
In 1995, Amidon and colleagues proposed the biopharmaceutical classification system (BCS) as a way to reduce the necessity for in vivo bioequivalence investigations by using in vitro disintegration tests instead. The BCS classification framework's standards can be used to approve NDAs and ANDAs, as well as scale up and post-approval adjustments in drug manufacturing. The BCS is a logical structure for organising pharmacological substances based on their aqueous solubility and permeability in the intestine. According to the BCS, medicines can be classified into

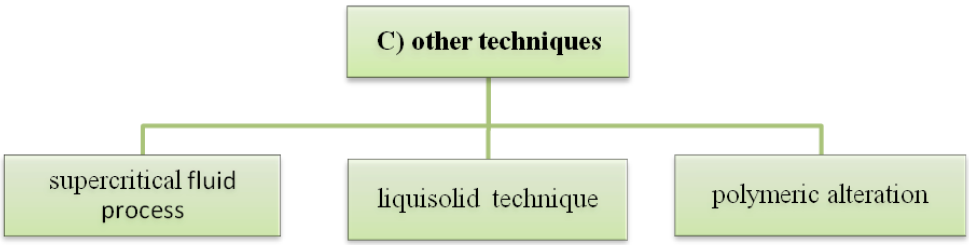
four basic classes based on their dissolvability and permeability in the GIT mucosa. (2010, Mhad et al.)

Table 2: biopharmaceutical classification.

BCS class I **High solubility and high permeability** **Examples -** Metoprolol, B-blocker Propranolol, Fluconazole, Doxycycline, Levonorgestrel.	**BCS class II** **Low solubility and high permeability** **Examples - NSAIDs**, Ketoprofen, Antiepileptic, tamoxifen citrate Carbamazepine, Ibuprofen, Eplerenone.
BCS class III **High solubility and low permeability–** **H**2 antagonist, Ranitidine, b-blocker, Atenolol, Abacavir, Cimetidine, Acyclovir, Allopurinol.	**BCS class IV** **Low solubility and low permeability** **Examples –**Diuretics, Hydrochlorothiazide, Ritonavir, Indinavir, Acetazolamide, Famotidine, Furosemide.

SOLUBILITY-ENHANCEMENT TECHNIQUES – There are three types of solubility improvement tactics: actual change, chemical substance attention, and additional strategies. Chemical alterations include salt production, PH adjustment, and buffer usage. The following strategies have been used to improve the solubility and dissolution rate of medications that are insufficiently water-soluble. (2018, Sneha Jagtap et al.)





A) CHEMICAL MODIFICATION

Cosolvency

Cosolvency is the process of increasing the solubility of a medicine that is poorly soluble in water by mixing it with a water miscible dissolvable in which the drug is readily soluble. Cosolvency is the name given to this interaction, while cosolvent is the name given to the solvent utilised in the combination. Solvent mixing is a technique for achieving cosolvency. It reduces the interfacial tension between the aqueous solution and the hydrophobic solute. With a tiny hydrocarbon area, the cosolvents have hydrogen acceptor or donor groups. The main benefit of using a cosolvent is that it has a high solubilization capacity for drugs that are poorly water soluble. Because it is straightforward to make and analyse, this technique has been widely employed in the past. Cosolvents can be used in conjunction with other solubilization procedures and pH adjustments to boost the solubility of poorly soluble materials even further. (Vemula et al., 2010).

Co-crystallization – co-crystallinity changes the Molecular Interaction and is considered promising alternative to improve drug properties. "Multicomponent crystal that is created between two substances that are solids under encompassing conditions, where no less than one component is an appropriate particle or atom" is a more refined definition of co-crystal. The physical, chemical, and physiological limitations of an API are controlled through co-crystallization. The main distinction among solvates and co-crystals is actual condition of the parts. If one of the components is solid and other is liquid, then it is termed as solvents but on the other hand if both exists in solid form then it is termed then they are termed as co-crystal. Mechanism of co- solvency leans toward the dissolution of a non – polar solute by bringing down the interfacial tension. The most appropriate co-crystal can be chosen utilizing logical methods and reasonable physicochemical examinations that incorporate examination of solubility and stability (2010, Patole et al)

Different techniques for Co-crystallization

1)Sonocrystalization method 2) hot melt extrusion 3) high throughput Co-crystallization 4)solvent evaporation 5) grinding 6) solvent drop grinding

Co-crystal characterization parameters

1) Stability 2) maximum wavelength 3) Melting point 4) solubility 5) scanning calorimetry (DSC) 6) melt 7) intrinsic dissolution 8) XRD 9) Bioavailability 10) vibrational spectroscopy

Hydrotropy

Hydrotropy is a solubilization property in which the addition of a large amount of a second solute causes the existing solute's Watery solvency to increase. The aqueous solubility of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate has been reported to be enhanced by concentrated watery hydrotropic solutions. Ionic natural salts are hydrotropic experts. Hydrotropic arrangements do not show colloidal properties and include a week Interaction between the hydrotropic specialist and Solute. Mixed hydrotropy is one of the new methods of Hydrotropy. It is safe, accurate, cost effective, precise, and simple method. Which gives synergistic effect on the solubility of poorly Water-soluble drug. The most significant benefit of hydrotropy is that it has been observed in a wide range of substances. (Purwa Jain et al., 2010).

Table 3: Classification of hydrotropy.

Class	Aromatic anionics	Aromatic cationic	Aliphatics and linear Anionics
Examples	Sodium benzene, sodium-Salicylate, sodium benzene Sulphonate, sodium cinnamate Sodium benzoate.	Caffeine, procaine hydrochloride, P-amino benzoic acid hydrochloride	Sodium Alkenoate.

Salt formation

Around 300 new substances supported by the FDA during a long time from 1995 to 2006 for highlighting, 120 were in salt structures. Likewise, out of the 101 endorsed salts of fundamental medications, 54 salts were ready with hydrochloric corrosive, demonstrating the hydrochloride was the dominating salt form. (Serajuddin et al., 2007).

Nano technology

As of late, different nanonization techniques have arisen to increment the dissolution rate and bioavailability of

various drugs that are poorly soluble in water. The term "nanonization" refers to the study and application of materials and structures at the nanoscale level of 100 nanometres or less. Nanonization can increase a medication's solubility and pharmacokinetics while also reducing systemic negative effects. Nanonization is accomplished in a variety of ways: 1) homogeneity 2) milling in the water 3) milling of the pears 4) Emulsification is a process for evaporating solvent. One of the most significant advantages of nanotechnology is the ability to create nano- or micro-sized spherical particles with a smooth surface and small particle size distribution, hence boosting dissolution rate and solubility. (ahemad et al., 2011).

Solubilizing agents – Superdisintegrants, such as croscarmellose sodium, crospovidone, and sodium starch glycolate, are used as solubilizing agents in a variety of formulations to promote solubility. Superdisintegrants act as a hydrophilic carrier for drugs that are poorly water soluble. PEG 400 is used to make hydrochlorothiazide more soluble. A newly developed excipient, modified gum karaya, was tested as a carrier for improving the breakdown of a poorly soluble medication. (Zameerruddin and colleagues, 2014).

B) PHYSICAL MODIFICATION

Particles size reduction

The solubility of a drug is influenced by its particle size. As particle size reduced, the surface area to volume ratio increased. Solubility increases when the particle's surface area expands and interacts more with the solvent. The surface area of smaller particles rises, which improves dissolving properties. The size of the medication particle has an impact on its solubility. The surface area to volume ratio increases as particle size decreases. Solubility rises as the surface area of the surface area interacts more with the solvent. The bioavailability of a medicine is proportional to its particle size; smaller particles have a higher surface area, which improves dissolving qualities. (Savjani et al., 2012)

1) Conventional method
2) Micronization
3) Nano suspensions

Conventional method

Attrition, compression impact, cutting, and combined impact are some of the mechanisms connected with standard molecular size reduction strategies. Spray drying and other traditional particle size reduction procedures rely on mechanical stress to disaggregate the active component and comminution. The essential parameters of comminution are well-known in the industry, allowing for a productive, repeatable, and cost-effective approach of Molecular size reduction. (Jadhav and colleagues, 2014)

Micronization – Micronization is one more regular strategy for the Molecular size reduction. As micronization happens surface area region increases with decreasing Molecule size and increase solubility. It is high energy molecule size decrease technique that can change over coarse particles into particles of less than 5 µ diameter. Jet milling, micronizer, microprecipitation, micro crystallisation, and supercritical fluid t Solubility of medication are some of the procedures used to micronize drugs. There are three sorts of particle size reduction strategies. spray freezing into liquid, rotor stator colloidal mills, and technology Micronization is not recommended for drugs with a high dosage number because it does not improve the drug's saturation solubility. (Nikita N. and colleagues, 2012)

Nanosuspension – This breakthrough is used to treat medications that are poorly soluble in both water and oils. A pharmaceutical nanosuspension is a biphasic framework made up of nano-sized drug particles suspended in a fluid vehicle stabilised by surfactants for administration via the mouth, skin, or parenteral and pulmonary routes. There are two important strategies for nanosuspension arrangement. (Singh and colleagues, 2016)

a) Bottom-up technology
b) Top-down technology

a) Bottom-up technology – In bottom-up innovation, the medication is dissolved in a solvent and then introduced to a nonsolvent, causing fine medication particles to precipitate. The technique of precipitation is irrelevant for drugs that are ineffectively soluble in both aqueous and non-aqueous environments.

b) top-down technology – Separating larger particles via media milling or high-pressure homogenization are examples of top-down approaches (HPH). Particles are crushed in media milling by strong shear forces caused by the movement of milling pearls/beads, but in high pressure homogenization (HPH), particles are confined to go through a small hole at high speed, causing cavitation to reduce particle size. (Surawase and colleagues, 2020)

Modification of crystal habit

1) Polymorphs 2) pseudo polymorphs

Polymorphism refers to a component's or compound's ability to take on several crystalline forms. Drug polymorphs are chemically identical, yet they have varied physicochemical qualities such as solubility, melting point, texture, density, and stability. Due to increased energy associated to expansion in the surface region, the amorphous form of the drug is more suited than the crystalline form. Ordering a variety of powerful medications. Amorphous polymorph >Stable polymorph >Metastable polymorph

Metastable structures are associated with higher energy and an expanded surface region, resulting in increased solubility, bioavailability, and efficacy among the steady, unstable, and metastable crystalline polymorphs. (2018, Jagtap et al.)

Complexation – Complexation is the formation of a non-bonded substance with a well-defined stoichiometry by the interaction of at least two atoms. Complexations can be divided into two categories.

1) Stacking complexes
2) Inclusion complexes

Stacking complexes – Stacking complexes is caused by an interaction between the non-polar area of the drug and the complexes agent, which results in the non-polar portion of the medication being prevented from coming into touch with water.

Inclusion complexes – It is made by embedding a non-polar molecule, an atom's area into the depression of another atom, or a collection of particles. Cyclodextrin and its derivatives are commonly used in complexation. The most usually utilized have atom are cyclodextrins. Three naturally occurring CDs are cyclodextrins α, ß cyclodextrins and γ-CD. There are various advances adjusted to set up the inclusion complexes of poorly water-soluble drug with cyclodextrins. (Patil et al., 2010)

1) Physical mixture
2) Kneading method
3) Co-precipitate

1) Physical mixture

In this the CDs or appropriate polymer and drug are combined as one completely by pulverizing in mortar and pass-through suitable sieve to get the ideal particle size in the result. It is simple pulverizing method.

2) Kneading method

This strategy depends on impregnating the CDs with little measure of water or hydroalcoholic solution converted into paste. The drug is then added to the above paste and kneaded for specified time. The kneaded combination is then dried and gone through sieve if required. Parik et al have detailed the dissolution enhancement of nimusulide utilizing complexation strategy. In research centre scale Kneading can be accomplished by utilizing a mortar and pestle in large scope the Kneading can be done by using the extruders and different machines. This is most normal and simple method used for inclusion complexes and it presents extremely low cost of production. (Parikh et al.,2005)

3) Co-precipitate method

The necessary measure of drug is included the arrangement of CDs or reasonable polymer. The complex held under magnetic agitation with controlled process boundaries. The complex is shielded from the light the formed precipitate is isolated by vacuum filtration and dried at room temperature to stay away from the inclusion complex. This strategy is applicable to industry.

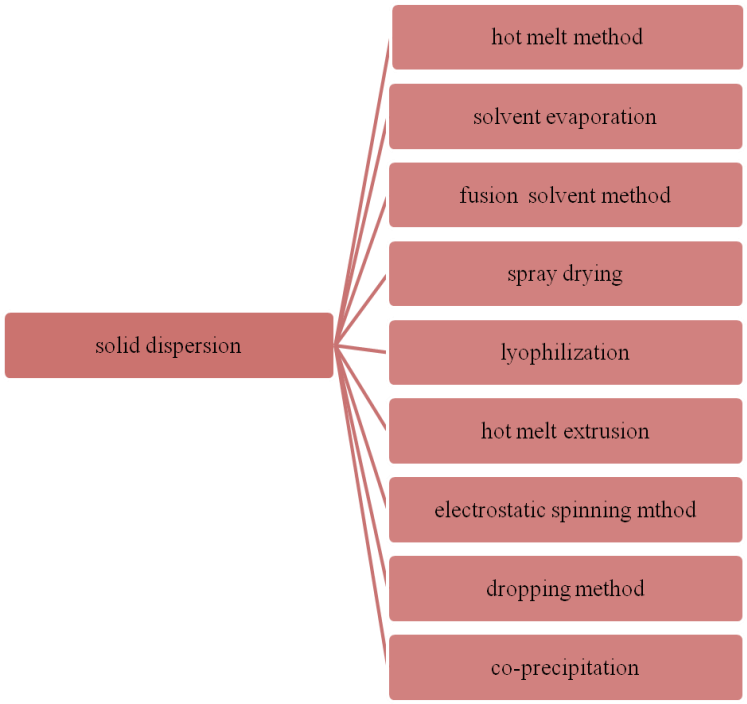
Inclusion complex formulation-based techniques –The solubility and oral bioavailability of piroxicam, carvedilol, glipizide, and rofecoxib can be moved along by using cyclodextrins inclusion complexes, which are framed by the housing of a non-polar particle or nonpolar area of one atom (known as guest) into the depression of another particle or gathering of atoms (known as host). The inclusion complex arrangement process has been used more unequivocally to work on the fluid solvency, dissolving, among all the solvency upgrading procedures. (Anuj Kumar and colleagues, 2011)

1) **Kneading method –** The kneading procedure is mentioned in the complexation section.
2) **Freeze drying technique / Lyophilization** - to obtain a porous, amorphous powder with a high level of drug-CD interaction. The solvent system from the arrangement is dispensed with through an essential freezing and subsequent drying of the arrangement including both medication and CD at reduced pressure during the lyophilization / freeze drying technique. Molecular mixing of medication and carrier in a conventional solvent is included in the freeze drying/lyophilization technique, which is an alternative to solvent evaporation. Lyophilization may successfully transform thermolabile substances into complex forms, which is an advantage of this technology. Lyophilization has a number of drawbacks, including the need for specialist equipment and a lengthy procedure. (Rangoni, M., et al., 2005)
3) **Microwave irradiation method –** includes microwave irradiation reaction among drug and complexing agent utilizing a microwave oven. The medication and CD are dissolved in a predetermined amount of water and organic solvent in a round bottom flask with an unambiguous molar proportion. In the microwave, the mixture is heated for one to two minutes at 60 degrees Celsius. Following the completion of the reaction, a sufficient amount of solvent blend is added to the aforementioned reaction mixture to remove any remaining uncomplexed free drug and CD. The precipitate is then isolated using Watman filters paper and dried at 40°C in a vacuum oven. Microwave irradiation is a novel technology for modern scale planning because of the major advantages of faster response times and improved item return. (2004, X.Wen et al.)

Solid dispersion

In the mid 1960s, Sekiguchi and obi introduced the concept of solid dispersion while researching the formation and dissolution of eutectic melts of a sulphonamide medication and a water-soluble carrier. A solid dispersion is a collection of solid things made up of at least two distinct components: a hydrophilic matrix and a hydrophobic medication. Solid dispersion was defined by Chiou and Riegelman as. "a dispersion consisting of the formation of a eutectic combination of drug and water soluble carriers through the melting of their physical mixes" Polyethylene glycol (PEGs), polyvinylpyrrolidone (povidone, PVP), and plasdone-s630 are the most commonly used hydrophilic carriers for solid dispersion. Different strategies are being used to

increase the solid dispersion of hydrophobic drugs in order to work on fluid solubility. (muller et al., 2000).



Hot melt method / Fusion process

The liquefy strategy is a term used to describe the Fusion process. The Fusion process was used to prepare the main solid dispersion used in medication applications. For fast release solid dispersions, Sekiguchi and obi presented the melting or fusion technique initially. The physical mixes of medication and water-soluble carrier were heated until softened. In an ice bath, the melt mixture was swiftly cooled and hardened. Crush was the last solid mass (Goldberg et al.) used a pulverised, sieved method with some modifications. Furthermore, Chiou and colleagues discovered that hardening and powdering take at least 1 day in desiccators at ambient temperatures. (Kamalakkannan et al., 2010).

Solvent evaporation method

The carrier and dynamic ingredient are dissolved in a suitable organic solvent in the solvent evaporation technique of planning. As the solvent is evaporated at a higher temperature or under vacuum, super immersion occurs, followed by simultaneous precipitation of the contents, resulting in a solid residue. The Co-precipitate is next dried under vacuum to remove any solvent that may have remained on the molecule surface. It is suggested that even follow-up solvent measures be evacuated. To demonstrate 100% solvent evacuation, extremely delicate technologies such as differential thermal analysis (DTA), thermogravimetric investigation (TGA), and differential scanning calorimetry (DSC), as well as less delicate systems such as spectroscopy, gravimetry, and can be used. (1974, Higuchi et al.)

Fusion solvent method

Carrie (s) is/are liquefied, and the drug (s) is/are in solution form. The demand for solvent evacuation is eliminated if the carrier is capable of storing a specified amount of fluid while maintaining its solid qualities, and if the fluid is nontoxic. This technique is useful for drugs with high liquifying focuses or that are thermolabile.

Spray drying – The carrier and active component are dissolved and suspended in an appropriate solvent in this type of arrangement. Due to the large surface area of the droplets, the solvent quickly evaluates and is evaporated by drying it and applying a rush of warmed air to eradicate the solvent (hart et al., 2013).

Lyophilization – Spray freezes drying technique

Spray freeze drying (SFD) has been effectively evolved to plan solid dispersion to surrounding temperature, which was made critical improvement by William III's exploration work. SFD innovation includes the atomization of a feed liquid containing inadequately water soluble or insoluble APIs and Excipient straight forwardly into a cryogenic fluid at surrounding temperature. When opposed to traditional progression structures and high surface areas, the cycle provides a number of advantages. (Rogers et al., 2002)

Hot melt extrusion –. It is a very common strategy in the polymer business. Speiser and Huttenrach, on the other hand, were the first to apply this technology to pharmaceuticals. The sections of a melt extrusion are as follows: An opening for crude materials, a warmed barrel with extruder screws to convey and blend the fed

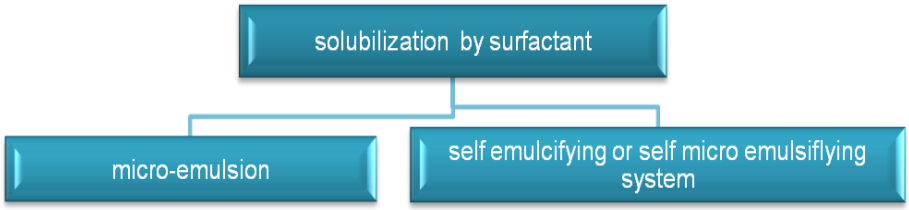
ingredients, and a leave port with an optional die to shape the expelling mass, the active component, and the carrier are all taken care of at a constant pace into the warmed barrel of the extruder. When a mixture of active ingredient and carrier is passed through warmed screws, it transforms into a "liquid-like condition," which allows for personal and homogeneous blending thanks to the strong shear of extruder screws. A depart port with a die form that can be chosen. Melt into the desired shape, such as granules, pallets, films, or powder. This approach allows for consistent output, which makes it suitable for large-scale manufacturing; also, the item is easier to handle or deal with because the shape may be altered to the next processing stage without crushing at the extruder's power source. (1971, Adel et al.)

Electrostatic spinning method - This technology is used in the polymer sector, where it blends solid solution / dispersion technology with nanotechnology. A potential of between 5 and 30 kV is applied to the fluid stream of the drug/polymer solution in this cycle, and when the electrical powers overcome the surface pressure, the cycle ends. Fibers of submicron breath are produced from the drug/polymer solution at the air interface. The formed Fibers can be gathered on a screen when the solvent has evaporated. Gautam et al. (Gautam et al., 2015).

Dropping method – A solid dispersion of a melting drug-carrier mixture. It's pipetted out and then deposited onto a plate, where it hardens into spherical bits. Variables such as the consistency of the melt and the size of the pipette can affect the size and shape of the particles. Because viscosity is very temperature dependent, it is critical to vary the temperature so that the melt hardens to a spherical shape when dropped on the plate. (Pawar et al., 2012).

Co-precipitation method -In this technique, a non-solvent is introduced drop by drop to the drug and carrier solution while constantly stirring, and the drug and carrier are co-hastened to produce micro particles, after which the macromolecule suspension is separated and dried. The primary advantage of the precipitation technique is the low cost of the equipment. The most important test of this method is that the development of drug crystals should be regulated throughout the precipitation process by adding a surfactant to prevent the formation of microparticles. (Jain et al, 2012).

Solubilization by surfactant- Particles containing polar and non-polar areas are known as surfactants. Most surfactants are made up of a hydrocarbon fragment and a polar group, which can be anionic, non-ionic, Cationic, or Zwitterionic. When tiny polar molecules are added to micelles, they can cluster in the hydrophobic centre. The expansion of surfactants lowers the surface tension and increases the drug's dissolution solubility by expanding the dissolution of lipophilic drugs in aqueous medium, which is very important in modern and regular cycles. Surfactants are also used in the settlement of drug suspensions. Micelle arrangement occurs when the convergence of surfaces exceeds their critical micelle concentration (CMC), which is typically in the range of 0.05-0.10 percent for most surfactan**ts.** (F. Podlogar et al., 2004).



Micro-emulsions

Micro emulsions have been used to increase the solubility of numerous drugs that are insoluble in water, as well as the inclusion of proteins for oral, parenteral, and percutaneous/transdermal administration. A micro emulsion is an optically clear pre-concentrate that dissolves an insufficiently water-soluble medication using a combination of oil, hydrophilic surfactant, and hydrophilic solvent. When the details come into touch with water, they immediately scatter (or 'self-emulsify') to form a tiny emulsion. And homogeneous oil drops carrying the poorly soluble medication that has been solubilized. Microemulsions are translucent (or clear) isotropic, thermodynamically stable frameworks of oil, water, and surfactant, sometimes in combination with a cosurfactant, with droplet sizes ranging from 20 to 200 nm. (Holm and et al., 2003)

Self-emulsifying or Self-micro emulsifying system - Frameworks that are self-emulsifying or self-micro emulsifying are based on the principle of emulsion creation in situ in the gastrointestinal tract. Oil, surfactant, co-surfactant, at least one hydrophilic Solvent, and co-solvent structures are used in conjunction. Without any outside step (water), forms a transparent isotropic arrangement called as a self-emulsifying or self-micro emulsifying drug delivery system (SEDDS). Fine o/w emulsions or micro emulsions are formed unexpectedly when the Watery stage in the GIT is diluted, and they are employed to

further develop lipophilic drug solubility and absorption. Water penetrating the various liquid crystalline or gel phase created on the outer layer of the droplet could be related to the ease of emulsification without breaking a sweat. SEDDS are similar to increase and make in that they arise spontaneously after blending their constituents under gentle perturbation and are thermodynamically stable. Godse et al. (Godse et al., 2013).

(Super critical fluid process (SCF)

Super critical fluid is liquid which exists as single liquid over its basic temperature and pressure. SCF shows the properties of both fluids also a gas over its basic condition. It is protected harmless to the ecosystem, and conservative. The low working condition (temperature and pressure) make SCFs appealing for drug research. At close critical temperatures, SCFs are high compressible permitting, moderate changes in pressure to significantly modify the thickness and mass transport characteristics of a fluid that generally decide it's solvent power. Once the drug Particles are solubilized inside SCF, they might be re-solidified at enormously diminished molecule size. carbon dioxide is the most ordinarily utilized SCF since it is chemically idle, non-harmful and non-flammable. other supercritical solvent incorporates nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia and water. (Rantakyla et al.,2004).

Liquisolid Methods

The liquisolid procedure is a novel idea where Fluid might be changed into a free streaming, promptly compressible and clearly dry of powder by basic actual mixing with chosen carrier and converging material. The liquid portion is linked, and this can be a solid drug suspension or a drug arrangement in non-volatile Fluid carriers. enters the pore-permeable carrier When the carriers are immersed in liquid, a coating of liquid forms on the molecule's surface, which is promptly absorbed by the fine covering particles. Dry free streaming and compressible powder can be obtained in this manner. (Bhambere and et al., 2016).

polymeric alteration- Polymorphs are different crystalline kinds of a medicine that may have diverse qualities. Polymorphs may differ in physical and chemical stability, shelf-life, melting temperature, fume pressure, inborn solubility, dissolving rule, morphological density, and natural exercises, as well as bioavailability. It is preferable to Foster the drug's most thermodynamically stable polymorph to ensure consistent shelf-life bioavailability under a variety of real-world storage conditions. (Argade et al., 2013).

CONCLUSION

We argue in this article that a medication's solubility is the most important actual attribute for its oral bioavailability, description, progression of numerous dose types of various drugs, therapeutic efficacy of the medicine, and quantitative investigation. Proper choice of solubility enhancement method is the key to guarantee the goals of good formulation like great oral bioavailability, minimal frequency of dosing and better patient compliance joins with low cost of creation. The various method described above alone or then in combination can be utilized to enhance the solubility of drug. Solubility can be improved by numerous methods and number of folds expansion in solubility. In view of Solubility issue of many drug the bioavailability of them gets affected and hence Solubility enhancement become essential. It is now possible that to increase the solubility of poorly soluble drug with the assistance of different strategies as mentioned above.

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