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NOVEL SOLUBILIZATION TECHNOLOGY AN ECO-FRIENDLY ANALYSIS TO IMPROVE SOLUBILITY, DISSOLUTION, AND BIOAVAILABILITY OF VARIOUS POORLY WATER SOLUBLE NSAID DRUGS

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Abstract

It is necessary for the drug to become soluble in order to generate the desired pharmacological reaction. Solubility is one of the most significant criteria for achieving the required drug concentration in systemic circulation and demonstrating pharmacological response. Medicine's therapeutic efficacy is determined by its bioavailability, which is determined by the solubility of the drug moiety. Several formulation techniques are now available to improve solubility and dissolution profile, which is helpful in increasing oral bioavailability. Nanocrystals are crystalline nanoparticles (200–500 nm) that contain a high concentration of medication and are stabilized by surface stabilizers. Hydrotrophy is a solubilization process in which the hydrotropic agent increases the water solubility of the first solute by adding a large amount of the second solute. Co-crystallization is one of the method of solubility enhancement which not only enhances the solubility of the drug but also brings a significant change in the physicochemical properties of the drug such as stability, bioavailability and dissolution rate. Combining poorly soluble pharmaceuticals with a water miscible solvent in which the drug is readily soluble can improve its water solubility. This is known as cosolvency, and the solvent that is used in conjunction is known as cosolvent. The cosolvent system reduces the interfacial tension between the aqueous solution and the hydrophobic solute.

Key Words: Solubility, therapeutic efficacy, bioavailability, solubilization process, Co-crystallization Etc.

INTRODUCTION

They are weak acids or bases, many drugs are less soluble in water. Poor absorption, variable bioavailability, and injury to the gastrointestinal mucosa are all caused by the drug's low solubility. The issue of solubility is a major concern for formulation experts. When it comes to dealing with pharmaceutical disintegration, formulation scientists have a considerable challenge. The major goal of this research is to find out how well the medicine dissolves in water in various dissolving media.(1) More than 40% of new chemical entities (NCEs) developed in the pharmaceutical industry are nearly insoluble in water. (2)

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Medicine's therapeutic efficacy is determined by its bioavailability, which is determined by the solubility of the drug moiety. Several formulation techniques are now available to improve solubility and dissolution profile, which is helpful in increasing oral bioavailability.[3]

Oral bioavailability is influenced by aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, systemic metabolism, and sensitivity to efflux mechanisms. Low oral bioavailability is caused by a variety of factors, including poor solubility and permeability. To obtain therapeutic plasma concentrations after oral administration, poorly water-soluble medicines require large doses. Low water solubility is a significant problem in the formulation of new chemical entities. Water is the chosen solvent for liquid medicinal formulations.

For orally given medicines to achieve the needed concentration in systemic circulation for a pharmacological response, solubility is the most important rate-limiting criteria.

What is a BCS class?

The Biopharmaceutics Classification System (BCS) of the US Food and Drug Administration assesses drug absorption in the intestine. Drug compounds are classified by BCS in a scientific framework based on equilibrium water solubility and intestinal permeability. Drugs are split into four groups as a result of this:

Drugs of class I are very soluble and permeable.Class II medications have a low solubility but a high permeability, class III drugs have a low solubility but a high permeability, and class IV pharmaceuticals have a low solubility but a high permeability.Drugs of class IV are highly soluble yet have poor penetration.

Why there is a need to increase the solubility of BCS class 2?

According to the BCS, improving the drug's solubility and dissolution rate in gastrointestinal fluids can improve bioavailability, especially for class II drugs (low solubility and high permeability). We can attain the necessary drug concentration in systemic circulation for pharmacological response by enhancing the solubility of BCS class II. Because there is a need to boost the drug's solubility and dissolution.[4][5]

Mechanism of solubility

A variety of ways have been used to increase the aqueous solubility of weakly water-soluble medications. The therapeutic efficacy of a drug is governed by its bioavailability and, eventually, its solubility in order to achieve the necessary concentration in the systemic circulation. Solubility is defined as the breaking of intermolecular or interionic bonds in the solute, the separation of solvent molecules to make room for the solute, and the interaction between the solvent and the solute molecule. The holes in the solvent are opened during the solubility process. Solid molecules, on the other hand, separate from the bulk. The released solid molecule is then inserted into the solvent's hole. Concentration, molality, mole ratio, and mole fraction are all terms used to describe solubility.

Techniques for Solubility Enhancement

Physical modifications, chemical modifications of the medication material, and other procedures are all examples of solubility improvement techniques.[2] However, several of the methods have some flaws. Some critical qualities, including as size, shape, surface-related properties, and electrostatic charges, are difficult to manage using the micronization approach. A high-energy process results in the formation of a thermodynamically unstable amorphous area.There is also a risk of precipitation of poorly water-soluble pharmaceuticals when using the salt production approach.

Thermal stress and product deterioration are possible with spray drying, therefore we can only utilise organic solvents.The toxicity potential of organic solvents is implicated in solvent evaporation.We can't employ a thermally sensitive medicine in hot melt extrusion since it can modify the drug's nature. In solid dispersion, a deficiency is the drug's and vehicle's instability, as well as the possibility of moisture. It has low scale-up and reproducibility, as well as a high cost of approach.

having a high methodological cost in microcapsules Biocompatible and biodegradable constitutions do exist. In addition, there is a risk of drug degradation or drug instability in micro-emulsions due to high melting point chemicals.[6][7]

Why organic solvent should avoid?

Organic solvents are carbon-based solvents, and their properties are essentially determined by their volatility, boiling point, molecular weight, and colour. Organic solvents, despite their huge dangers, are employed for excess of purposes, prompting us to wonder. more about the toxicity issues If consumed or inhaled, almost all of the solvents are harmful to one's health.When inhaled in excess of the recommended dose, and when they come into contact with the skin, the majority of

them cause irritation. Some Acetone, Ethyl Acetate, Hexane, Heptane, Dichloromethane, Methanol and others are common solvents.Ethanol, Tetrahydrofuran, Acetonitrile, Dimethylformamide, Toluene, Dimethylsulfoxide, and other similar chemicals.

The function of the CNS and other body parts will be adversely affected if exposed to solvents on a regular basis. The severity of the impact, signs, and symptoms will vary depending on the concentration, time, length, frequency, and nature of the solvents, resulting in common side effects such as headache, dizziness, weariness, blurred vision, behavioural abnormalities, unconsciousness, and death. To combat this, the green chemistry concept is fast gaining traction, and the solvent selection guide is being used by a number of large corporations and research institutions. A researcher or chemical worker is the principal individual who works with solvents, and they must keep these things in mind while they go about their work for their own health and the welfare of the world.The goal of this review is to provide basic information on common organic solvents and their possible toxicity, so that researchers would think twice and always consider their health as well as the environment through safe and environmentally friendly practises. [7]

NOVEL TECHNIQUES

Nanocrystals

Nanocrystals are crystalline nanoparticles (200–500 nm) that contain a high concentration of medication and are stabilized by surface stabilizers. Drug nanocrystals are a versatile formulation strategy for improving the pharmacokinetic and pharmacodynamic aspects of medicines that are poorly soluble. The increase in surface area produced by reducing the particle size of the active drug component to the nano size range while maintaining the crystal shape of the medication is the driving force behind nanocrystal technology.

mechanism of Solubility Enhancement

Nanocrystallization reduces particle size to the nano range. According to the Ostwald–Freundlich and Noyes–Whitney equations, this results in improved saturation solubility and dissolution velocity.[8]

Techniques for manufacturing of Nanocrystals

Bottom up Technology

- Anti-solvent precipitation
- Supercritical fluids
- Spray-drying

Top down Technology

- Media milling
- Bead milling
- Dry co-grind
- High pressure homogenization
- Homogenization in Aqueous media (Dissocubes)
- Homogenization in Non-Aqueous Media (Nanopure)
- Nanojet technology
- Emulsion solvent diffusion method

Other methods

- Solvent evaporation
- sonocrystalisation

- melt emulsification
- Bottom-Up NanoCrySP Technology[8][9]

The following scenarios can be considered for nanocrystals in particular:

1. According to the modified Noyes-Whitney law, a decrease in particle size leads to an increase in surface area accessible for interaction with the dissolving fluid, and hence an increase in particle dissolution rate.

2. According to Kelvin's equation, an increase in particle curvature (especially for colloidal particles) leads to a rise in dissolving pressure.

3. Greater solubility results in a higher concentration gradient at membranes, and consequently higher penetration or permeation through membranes.

4. High attachment to biological membranes of nanocrystals, encouraged by their size [97–100], also favours high penetration through membranes, but adhesion can be enhanced by coating with mucoadhesive polymer.

5. According to numerous publications, another factor for increased bioavailability is nanocrystal transcellular absorption through epithelial cells.

6. Nanocrystals can be delivered via intravenous injection (nanosuspensions) and have 100% bioavailability when reaching the target tissue or organ.

7. Nanocrystals can be coated with compounds that interact with specific substrates to help with targeting.[10]

Advantages

- Possibility of administering a drug through different administration routes (oral, intravenous,intramuscular, pulmonary, ocular, dermal)
- Possibility of formulating a drug under different pharmaceutical dosage forms (tablets, capsules, suspensions, ointments, etc.)
- Higher solubility (thermodynamic or kinetic depending on the solid physical state of the drug than conventional particles [11] [12]
- Faster dissolution rate than conventional particles
- Long circulating nanocrystals
- Potential for passive and active targeting of drugs
- Reduced tissue irritation in case of subcutaneous/intramuscular administration
- Possibility of obtaining hybrid nanocrystals for both diagnostic and therapeutic applications [13] [14]
- Fewer are the disadvantages, such as:
    1. Physicochemical-related stability problems
    2. Bulking sufficient care must be taken during handling and transport
    3. Uniform and accurate dose cannot be achieved[15] [16]

Disadvantages

- Physical stability, sedimentation & compaction can cause problems.
- Products are bulky thus require sufficient care during handling & transportation.
- Uniform & accurate dose cannot be achieved [17] [18] [19]

Case studies of various poorly water soluble NSAID Drugs.

Case study No. 1

Raj Kumar et al.(2019)

Griseofulvin (GF) is a medication that is poorly soluble in water and has a high permeability. It is classed as a Class II medicine by the Biopharmaceutical Classification System (BCS). Because of its ability to disrupt mitotic spindles and act as a possible inhibitor of centrosomal clustering in tumour cells, GF has recently attracted attention in the biomedical field. A drug's therapeutic applications are often limited by its water solubility. There are a variety of methods accessible, one of which being nanoparticle preparation. Milling, high-pressure homogenization, spray/freeze drying, emulsion solvent evaporation, antisolvent precipitation, and supercritical fluid processes are discussed briefly.The paper also includes a discussion of lipid-based formulations and silica nanostructures-based formulations for increasing GF availability and bioability. According to the literature, commercialization tactics include milling, high-pressure homogenization, and lipid-based formulations. With further improvement and control experimental design, the antisolvent precipitation method could be suitable for industrial applications, yielding high solid loading and continuous nanocrystallization. Formulations based on lipids are less dangerous than those based on silica. There's also a quick rundown of commercially available items. This review can be utilised as a jumping off point for more GF nanoformulation research.[20]

Case study No. 2

Radum Pundlikrao IGE et al.(2013)

The lipophilic drug fenofibrate (FBT) is used to treat hypercholesterolemia and hypertriglyceridemia. It has a log P5.375, is almost water insoluble, and has a low oral bioavailability (36 percent). This project's purpose was to develop FBT nanocrystals with improved solubility and oral bioavailability. A probe sonicator was used to make a fenofibrate nanosuspension, which was subsequently freeze dried into a dry powder. The product was characterised using DSC, FTIR, XRPD, SEM, particle size, polydispersity index (PDI), zeta potential, solubility, in vitro dissolution, in vivo bioavailability, and stability tests. In vitro dissolution of formulation FNS3 and pure medicine in 1 percent sodium lauryl sulphate (SLS) media was 73.89 percent and 8.53 percent, respectively.The saturation solubility increased dramatically when the particle size was lowered from 80,000 923 nm to 460 20 nm. In 0.5 percent and 1 percent SLS media, the saturation solubility of formulation FNS3 was determined to be 67.51 1.5 g/mL and 107 1.9 g/mL, respectively. In 0.5 percent and 1 percent SLS, the saturation solubility of pure medication was determined to be 6.02 1.51 g/ml and 23.54 1.54 g/ml, respectively. In a phar-macokinetic investigation in New Zealand white rabbits, optimised nanocrystals (FNS3) had a 4.73-fold higher relative bioavailability than the pure medication. Long-term stability experiments revealed that the mean particle size and PDI at 5 C 3 C did not change significantly after 180 days. This improved fenofibrate nanocrystal solubility and bioavailability.[21]

Case study No. 3

Zhigang Shen et al. (2005)

A unique direct approach for preparing nanosized cephradine with narrow particle size distribution was devised in this study, which included reactive precipitation with liquid anti-solvent precipitation in a high gravity environment. When utilised for injection, the produced cephradine demonstrated a considerable decrease in particle size, a significant increase in specific surface area, and a much shorter dissolving time when compared to commercial crude cephradine. The typical particle size ranged from 200 to 400 nanometers.After micronization, the specific surface area increased from 2.95 to 10.87 m2/g. The mixture of nanosized cephradine and l-arginine could still dissolve in 1 minute when the amount of l-arginin was reduced from 0.25 to 0.18 g. The physical features and molecular states were constant after the recrystallization procedure, according to X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR) analyses. Because of its low cost, efficient processing, and ease of scaling-up, this technology could be used in industrial settings.[22]

Case study No. 4

Xiaopeng Hana et al. (2013)

We previously studied the manufacture, characterisation, and pharmacokinetics of nimodipine nanocrystals for oral administration, finding that they exhibited lower solubility profiles but higher bioavailability than Nimotop®. The goal of this research was to figure out why NMD nanocrystals and Nimotop® had such a poor in vitro in vivo correlation, assuming that nimodipine nanocrystals have a unique oral absorption mechanism. Methods: Researchers used lymphatic models of everted stomach sacs to investigate nanocrystal oral absorption. lymphaticallyThe mesenteric lymph duct was used to cannulate SD rats, Caco-2 cell monolayers, and chylomicron flow blocking animals.

Results: Nanocrystal permeability was not superior to Nimotop® in the duodenum, ileum, or colon, indicating that different absorption mechanisms are involved. When the mesenteric lymph was blocked, nanocrystal exudates from entero-cytes were detected in mesenteric lymphatic fluids using a transmission electron microscope, and the bioavailability was only half that of the control. The nanocrystals were taken up by enterocytes via macropinocytosis and caveolin-mediated endocytosis.

Conclusions: Because portions of the nanocrystals underwent macropinocytosis and caveolin-mediated endocytosis by enterocytes as intact nanocrystal forms, they bypassed the liver first-pass metabolism, it was impossible to establish a favourable in vitro in vivo correlation for NMD nanocrystals and Nimotop®.[23]

Case study No. 5

Hak-Kim Chan et al. (2011)

The focus of this review is on bottom-up methods such as precipitation (or crystallisation) and single droplet evaporation to make nanoparticles with substantially pure medicines for pharmaceutical purposes. High-gravity, constrained impinging liquid jet mixing, multi-inlet vortex mixing, supercritical fluids, and ultrasonic waves are all effective precipitation procedures. Nanospray drying, aerosol flow reactor method, spraying of low-boiling point solvent under ambient circumstances, and electrospraying of low-electrical conducting solutions are all spray-based droplet evaporation processes. Controlling the particle development kinetics through the evaporation rate of the droplets or the mixing rate during precipitation is critical to the effectiveness of these various approaches in obtaining stable nanoparticles.[24]

Hydrotrophy

Hydrotrophy is a solubilization process in which the hydrotropic agent increases the water solubility of the first solute by adding a large amount of the second solute.

Ionic organic salts, also known as hydrotropic agents, are made up of alkali metal salts of different organic acids. Salts that improve the solubility of a solute in a particular solvent are called to "salt in," while salts that decrease solubility are said to "salt out." A phenomenon known as "hydrotropism" occurs when many salts with large anions or cations that are themselves very soluble in water "salt in" non-electrolytes called "hydrotropic salts."

The term "hydrotrophy" refers to the increase in water solubility caused by the presence of a substantial number of chemicals. The method by which it improves solubility is more closely linked to complexation, which involves a weak contact between hydrotropic agents such as Sodium Benzoate, Sodium Acetate, Sodium Alginate, and Urea.[25]

The mechanisms of hydrotrope are being studied in a variety of ways, both theoretically and experimentally. Three designs can be used to condense the available proposed mechanisms.

(a) Potential for self-aggregation

(b) Structure-breaker and structure-maker

(c) The ability to create micelles with a similar structure.

Hydrotrope assemblies are distinguished from other solubilizers by their distinct geometrical properties and different association patterns.

Advantages of Hydrotropic Solubilization Technique

- It's a new, simple, cost-effective, safe, accurate, and environmentally friendly technology for spectrophotometrically avoiding the use of organic solvents in the analysis of pharmaceuticals that are weakly water-soluble. Ornidazole table, for example, uses more expensive organic solvents for spectroscopic examination.
- Mixing the medicines and hydrotrope with water just takes a few minutes.
- It does not require the modification of hydrophobic medications chemically, the use of organic solvents, or the development of the emulsion system.
- It does away with the use of organic solvents, avoiding problems like residual toxicity, volatility-related errors, and environmental expenses, among others.
- The hydrotropy technique is believed to be superior to other solubilization methods such as miscibility, micellar solubilization, co-solvency, and salting in because the solvent character is independent of pH, has strong selectivity, and does not require Emulsification.[26]

Disadvantages of Hydrotropic Solubilization Technique

- Excessive usage of hydrotropic medicines has been connected to toxicity problems.
- The relatively large concentrations required to achieve the MHC (minimum h ydrotropic concentration) limit the economic use of hydrotropes.
- There's a chance that the hydrotropic agent and drugs will interact in a negative way.
- Water cannot be completely eliminated because it is utilised as a solvent.[27]

Case study of various poorly water soluble NSAID Drugs.

Case study No. 1

Maheshwari RK and Moondra S (2010)

proved that poorly water-soluble drugs can also have a better scope with the hydrotropic agent to carry out a titrimetric or spectrophotometric analysis. by using hydrotropic drugs we can avoid the harmful effect of costlier and unsafe organic solvents. in the BP, analysis of aceclofenac bulk drug is done by 40 ml of alcohol. instead of that using 40 ml of 2.5M sodium salicylate can help to enhance 400 fold solubility. Statistical data proved the accuracy,

reproducibility, and precision of the proposed method. [28]

Case study No. 2

Maheshwari R K et.al. (2009)

To facilitate titrimetric analysis of poorly water-soluble drug ibuprofen sodium solution as solubilizing agent is used. For the analysis of this drug, Methanol is used in British pharmacopeia. in this analysis methods of NSAID drugs like Naproxen tablet never used sophisticated instruments and costlier, toxic, pollutant organic solvent. in the results, they observed that 0.5M ibuprofen sodium solution enhances the solubility more than 350 folds as compared to distilled water. This proposed method is good is confirmed by using statistical parameters viz. standard deviation, percent coefficient of variation and standard error, etc.[29]

Case study No. 3

Abraham S et.al. (2021)

In this paper they describes, we can boost solubility of completely water insoluble drug like Lornnoxicam by using hydrotropic technique. To solubilize this they used 2M sodium benzoate. By using this method they proved that this is a novel, simple one, accurate, cost effective as well as never harming the environment. For routine analysis of lornoxicam tablets this is a well employed technique. [30]

Case study No. 4

Savjani K J, et.al.(2021)

in that they received the significance of solubility and expressed incompatible techniques for the solubilize drug. As per their study there are more than 40% drugs are insoluble in water therefore to increase solubility of these drugs is crucial in today's world. They differentiate techniques in physical, chemical and miscellaneous modification. According to them, hydrotropic agents are basically ionic organic salt and by "salting in" of non-electrolytes drugs get soluble in water. They also reviewed about drug solubility, there importance and enhancement techniques. In that the described that, according to BCS classes, class 2 drugs are having low solubility problem. If we increases the solubility of drugs comes under this class, then it will help to increase drugs bioavailability. [2]

Case study No. 5

Maheshwari R K.,et.al. (2021)

in this investigation hydrotropic solubilization technique poorly water soluble salicylic acid is solubilized in the hydrotropic agent such as 0.5M ibuprofen sodium solution and 2M sodium salicylate solution. In their results solubility enhanced more than 12 folds with ibuprofen sodium solution and more than 6 folds increased with sodium salicylate solution. In the Results they proved that analysis by proposed method and Pharmacopeial method are very comparable.[31]

Co-crystallization

Co-crystallization is one of the method of solubility enhancement which not only enhances the solubility of the drug but also brings a significant change in the physicochemical properties of the drug such as stability, bioavailability and dissolution rate. Any substance, let it be either acidic, basic, ionic or neutral compound whose solubility is less in a given solvent can be modified with co-crystallization technique and its solubility, stability and bioavailability parameters also enhanced. Because of its property of enhancing solubility as well as dissolution rate, it has become the most important technique in the pharmaceutical industry.

It works by mechanism of formation of complex crystals. In the complex crystal, there is involvement of drug and co-former. The co-former works for the formation of crystals. Both drug and co-former should be in appropriate stoichiometric ratio for formation of crystal. Drug and co-former us connected with synthon. The forces involved in synthon are hydrogen bonding, π-π electrons and Van der Waals interactions. With the help of the silico method we can determine the type of bond Present in the drug and the co-former.

The following are some of the procedures used to synthesise or create co-crystallization.

- Extrusion of melting
- Ultrasound
- Reduction of particle size
- drying by spray
- Evaporation of solvent
- Grinding
- Addition of anti-solvent
- Technology for supercritical fluids
- Screening with high throughput

The definition of cocrystals has caused some debate in the scientific community in recent years. Cocrystals are "homogeneous (single phase) crystalline formations made up of two or more components in a definite stoichiometric ratio where the organisation in the crystal lattice is not reliant on ionic bonding (as with salts)," according to the European Medicine Agency (EMA).The API and the coformer engage noncovalently to generate the cocrystal structure. Intermolecular interactions such van der Waals contact forces, stacking, hydrogen bonding, electrostatic interaction, and halogen bonding between stoichiometric concentrations of diverse compounds are all involved. Supramolecular synthons is the name used to describe the basic structural units found inside supermolecules. Supramolecular synthons are exceptional intermolecular interactions that can be produced by known viable interactions.

Operations[32] There are two types of supramolecular synthons: homosynthons, which are made up of comparable functional groups, and heterosynthons, which are made up of different but complimentary functional groups.[33] Crystal engineering works in this field, recognizing and designing . Syntons are attempting to increase API qualities without changing its intrinsic structure and function with the goal of cocrystal fast development. As a result, changes in crystal packing are made by altering the internal arrangement of the molecules, breaking and establishing noncovalent connections. The acid group of carboxylic acids (e.g., acetic acid, benzoic acid, fumaric acid, maleic acid, malonic acid), the amide group (e.g., nicotinamide and urea), the amine group (e.g., benzamide, picolinamide, adenine), and the alcohol group are the most common functional groups used for formation of supramolecular synthons by H-bonding. Coformers and API might be acidic, basic, or neutral. Ionic chemicals should have non-ionic interactions, permitting cocrystal formation rather than salt formation.[34]

ADVANTAGES

Pharmaceutical cocrystallization can be used instead of salt production for all APIs. Food additives, preservatives, medicinal excipients, vitamins, minerals, amino acids, and other biomolecules, as well as other APIs, are all available as counter molecules.

co-crystallization.[35]

- Cocrystal formation is easier in polymorphic compounds than in compounds that do not show polymorphism. Polymorphic molecules have the potential to generate hydrogen bonds in a variety of well-defined and robust intermolecular interactions.[36]

- Cocrystallization and recrystallization are distinguished by the fact that they deal with heteromeric and homomeric molecules, respectively. As a result, API purification in the form of cocrystals may be possible. According to industrial use, the solvent drop grinding method used to make cocrystals used less solvent. The solvent drop grinding method, also known as kneading, does not necessitate the evaporation of large volumes of solvent. As a result, it is both cost-effective and illustrates the use of green chemistry.[37]

- In addition grinding method also does not require any purification or filtering procedure.[38]

LIMITATIONS

Although cocrystal fabrication is straightforward, the exact link between cocrystal structure and physical attributes remains unknown.

Because excessive heating can produce phase change, conglomerate crystallisation, or polymorphism, the optimum temperature range for solid-state grinding should be determined.

The solid state grinding process produces excessively tiny particles, making X-ray structural identification problematic.crystallography.

Phase separation of Its usefulness is additionally hampered by the transformation of cocrystals into individual components during storage at specific relative humidity conditions.

Another drawback is phase change during API formulation development. Excipients may also cause counter ion displacement in cocrystals during production.[39]

Case study of various poorly water soluble NSAID Drugs.

CASE STUDY NO. 1

Isaac A. Cuadraa and colleagues (2015)

The SAS method, which uses supercritical CO2 as an antisolvent, is examined as a co-crystallization procedure. Co-crystallization is a novel and effective method for enhancing the physicochemical properties of an active medicinal component. Solid-state and solution co-crystallization techniques, which are widely utilised, have substantial limitations. The SAS approach has a low environmental impact and eliminates some of the disadvantages of older procedures.

SAS is the first company to develop 2:1 co-crystals of diflunisal (DIF) and nicotinamide, an anti-inflammatory drug (NIC). The medication concentrations used match the stoichiometric composition of the co-crystals. Temperature (35 and 40 degrees Celsius), pressure (10.0 and 12.0 MPa), drug concentration (two levels), and solvent are all factors that influence co-crystal formation (acetone and ethanol). The final output is a crystalline needle-like substance with varying lengths but uniform widths. SAS, on the other hand, can handle both DIF and NIC data. Crystallinity, thermal behaviour, coformer interactions, and drug release are all characteristics of co-crystals, and their dissolving rate is faster than that of pure DIF. SAS co-crystals have the same crystal structure, melting point, and FTIR spectrum as those previously generated in a liquid assisted ball mill.[40]

CASE STUDY NO. 2

André L.C.S. Nascimento and colleagues (2021)

Pharmaceutical co-crystals have been studied by several academics as a strategy to improve the physicochemical properties of solid-state medications. Pharmaceutical co-crystals have several advantages over conventional solid forms, including enhanced solubility, bioavailability, and reduced phase transition susceptibility. The Biopharmaceutical Classification System classifies nonsteroidal anti-inflammatory medicines (NSAIDs) as class II medications (BCS). Co-crystallization offers the potential to improve NSAID product qualities due to their low water solubility. Current breakthroughs in NSAID co-crystals, co-formers, synthesis, techniques, and applications, as well as some exciting in vitro and in vivo co-crystal properties, are highlighted in this review

A celecoxib-tramadol co-crystal has advanced to phase III clinical trials, showing superior analgesic effect to either API alone. The water solubility of the co-crystal formed by l-proline and diclofenac is particularly high when compared to the pure medication. Naproxen co-crystals with urea and thiourea improve medication release by about 60 percent. Because the co-former used in co-crystal design can also be a physiologically active component, it allows for the mixing of several anti-inflammatory drugs with different analgesic, antipyretic, and anti-inflammatory properties.[41]

.CASE STUDY NO. 3

Shing Fung Chow and his colleagues (2012)

Purpose To be completely exploitable in both formulation and manufacturing, a drug cocrystal must show simultaneous advantages in multiple critical therapeutic qualities over the pure drug crystal. To investigate this possibility, researchers employed two model profen-nicotinamide cocrystals.

Phase pure 1:1 ibuprofen-nicotinamide and flurbiprofen-nicotinamide cocrystals prepared from solutions through rapid solvent removal using rotary evaporation were characterised using DSC, PXRD, FTIR, phase solubility measurements, equilibrium moisture sorption analysis, dissolution testing, and tabletability analysis.

Results The unique melting point of the 1:1 cocrystal, as well as the eutectic temperatures and compositions, were revealed by temperature-composition phase diagrams created from DSC data for each profen and nicotinamide crystal. The inherent dissolving rate of both cocrystals is higher than that of other crystals.[42]

CASE STUDY NO. 4

Mutalik and his associates (2008)

This study revealed that chitosan had a significant impact on increasing the solubility rate and bioavailability of aceclofenac using a simple solvent change technique. Chitosan was precipitated on aceclofenac crystals using the salting out agent sodium citrate. On the pure drug and the prepared co-crystals with different concentrations of chitosan (0.05–0.6 percent), solubility, drug content, particle size, thermal behaviour (differential scanning calorimetry, DSC), X-ray diffraction (XRD), morphology (scanning electron microscopy, SEM), in vitro drug release, and stability studies were all performed. In vivo performance was assessed using preclinical pharmacodynamic (analgesic and anti-inflammatory activity) and pharmacokinetic studies.During the formulation process, the particle size of the prepared co-crystals was dramatically reduced. The melting enthalpy decreased in the DSC, indicating a disordered crystalline composition. Crystallinity had dropped significantly, according to XRD. The dissolve rate in the dissolution studies was significantly higher than in pure medication. The wetting impact of chitosan, decreased drug crystallinity, altered surface shape, and micronization all contributed to the significant increase in aceclofenac dissolving rate from the optimised crystal formulation. Under accelerated storage circumstances, the optimised co-crystals showed exceptional stability. The new crystal formulation provided a rapid pharmacological response in mice and rats, as well as better pharmacokinetic properties in rats, according to in vivo testing.[43]

CASE STUDY NO. 5

S Mittapalli and colleagues used glutaric acid (1:1), adipic acid (2:1), suberic acid (1:1), and caprolactam to co-crystallize etoricoxib (2016). (ETR). The solid forms produced by ETR hemihydrate were characterised using powder XRD, DSC, IR, and single crystal X-ray diffraction. Form I. Water exchanges with an organic acid coformer in the crystal structure, according to lattice energy calculations.

Powder X-ray diffraction reveals the production of a new solid form and overlay of calculated powder when the powder pattern of the product cocrystal differs from that of the beginning components.

The bulk purity is indicated by the pattern with the experimental pattern.

stage of production stage of production.[44]

Co-solvency

Combining poorly soluble pharmaceuticals with a water miscible solvent in which the drug is readily soluble can improve its water solubility. This is known as cosolvency, and the solvent that is used in conjunction is known as cosolvent. The cosolvent system reduces the interfacial tension between the aqueous solution and the hydrophobic solute. Another name for it is solvent mixing. The solubility of pharmaceuticals is substantially altered when an organic co-solvent is added to water. Hydrogen acceptor or donor groups exist in cosolvents with a small hydrocarbon area. The hydrophobic hydrocarbon region usually interferes with water's hydrogen bonding network, lowering intermolecular attraction, whereas the hydrophilic hydrogen bonds ensure it.[45]

Water can help poorly soluble medicines become more soluble. Cosolvents, which are water miscible solvents with high solubility, can be used to improve the solubility of a drug that is poorly water soluble. 17 Co-solvents are water-based solutions containing one or more water miscible solvents that help poorly soluble compounds dissolve better. This has historically been one of the most often used tactics due to its ease of implementation and evaluation. Solvents utilised in co-solvent combinations include PEG 300, propylene glycol, and ethanol. In co-solvent formulations, poorly soluble drugs can be given orally or parenterally. In parenteral formulations, water or a dilution step with an aqueous media may be necessary. Pharmaceuticals are always in liquid form. A co-solvent technique may be appropriate for poorly soluble lipophilic or highly crystalline molecules with a high solubility in the solvent mixture. When compared to the water solubility of the medicine alone, CoSolvents can boost the solubility of weakly soluble molecules by thousands of times. When compared to other solubilization methods, very high drug concentrations of weakly soluble substances can be dissolved. However, because the poorly soluble medication will often uncontrollably crash out when diluted into a crystalline or amorphous precipitate, the bioavailability may not be significantly boosted. For oral absorption, breakdown of this precipitate is essential in this circumstance. To boost the solubility of weakly soluble substances, co-solvents can be used with various solubilization

procedures and pH adjustments. The use of co-solvents to improve the solubility of poorly soluble medicines is a highly effective strategy. [46] Propylene glycol, ethanol, glycerin, and polyethylene glycol are the most often utilised low-toxicity cosolvents for parenteral usage. Because of their considerable solubilization capacity for poorly soluble medicines and low toxicity, dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely employed as cosolvents..[47]

Co-solvents, which are water miscible solvents with high solubility, can often improve the solubility of a drug that is weakly water soluble. These are water-based solutions containing one or more water miscible solvents that are used to increase the solubility of water-insoluble compounds. This has historically been one of the most often used tactics due to its ease of implementation and evaluation.Co-solvency has been used in a variety of compositions, including solids and liquids. PEG 300, propylene glycol, and ethanol are examples of solvents used in co-solvent combinations. To increase meloxicam solubility and dissolution, several concentrations (5-40%) of solid binary systems with polyethylene glycol 6000 were used. Spray freezing of liquids, such as danazol with polyvinyl alcohol, poloxamer 407, and poly vinyl pyrrolidone K-15 in a micronized powder formulation, has also benefited from co-solvency procedures.Pharmaceuticals are always in liquid form. A co solvent method may be appropriate for poorly soluble chemicals that are lipophilic or highly crystalline and have a high solubility in the solvent mixture. When compared to the water solubility of the medicine alone, co-solvents can boost the solubility of weakly soluble substances by thousands of times. 37-40

Advantages:

Formulation and production are simple and quick.

Disadvantages: □

The toxicity and tolerability of the solvent level provided, as with other excipients, must be taken into account. When dilution with aqueous media, uncontrolled precipitation occurs. Amorphous or crystalline precipitates of various sizes can form. Many of the insoluble chemicals Phares works with are unsuitable for intravenous delivery without the use of co-solvents. This is due to the medicines' severe insolubility in water and their inability to rehydrate after precipitation from the co-solvent mixture. Embolism and local adverse effects at the injection site are possible risks in these cases. The chemical stability of the insoluble drug is lower than in a crystalline state, as it is with all solubilized forms.[48]

Case study of various poorly water soluble NSAID Drugs.

Case study No. 1

Nayak AK et al. (2012)

Because solubilization of nonpolar pharmaceuticals is an important challenge in the formulation design of liquid dosage forms, this study compared the effects of three distinct cosolvents, namely PEG 400, PG, and glycerin, on the aqueous solubility enhancement of etoricoxib, a poorly aqueous soluble medication. Etoricoxib had a solubility of 0.0767 0.0018 mg/mL in water, which was considerably improved by adding cosolvents like PEG 400, PG, and glycerin. Less polar solvents were discovered to boost aqueous solubility more, highlighting the hydrophobic interaction mechanism. Of all the solvent-cosolvent mixtures examined, Water-PEG 400 exhibited the best solubilization potential. As a result, the study produced a substantial amount of data that could be used to compare the effects of various variables.[49]

Case study No. 2

Ming-Kung Yeh et al. (2009)

A formulation research was used to create tenoxicam, a weakly water-soluble medicine.The ternary cosolvent solution's solubility has substantially enhanced. A single i.m. injection in a New Zealand rabbit was used to examine the relative bioavailability of the tested formulation. injection. The three-phase diagram for dimethylsulfoxide (DMSO)/propylene glycol/water, DMSO/propylene glycol/water, DMSO/propylene glycol/water, DMSO/propylene glycol/water, DMSO/propylene glyco The ethanol/water and DMSO/polyethoxylated castor oil/ethanol systems were developed. The 5:4:1 volume ratio of DMSO/polyethoxylated castor oil/ethanol generated a more acceptable vehicle than other systems, with a high solubility (20.73 mg/ml) and low viscosity (10.0 Cp). There was also a bioequivalence pharmacokinetic study

(Frel=0.89). The current research not only introduces a novel method for enhancing tenoxicam solubility, but it also advances scientific knowledge.(50)

Case study No. 3

P. R. Sathesh Babu et al. (2008)

Meloxicam and rofecoxib, which are weakly soluble in water, were tried to improve their solubility. Due to their limited water solubility, they are only accessible in solid dosage forms and not in solution dosage forms. The biocompatible solvents ethanol, propylene glycol, glycerin, and PEG 400 were used to increase the water solubility of meloxicam and rofecoxib. The key factors involved in drug dissolution were determined to be physico-chemical features of the solvents, such as intermolecular interactions and the solvent's ability to create a hydrogen bond with the drug molecules. It was discovered that less polarised Solvents were discovered to boost solubility more, emphasising the hydrophobic contact process. The water-PEG 400 solvent blend outperformed the others.(51)

Case study No. 4

Shikha Agrawal et al. (2012)

Celecoxib is a diaryl substituted pyrazole that is nearly water insoluble.Its usage in parenteral and liquid dosage forms is prohibited. This research investigates Hydrotropy and cosolvency were used to improve the solubility of celecoxib.methods to solubilization The hydrotropes piperazine, sodium citrate, and urea, as well as cosolvents PEG, were used in the equilibrium solubility investigations.At various concentrations, PEG 200, PEG 400, PEG 600, DMA, ethanol, and propylene glycol temps. Hydrotrope and cosolvents in parenteral formulations For an accelerated stability research, they were built and studied. The soluble nature of In 3M piperazine solution, celecoxib increased up to 45 times and PEG 600 at 2520 times up to 10232 times

The findings of the solubilization investigation revealed that when piperazine and urea were employed alone, the increase in solubility of celecoxib was lower than when these hydrotropes were combined with cosolvents PEG 600, PEG 400, DMA, and Eth. Stability tests revealed that all of the formulations stored were stable in terms of drug concentration, pH, and physical appearance (colour, precipitation).(52)

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