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SOLUBILITY ENHANCEMENT AND ANALYTICAL TECHNIQUES: A COMPREHENSIVE REVIEW ON IMPROVING BIOAVAILABILITY OF POORLY SOLUBLE DRUGS WITH EMPHASIS ON HPLC

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ABSTRACT: Aqueous solubility refers to a drug's ability to dissolve in water or an aqueous medium, and this property plays a pivotal role in determining its effectiveness. A major challenge in modern drug development is that a large proportion around 70–90% of investigational compounds and approximately 40% of marketed drugs exhibit low solubility. This limitation often results in insufficient absorption, compromised therapeutic action, and the need for higher dosages. To address this, a variety of physical and chemical strategies have been explored, such as reducing particle size, formulating solid dispersions, employing supercritical fluids, using cryogenic processing, and developing inclusion complexes. Other advanced approaches include the use of prodrugs, salt forms, co-crystals, co-solvents, hydrotropes, and pH-based solubility modulation. Additionally, nanotechnology-based systems like liposomes, micelles, dendrimers, nanogels, and nanosuspension have shown promise in enhancing drug solubility. Despite these advances, no universal solution exists, highlighting the ongoing need for simplified and scalable techniques that can broaden commercial applicability.

INTRODUCTION: A solute's temperature-dependent saturation point in a solvent is known as its solubility. The mass of solute that dissolves in 100 grams of solvent is a typical way to express concentration. When assessing how compounds mix equally in specific environmental conditions, this feature is crucial [1]. Once the saturation threshold is reached, any additional solute remains undissolved. Solutions are classified based on their solute concentration into unsaturated, saturated, or supersaturated systems [2].

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The measurement of concentration varies and includes units such as molarity, molality, mass percent, and mole fraction. These solubility principles work whether you're mixing a solid and a liquid, two liquids, or a gas and a liquid [3]. When dealing with liquids or gases mixing together, the term "miscibility" is often used, though it's basically the same idea as solubility. However, just because something is soluble doesn't mean it dissolves quickly [4]. For instance, hydroxypropyl methylcellulose is known for its high solubility in water, yet it dissolves slowly due to extended hydration times. Drug bioavailability depends on several factors: the release rate of the drug from its formulation, the efficiency of its absorption once dissolved, and metabolic transformations during absorption. All these factors must be optimized to ensure therapeutic efficacy [5].

TABLE 1: USP AND BP SOLUBILITY CRITERIA [6]

Class	Parts of solvents required for one part of solute (in ml)
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 10,000
Insoluble	10,000 and Over

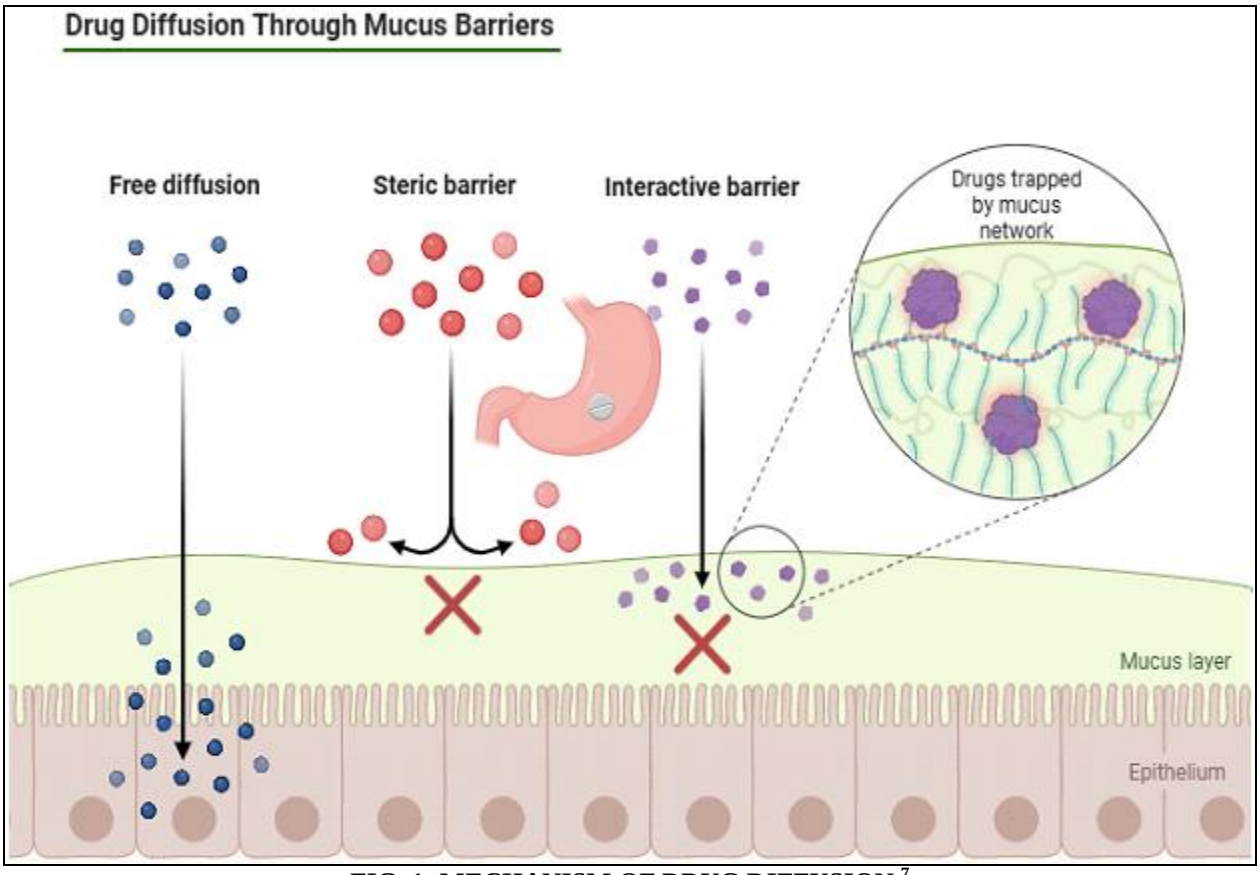

FIG. 1: MECHANISM OF DRUG DIFFUSION [7]

Factors Affecting Solubility: The solubility of a solid is affected by its physical structure, as well as characteristics of the solvent (its type and composition), the temperature of the system, and the pressure.

TABLE 2: FACTORS AFFECTING SOLUBILITY

Factor	Effect on Solubility
Particle Size	Smaller particles have higher surface area, allowing better interaction with the solvent and improving apparent solubility[8].
Temperature	Solubility of solids generally increases with temperature if the process is endothermic; gas solubility decreases as temperature rises[9].
Pressure	Increases gas solubility with higher pressure; has negligible effect on solids and liquids[9].
Solvent and Solute Characteristics	Chemical properties determine solubility; e.g., zinc chloride dissolves more in water than lead(II) chloride due to their different chemical nature[9].
Molecular Size	Larger or heavier molecules are less soluble; however, branching in organic compounds can enhance solubility[9].
Polarity	Dipole-dipole interactions allow polar solutes to dissolve readily in polar liquids. In a similar vein, non-polar solvents dissolve non-polar solutes better[9].
Polymorphism	Different crystal forms of the same substance can have varying solubility's due to structural differences in the crystal lattice[9].
Stirring	Agitation increases solubility by exposing fresh solvent to the solute, enhancing the dissolution rate[9].

Bioavailability: The pace and quantity of an active ingredient in a medication that enters the bloodstream and reaches the site of action is measured by its bioavailability. It is primarily impacted by the drug's release from the dosage form, absorption through the gastrointestinal tract, and metabolism prior to entering the bloodstream [10]. Drugs are categorized into four types by the Biopharmaceutics Classification System (BCS) according to intestinal permeability and solubility **Table 3**. This helps guide the development of drug formulations. A good example is BCS Class II drugs. Because they don't dissolve well but are easily absorbed, special formulation methods are often needed to improve their oral absorption [10].

Effective oral formulations are essential for ensuring consistent and efficient drug uptake in the gastrointestinal tract. To improve how poorly soluble drugs work, formulators often use a variety of methods.

These Include: Reducing particle size through micronization and nanosizing. Modifying the crystal structure of the drug. Creating solid dispersions (distributing the drug within a carrier). Forming inclusion complexes, often with cyclodextrin Using lipid-based delivery methods, like self-emulsifying drug delivery systems (SEDDS) or liposomes. Many of these strategies rely on Generally Recognized As Safe (GRAS) excipients to streamline development and regulatory approval [11].

Ultimately, the selection of a suitable enhancement technique depends on multiple factors, including the physicochemical properties of the drug, the desired dosage form, and compatibility with excipients. Time-tested methods such as solid dispersion, particle size reduction, and complexation remain foundational in tackling solubility challenges [12].

TABLE 3: CLASSIFICATION OF DRUGS USING BIOPHARMACEUTICAL [9]

BCS Class	Solubility/ permeability	Problems	Drug Molecules Examples
Class I	High solubility High permeability	Enzymatic degradation, gut wall efflux	Mefloquine hydrochloride, Nelfinavir mesylate, Quinine sulphate, Clomiphene citrate
Class II	Low solubility High permeability	Solubilization and bioavailability	Ibuprofen, Nifedipine, Carbamazepine, Diazepam, Efavirenz
Class III	High solubility Low permeability	Enzymatic degradation, gut wall efflux, Bioavailability	Cimetidine, Acyclcovir, Atenolol, Metformin, Gabapentin, Ranitidine, Neomycin
Class IV	Low solubility Low permeability	Solubilization, enzymatic degradation, gut wall efflux and bioavailability	Acetazolamide, Dapsone, Doxycycline, Nalidixic acid, Theophylline

Necessity of Accurate Analytical Techniques like HPLC to Assess Drug Release and Absorption:

Precise Measurement of Low Concentrations: Low-solubility drugs dissolve poorly in aqueous environments, leading to low measurable concentrations. Accurate detection using sensitive methods like HPLC is crucial to avoid underestimating drug release [13].

Reliable Assessment of Formulation Performance: To improve the dissolution and absorption of poorly soluble medications, formulation strategies such as solid dispersions, nanoparticles, and inclusion complexes are employed.

To properly evaluate drug release over time, precise analytical techniques are necessary [13].

Understanding Pharmacokinetics and Bioavailability: Drug dissolution significantly influences its absorption and bioavailability. Precise plasma concentration measurements are vital for accurate Cmax and AUC values, which guide proper dosing [13].

Comparative Analysis across Formulations: When assessing solubility-enhancing formulations, sensitive analytical methods are crucial for detecting variations in drug release and absorption profiles. These precise techniques ensure valid comparisons and statistically significant conclusions that support formulation optimization decisions [13].

Quality Control and Regulatory Compliance: Regulatory approval of drug formulations demands

precise analytical data to ensure reliability. Accurate testing is critical for quality control and meeting FDA standards [13].

Solubility Enhancement Techniques: Oral drug delivery is preferred for convenience, but poor solubility especially in BCS Class II drugs limits absorption and bioavailability in over 40% of new drugs. This review outlines solubility enhancement strategies through physical, chemical, and alternative approaches, emphasizing the role of analytical tools like HPLC [14].

Physical Modification: Solubility enhancement through physical means involves particle size reduction (e.g., micronization, nanosuspension) to increase surface area and dissolution rate.

Techniques like eutectic mixtures, solid dispersions, and cryogenic methods further improve drug solubility by altering physical structure.

Chemical Modifications: Solubility enhancement can be achieved through pH modification, salt formation, co-crystallization, prodrug design, carrier systems like cyclodextrin, micelles, lipid films, and advanced platforms like nanocrystals, liposomes, and supercritical fluid techniques.

Particle Size Reduction: Various methods are used to lower the particle sizes of natural substances, potentially increasing their surface area. A higher surface area could eventually lead to better aqueous solubility [15]. The bioavailability of poorly soluble medications is directly impacted by the drug powder's primary molecular size. Because of the increased surface area brought about by the reduction in particle size, the dissolving properties are further enhanced by the larger area of contact with the solvent. Reduced particle size also makes it possible for the solvent to diffuse quickly. The particle size of drug raw materials is decreased using milling methods such rotor-stator colloid mills, jet mills, and other mill types [15]. A study by Charoenchaitrakool *et al.* (2000) found that employing a micronization approach in conjunction with rapid expansion of supercritical fluids greatly increased the solubility of the racemic form of ibuprofen by around 60% [16]. Similar to this, Sievers *et al.* (2003) found that micronization increased the solubility of both natural and synthetic medications, and they hypothesized that this method would make them more suitable for pulmonary delivery. In a separate study, the author explained how supercritical solution expansion decreased particle size and enhanced salicylic acid and taxol solubility. Furthermore, the author asserted an inverse relationship between micronization and particle size and temperature. Additionally, it has been demonstrated that the method has no impact on the chemical composition of the substances [17]. Particles can be uniformly sized and have their diameter down to less than 5 m by using micronization processes. The properties of the final micronised pharmaceutical substance can be affected by a number of micronization processes, including as milling, supercritical fluid technology, micro-precipitation and micro-crystallization, and spray freezing into liquid [17].

Solid Dispersion: Sekiguchi and Obi initially proposed the concept of solid dispersions when they investigated the preparation and dissolution behavior of sulfonamide eutectic mixtures. During the early 1960s, they used a drug blended with a water-soluble carrier to study this method [18]. A useful formulation method for enhancing the rate of dissolution, absorption, and overall therapeutic activity of poorly soluble drugs is the application of solid dispersions. A hydrophilic carrier matrix and a water-poorly soluble drug are typically the two key elements of such systems. Polyethylene glycols (PEGs), Plasdone S-630, and polyvinylpyrrolidone (PVP) are some of the most widely employed carriers. In addition to improving the solubility and dispersion of drugs, surfactants like Tween 80, sodium lauryl sulfate (SLS), Pluronic F68, Myrj 52, and docusate sodium are also often incorporated. This technique helps facilitate greater bioavailability and better reproducibility of drug release [19, 20].

Solid dispersions, which are a mixture of a drug and a hydrophilic carrier, can improve the solubility in water of poorly soluble drugs such as ritonavir, celecoxib, and halofantrine by a large margin. Ritonavir, for example, is enhanced in dispersion with Gelucire, whereas celecoxib is improved in solubility by polyvinylpyrrolidone (PVP). There are various techniques to achieve solid dispersions to enhance the dissolution and bioavailability of hydrophobic drugs [21].

Hot-Melt Method (Fusion Method): The direct melting method's simplicity and affordability are two of its main advantages. This method was created to produce solid dispersions with improved drug release characteristics and was first presented by Sekiguchi and Obi. This method involves melting a drug and a water-soluble carrier together by heating them. The melted mixture is then quickly cooled, often in an ice bath, while being stirred well. The resulting solid is then broken down, sieved to the correct particle size, and mixed with other ingredients before being made into tablets. The type of carrier utilized and the amount of drug in the combination are two examples of parameters that affect the melting behavior of the resulting binary system [18].

Solvent Evaporation Method: Tachibana and Nakamura pioneered a technique for creating solid solutions by first dissolving both the active drug and a suitable carrier in a shared solvent. The solvent is then removed under vacuum, leaving the solid solution [18]. They demonstrated the effectiveness of this method by successfully encapsulating the highly water-repelling β-carotene within the water-loving polymer povidone. Subsequently, numerous research groups have explored solvent evaporation approaches for preparing solid dispersions containing poorly water-soluble compounds including naproxen, meloxicam, and nimesulide. These investigations demonstrate that the technique effectively addresses both solubility enhancement and stability improvement challenges associated with hydrophobic pharmaceutical compounds [22].

A primary advantage of the solvent evaporation methodology lies in its capacity to prevent thermal degradation of temperature-sensitive active ingredients or pharmaceutical excipients through low-temperature processing conditions. Nevertheless, the technique encompasses several limitations, including elevated manufacturing expenses, difficulties in achieving complete removal of residual organic solvents presenting potential regulatory compliance issues and possible adverse effects of trace solvent remnants on drug chemical integrity. Further constraints involve the requirement for identifying mutually compatible volatile solvents suitable for both drug and carrier dissolution, along with challenges in maintaining consistent polymorphic control during processing [22].

Hot Melt Extrusion: Hot-melt extrusion is a modification of the fusion process, characterized by the vigorous mixing effect afforded by the extruder. Like the conventional fusion technique, drug-carrier matrix compatibility is still a possible drawback. Moreover, the intense shear forces in the extruder can cause localized heat generation, which may be hazardous for thermolabile compounds. Despite these drawbacks, hot-melt extrusion offers several advantages, such as its compatibility with continuous manufacturing, which makes it highly suitable for large-scale production. In addition, the extrudate could be directly shaped or processed without preliminary milling, enhancing the overall manufacturing process [19].

Evaluation Parameter of Solid Dispersion:

Phase Solubility Study: To perform this experiment, you start by adding extra drug to a water-based solution containing different amounts of a carrier. This mixture is placed in a flask and shaken in a temperature-controlled water bath at 37°C. After enough mixing, the solution is filtered, and the filtered liquid is diluted. Finally, the diluted samples are analyzed using a spectrophotometer at the correct wavelength for the specific drug being tested [21].

Drug Content: This method involves dissolving a known quantity of the solid dispersion in an appropriate solvent, followed by dilution. The amount of drug in the solution is then determined using either UV spectrophotometry or High-Performance Liquid Chromatography (HPLC). For accurate measurements, a calibration curve is created by plotting the instrument's response (peak area) against known drug concentrations [21].

Powder X-ray Diffraction Studies: An X-ray diffractometer is used in the powder X-ray diffraction (PXRD) technique to examine the structure of crystalline materials. It functions by aiming an X-ray beam at a crystal, which scatters the rays in various ways. A three-dimensional picture of the electron density in the crystal is produced by the diffractometer using the angles and intensities of the scattered X-rays. Atomic

locations, chemical bonding, and other structural details can be deduced from this picture [20].

Dissolution Studies: The USP paddle method is used to evaluate the solid dispersion's dissolution at 100 rpm in either distilled water or 0.1N HCl while the mixture is kept at 37 ± 0.2°C. Five millilitre samples are collected at 5, 10, 15, 30, 35, 60, and 100 and 20 min. Every sample is promptly swapped out for five millilitres of brand-new dissolving medium. A 0.45-µm membrane syringe filter is then used to filter the samples. Finally, UV spectrophotometry at the proper wavelength is used to determine the amount of medication released [22].

Cryogenic Technology: Cryogenic methods are employed to improve drug dissolution by producing nanostructured, amorphous particles with a highly porous structure, formed under extremely low temperature conditions [23]. Classification of cryogenic technologies considers factors like the injection system used (e.g., capillary, rotary, pneumatic, or ultrasonic nozzles), the nozzle's placement (above or below the liquid surface), and the type of cryogenic fluid employed (e.g., hydrofluoroalkanes, nitrogen, argon, oxygen, or organic solvents). A common outcome of cryogenic processing is the production of a dry powder, achieved through techniques such as spray freeze-drying, air freeze-drying, vacuum freezedrying, or lyophilization [24].

Spray Freezing onto Cryogenic Fluids: Briggs and Maxwell introduced the technique of spray freezing with cryogenic liquids. In this method, the medication of interest is dissolved in an aqueous solution that also contains a carrier material. Examples of suitable carrier materials include mannitol, maltose, lactose, inositol, and dextran. After that, the resultant solution is atomized on top of a boiling fluorocarbon-based refrigerant that is being vigorously agitated. To enhance the distribution of the sprayed droplets within the cryogenic medium, a sonication probe may be used to assist dispersion during the process [24].

Spray freezing into cryogenic fluids (SFL): Spray-freezing into liquid (SFL) technology has been applied to generate amorphous, nanostructured drug particles that exhibit a large surface area and enhanced wettability, contributing to improved dissolution characteristics [25]. This method enhances atomization by enabling direct liquid–liquid collision between the cryogenic medium and the feed solution, resulting in the formation of micro-droplets and achieving extremely rapid freezing. The frozen droplets are then subjected to lyophilization to obtain dry, free-flowing micronized powder. Using this spray freezing technique, researchers successfully developed highly potent and rapidly dissolving granules of Danazol [24].

Spray Freezing into Vapour Over Liquid (SFV/L): In spray freezing with vapour over liquid (SFV/L), atomized droplets of a drug solution typically freeze in the vapour phase of the cryogenic fluid. This rapid freezing leads to solvent removal, resulting in fine drug particles with improved wettability. The freezing process causes super saturation of the drug in the remaining freezable regions, which then drives the nucleation and growth of these fine particles [24].

Ultra-Rapid Freezing (URF): Cryogenic ultra-rapid freezing rapidly solidifies drug solutions on a chilled surface, generating nanostructured drug particles. These particles possess an increased surface area, and their solubility is further enhanced through lyophilization to remove the solvent. This method inhibits crystallization and phase separation, encouraging the formation of amorphous solid dispersions, which is particularly beneficial for poorly soluble medications like rapaglinide [26].

Salt Formation: The dissolution rate of a drug salt often differs from that of its original compound. For instance, sodium and potassium salts of weak acids generally dissolve more quickly than their non-salt counterparts. However, salt formation has certain drawbacks, such as the potential to cause gastric irritation due to increased alkalinity, sensitivity to moisture and carbon dioxide in the air which can lead to precipitation and challenges related to patient tolerability and commercial viability [26].

Co-crystallization: Co-crystallization alters molecular interactions and serves as a promising alternative for enhancing drug properties. A more precise definition of a co-crystal is a

"multicomponent crystal formed between two compounds that are solids under ambient conditions, where one or more components is an acceptable ion or molecule." the technique of co-crystallization allows for the circumvention of certain shortcomings associated with an active pharmaceutical ingredient (API), be they physical, chemical, or physiological in nature. Co-solvency, a phenomenon characterized by the reduction of interfacial tension, aids in the dissolution of non-polar solutes that might otherwise be difficult to solubilize.

Selection of the most suitable co-crystal candidate is achieved through a combination of analytical methodologies and rational physicochemical evaluations, encompassing assessments of both solubility and stability. The critical distinction between solvates and co-crystals resides in the physical state of their constituent components: a solvate is defined by the presence of one liquid and one solid component, whereas a co-crystal is characterized by the presence of two solid components. In essence, pharmaceutical co-crystals are composed of two elements: the API itself, and the co-crystal former(s) that facilitate the co-crystallization process [27].

Prodrug Design: Prodrugs can be broadly divided into two categories: carrier-linked prodrugs and bioprecursors. Two types of carrier-linked prodrugs exist: bipartite prodrugs, where the carrier is directly bonded to the primary drug, and tripartite prodrugs, where a spacer molecule links the carrier to the parent drug [28]. Employing prodrugs is a successful strategy for boosting solubility, attracting significant interest in pharmaceutical research. Numerous prodrug formulations have been developed to enhance the solubility and dissolution of natural compounds. For instance, research by Kim *et al.* (2009) illustrated the transformation of Quercetin a natural flavonoid (3,3',4',5,7-pentahydroxyflavone) into a prodrug form called 3-n-n-dimethyl carbamoyl quercetin. This alteration not only increased the compound's solubility but also augmented its anticancer properties, as the modified form exhibited stability against hydrolysis in cell culture media [28]. Polyethylene glycol (PEG), and α-tocopherol polyethylene glycol succinate (TPGS) to create a polymer-based prodrug formulation. Their results showed that TXA9's solubility and anticancer efficacy were greatly enhanced by this formulation, especially when treating lung cancer [28].

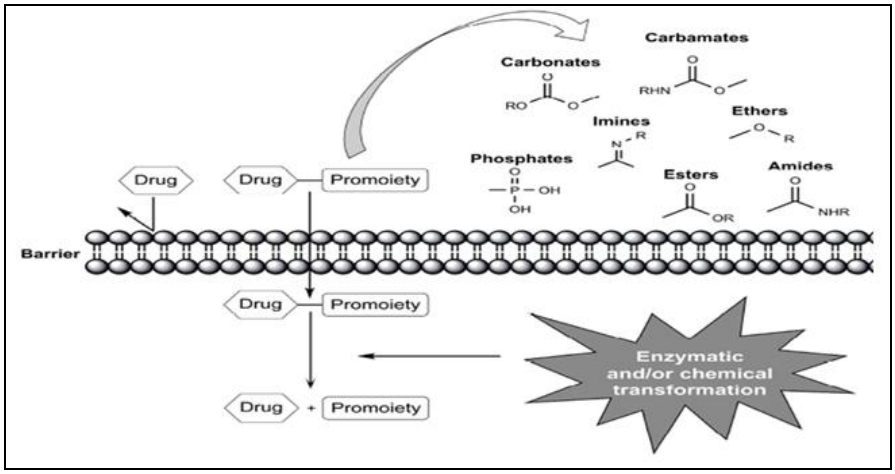

FIG. 2: *IN-VIVO* BIOACTIVATION OF PRODRUGS BY ENZYMATIC AND CHEMICAL TRANSFORMATION [28]

Cyclodextrin Complexes: Among the various methods used to raise the aqueous solubility, dissolving rate, and bioavailability of drugs with low water solubility, the formation of inclusion complexes is one of the most effective strategies to improve solubility. These combinations are created when a guest, which is a nonpolar molecule or a nonpolar portion of a molecule, fits into the cavity of the host, which is another molecule or collection of molecules. The most popular host molecule for this is cyclodextrin. They are created when cyclodextrin glycosyltransferase (CGT) breaks down starch enzymatically, producing cyclic oligomers called cyclodextrin (CDs). With an outer hydrophilic cavity and an inner hydrophobic cavity, the doughnut-shaped toroidal structure of these crystalline, water-soluble, non-reducing cyclic oligosaccharides is composed of glucose units.

There are three types of cyclodextrins: α-, β-, and γ-cyclodextrin. The following is a brief summary of the various methods that have been developed to create inclusion complexes between cyclodextrins and weakly water-soluble medications [29].

Kneading Method: To create a paste, cyclodextrin is moistened with a little amount of water or a hydroalcoholic solution. After adding the drug to this paste, the mixture is kneaded for a predetermined amount of time. The mixture is kneaded, dried, and sieved if needed. Although a mortar and pestle are often used in a laboratory environment for this process, extruders and other instruments are used in an industrial setting [30].

Lyophilization/Freeze-Drying Technique: For the formation of porous, amorphous inclusion complexes with potent drug–cyclodextrin interactions, the lyophilization (freeze drying) technique works well. A drug-CD solution is frozen, and the solvent is extracted with less pressure. This method works well for medications that are sensitive to heat, but it takes a lot of time and specialized equipment, and it frequently results in powders with poor flow characteristics [31].

Microwave Irradiation Method: Using a microwave irradiation method involves the drug and cyclodextrin are reacted in a particular molar ratio in the microwave irradiation method. They are heated for a short time, usually one to two minutes at 60°C, after being dissolved in a mixture of water and organic solvent. The precipitate that results from the reaction is filtered and vacuum-dried after further solvent is applied to eliminate any uncomplexed components. This method's quick processing time and excellent yield make it effective for large-scale production [32].

Polymeric Micelles: Amphiphilic block copolymers self-assemble to create polymeric micelles, which are efficient nanocarriers with a hydrophilic shell that stabilizes the structure in aqueous settings and a hydrophobic core that solubilizes poorly water-soluble medications. This enhances drug solubility and stability by protecting sensitive molecules from degradation. Camptothecin (CPT), a drug with an active lactone form prone to hydrolysis, benefits significantly from encapsulation in polymeric micelles [33].

For instance, CPT loaded into N-phthaloylchitosan-grafted PEG methyl ether (PLC-g-MPEG) micelles showed sustained release over 96 hours and protected the lactone form, extending its half-life from 94 minutes to 76.15 hours in biological fluids. Similarly, Pluronic-poly(acrylic acid) (Pluronic-PAA) micelles prevented hydrolysis for up to 2 hours at pH 8 and increased CPT's half-life from 0.16 hours to 1.1–1.7 hours in serum. These micelles improve CPT's therapeutic efficacy and reduce toxicity by stabilizing its active form and enabling controlled release [34].

Lipid Based Systems: There is increasing demand for efficient drug-carrier systems to advance drug delivery through improved control, targeting, and efficiency. Lipid-based drug delivery systems (LBDDS) assist in bypassing the prevalent problem of poor dissolution of poorly soluble drugs. The systems encourage the evolution of solubilized drug structures in the gastrointestinal tract upon digestion to allow improved absorption [35].

Class I systems are oil solutions that only contain mono, di, and/or tri-glycerides and no surfactants. Lipophilic surfactants are added to the oil phase of Class II systems in order to improve the encapsulated medicines' solubility in the systems and to support emulsion stability during dilution. SEDDS is another name for these LBDDS. Class III SMEDDS are produced by combining hydrophilic additives (surfactants and/or co-solvents) with the oil phase. Class IV, the most aquatic members of the class, consists of systems composed of hydrophilic co-solvents and surfactants that, when diluted with aqueous media, create a colloidal micellar dispersion. LBDDS techniques for improving medication bioavailability include increased solubilization, prolonged stomach retention, and integrated medications [36], biochemical barrier changes [37], physical barrier changes [37], stimulation of, intestinal lymphatic transport [37].

Nanocrystals: Nanocrystals, solid drug particles typically under 100 nm, have significantly advanced nanoscience since the 1980s Unlike other delivery systems, they consist entirely of the active pharmaceutical ingredient, stabilized by surfactants or polymer-based agents [38]. Their small size increases surface area, enhancing solubility,

dissolution rate, and membrane affinity especially for BCS Class II and IV drugs. Though termed "crystals," their structure can be crystalline, partially crystalline, or amorphous depending on manufacturing methods like precipitation. When dispersed in a liquid, they form nanosuspensions requiring stabilizers to prevent aggregation. The term "amorphous nanocrystals," while technically incorrect, is often used informally. Nanocrystals offer advantages like high drug loading, controlled release, reduced risk of dose dumping, and improved bioavailability [39]. Their production is relatively simple, making them suitable for formulating poorly water-soluble drugs. This nanosizing approach plays a pivotal role in overcoming biopharmaceutical limitations, ensuring more efficient drug delivery and therapeutic effectiveness across various pharmaceutical applications [40].

Liposomes: Liposomes are microscopic vesicles composed of phospholipid and cholesterol bilayers that were created as medication delivery vehicles in the 1970s. Both hydrophilic and lipophilic medications can be encapsulated in their lipid layers and aqueous core, respectively. They were first fashioned after cell membranes [41]. Peptides, polymers, and antioxidants like tocopherol can be added to lipid vesicles to enhance targeting and improve stability.

Based on size and structure, liposomes are categorized as small unilamellar vesicles (20–100 nm), large unilamellar vesicles (>100 nm), and multilamellar vesicles (>500 nm) [40]. Encapsulating drugs in liposomes shields them from enzymatic degradation and can lower toxicity. Liposomes are biocompatible, biodegradable, and non-immunogenic, capable of carrying lipophilic drugs and allowing physicochemical modifications for controlled delivery [41]. Liposomes are used to enhance drug stability, improve cellular uptake, and enable targeted delivery. However, their use is limited by issues such as short shelf life, low stability, rapid clearance by the reticuloendothelial system, and limited drug encapsulation efficiency [42].

Supercritical Fluid Techniques: Particle size reduction utilizing supercritical fluid (SCF) technology is a new method for nano-sizing and improving solubility that has gained popularity recently. Supercritical fluids, which have characteristics of both liquids and gases, exist at pressures and temperatures higher than their critical points. SCFs are extremely compressible close to their critical temperature, and even slight pressure variations can have a big impact on their solvent capabilities and density [43]. Medications dissolved in supercritical carbon dioxide (SCFs) have the ability to recrystallize into considerably smaller particles. Particles in the submicron range are frequently produced with this approach, which allows for exact control over particle size. Suspensions of nanoparticles with sizes ranging from 5 to 2,000 nm can be produced using current SCF methods. SCF-based particle engineering is being actively used by pharmaceutical companies such as Lavipharm Therapeutics to decrease particle size and increase solubility. Supercritical antisolvent (SAS), solution-enhanced dispersion by SCF (SEDS), gas antisolventre crystallisation (GAS), rapid expansion of supercritical solutions (RESS), precipitation with compressed antisolvent (PCA), and aerosol supercritical extraction system (ASES) are a few of the SCF techniques that have been developed [44].

Role of Analytical Techniques in Evaluation of Solubility and Bioavailability:

High Performance Liquid Chromatography: An improved analytical method for separating, identifying, and quantifying components in complicated mixtures was created in the late 1960s: High-Performance Liquid Chromatography (HPLC). It works by running a liquid sample through a stationary phase-filled column, which separates the components according to how they interact with the stationary and mobile phases, producing different retention durations [45]. HPLC is appropriate for a wider range of chemicals than Gas Chromatography (GC) since it can evaluate non-volatile and thermally unstable molecules. Pharmaceuticals, biotechnology, environmental monitoring, and food safety all make extensive use of HPLC for activities including contaminant identification and drug purity evaluation. Because of its accuracy and adaptability, HPLC is now a fundamental component of contemporary analytical labs [45].

Application in Solubility and Drug Release Studies:

Quantitative Determination of Drug Solubility: HPLC is commonly employed to determine the equilibrium solubility of drugs in different solvents, oils, surfactants, and bio relevant media like FaSSIF and FeSSIF. This analysis is essential for evaluating drug solubility under physiological conditions, aiding in effective formulation design [46].

Method Validation and Specificity: HPLC methods are developed and validated following regulatory standards, such as ICH guidelines, to ensure specificity, accuracy, precision, linearity, LOD, and LOQ. For instance, a validated reverse-phase HPLC method was utilized to evaluate the solubility of Gefitinib in different oils and surfactants, providing accurate results with a retention time of approximately 4.78 minutes [46].

Detection of Impurities and Degradation products: Unlike simpler methods such as UV spectroscopy, HPLC can separate and detect impurities or degradation products, ensuring that solubility measurements reflect the truce concentration of the intact drug molecules [46].

Assessment under Physiological Conditions: Using biorelevant media in combination with HPLC enables simulation of *in-vivo* conditions, such as assessing the impact of food on drug solubility by comparing results in FaSSIF and FeSSIF [46].

Quantification of Drug Release from Formulation: HPLC is utilized to evaluate drug release profiles from a range of dosage forms, including tablets, nanoparticles, ethosomes, and lipid-based carriers. It ensures quick and reliable determination of drug concentrations in the dissolution medium over time [46].

Evaluation of Drug Entrapment Efficiency and Content: HPLC is used in formulations like ethosomes to quantify drug entrapment efficiency and total drug content. These measurements are vital for assessing and refining the performance of the drug delivery system [46].

Kinetic Modelling of Drug Release: Drug release data obtained through HPLC can be applied to various kinetic models, such as zero-order and first-order, to interpret the release mechanism and forecast *in vivo* performance [46].

Method Development and Validation: The suitable chromatographic parameters, including temperature, flow rate, detection wavelength, stationary phase (column), and mobile phase composition. Achieving ideal peak form, high sensitivity, constant repeatability, and successful separation were the goals. To ensure proper retention periods, resolution, and peak symmetry for the analyte as well as any possible contaminants or degradation products, optimization entails adjusting parameters [47].

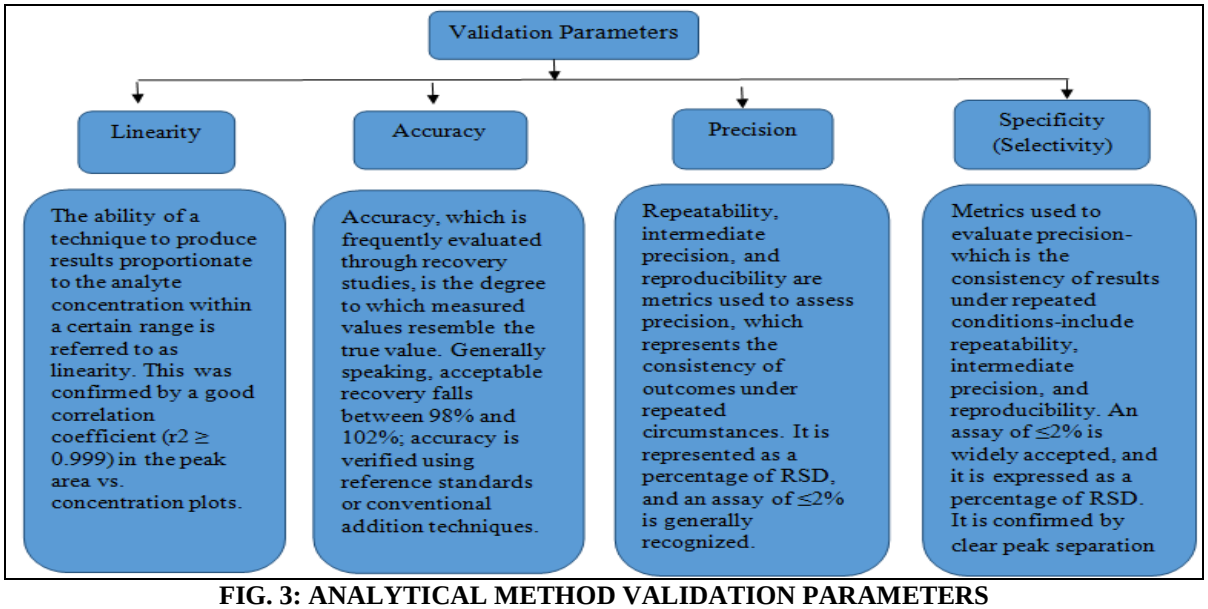

FIG. 3: ANALYTICAL METHOD VALIDATION PARAMETERS

Retention Time: The amount of time it takes for a compound to move through the chromatographic column and be measured is known as the retention time. The way the analyte, stationary phase, and mobile phase interact determines this. In reversed-phase HPLC, a higher polarity of the mobile phase results in a longer retention time, whereas a lower polarity has the opposite effect. Changing the polarity of the mobile phase will also impact retention time. Retention time can also be increased by modifying the flow velocity, column temperature, and stationary phase characteristics such particle size and column length [47].

Mobile Phase Optimization: Optimizing the mobile phase is essential for controlling analyte retention and selectivity in HPLC. Key factors include the proportion of aqueous to organic solvents, pH, and buffer strength, which influence analyte ionization and interactions with the stationary phase. Buffers and additives like phosphate, formic acid, or trifluoroacetic acid help maintain pH and enhance peak shape. Adjusting solvent strength can fine-tune retention time and improve resolution [47].

Wavelength Selection Criteria: In HPLC with UV detection, wavelength selection is guided by the analyte's absorbance profile. Choosing the wavelength at or near the analyte's maximum absorbance (λmax) enhances sensitivity and detection. This approach improves the signal-to-noise ratio and ensures accurate quantification, which is especially important when analyzing complex mixtures [48].

UV-Visible Spectrophotometry:

Derivative Spectroscopy: Derivative spectroscopy improves selectivity by converting absorbance spectra into their derivatives to resolve overlapping peaks. The first derivative shows absorbance change with wavelength, while higher-order derivatives enhance spectral detail. It minimizes background interference, improving sensitivity for trace detection. Smoothing techniques like Savitzky-Golay filtering reduce noise, making it valuable in pharmaceutical and multicomponent analysis [49].

Area under the Curve (AUC) Method: The AUC method quantifies analytes by integrating absorbance over a wavelength range, ideal for broad or overlapping peaks [50]. It enhances robustness against baseline noise and spectral drift, enabling simultaneous estimation of multiple compounds. This method shows good linearity, accuracy, and precision, aligning with ICH validation standards [49].

Comparison with HPLC: Both HPLC and UV-Visible spectrophotometry are very common in pharmaceutical and analytical chemistry. The UV-Vis techniques, such as derivative spectroscopy and AUC, are characterized by simplicity, speed, cost, and convenience without needing to employ complex sample preparation procedures or costly solvents. They are sufficiently sensitive and precise for most routine quality control tests [51]. Nevertheless, HPLC offers greater specificity and precision by actually purifying analytes from impurities, excipients, and degradation products. The chromatographic separation eliminates interference to a high degree, producing more accurate quantitation, particularly in complicated matrices where interfering impurities impair UV absorbance. HPLC assays generally have wider linear ranges and lower detection and quantitation limits than UV-Vis [52].

Case studies reveal that although UV-Vis methods can agree well with HPLC data in uncomplicated formulations, UV-Vis tends to overestimate concentration in samples containing more than one impurity because of absorbance interference, which restricts it in such situations. HPLC is used for complicated samples, extended-release drug delivery systems, and biological matrices because of its excellent resolution and capability to cancel out impurity effect [49].

Comparative Evaluation of Techniques:

Efficiency:

Physical Modification: Improve solubility mainly through enhanced dissolution rate and surface area methods such as micronization and nano suspensions enhance bioavailability considerably, though they do not generally alter equilibrium solubility. Solid dispersions enhance dissolution and solubility by dispersing drugs in hydrophilic carrier [53].

Carrier Complex Technologies: Cyclodextrin inclusion complexes and micellar solubilization improve solubility by forming host-guest systems that increase drug stability and solubility. These methods are widely used for poorly soluble drugs, offering enhanced dissolution and improved bioavailability [53].

Scalability: Physical Modification: Hot-melt extrusion is a scalable technique commonly used in pharmaceutical manufacturing. While micronization and nanosuspension methods are also adaptable to large-scale production, they often demand high-end equipment and strict process control, which can increase cost [54].

Chemical Modification: Salt formation and the use of co-solvents are typically easy to scale up for industrial production. However, more complex chemical modifications can present challenges in synthesis and may encounter regulatory hurdles that limit their scalability [55].

Carrier Complex Technologies: Techniques such as kneading and microwave-assisted processing are suitable for scale-up. Freeze-drying is also scalable but involves higher time and cost investments. Cyclodextrin complexation can be scaled effectively, though it demands careful control of processing conditions [53].

Analytical Complexity:

Physical Modification: These techniques necessitate analysis of particle size and shape using methods like microscopy or laser diffraction, along with solubility and dissolution testing. Solid-state characterization tools such as DSC and XRD are also essential to confirm uniformity and functional performance [56].

Chemical Modification: Key analytical challenges involve verifying the chemical identity, purity, polymorphic forms, and stability of salts or chemical derivatives. Additionally, reliable methods are required for assessing pH, solubility, and dissolution profiles [56].

Carrier Complex Studies: These methods are complex as they require validation of complex formation, stoichiometry, stability, and interaction mechanisms. Analytical tools like NMR, DSC, FTIR, and chromatography are employed for detailed characterization [53].

Case Studies and Marketed Formulations: A popular technique for reducing particle size, micronization significantly enhances the absorption and dissolving of medications that are not very soluble in water. Drugs with poor water solubility, such as griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate, have been effectively micronized. With smaller particle size, more surface area is available for dissolution, allowing more efficient and quicker absorption from the gastrointestinal tract. For example, micronization of fenofibrate showed a spectacular enhancement of dissolution from 1.3% to 20% in 30 minutes in biorelevant media, an over 10-fold increase. Such enhanced dissolution translated linearly into improved oral bioavailability and therapeutic efficacy. Likewise, micronization of griseofulvin resulted in increased plasma levels and enhanced antifungal activity. Micronization of progesterone increased its therapeutic effect in hormone replacement therapy. Diosmin and spironolactone similarly displayed enhanced pharmacokinetics after micronization, affirming the utility of this method for BCS Class II drugs [57].

ICH Q2 (R1) Guidelines for Method Validation: Analytical data must be reliable and fit for its intended purpose to support sound decision-making. Analytical method validation follows a life cycle approach involving three key steps: procedure design, performance qualification, and continual verification [52].

Revalidation becomes necessary under certain changes, such as new drug potency, lab transfer, process modifications, or updated specifications, as per ICH Q10, Q6A, and Q6B.The Analytical Target Profile (ATP) supports Quality by Design (QbD) in method development by defining the method's objective and performance criteria, much like the Quality Target Product Profile (QTPP) in ICH Q8(R2) [58].

Techniques should ideally be independent of specific instruments to enable seamless technology transfer, provided that equipment qualification is upheld. ICH Q2(R1) lists several important validation factors, including specificity, accuracy, precision, repeatability, intermediate precision, reproducibility, detection and quantitation limits, linearity, range, and robustness. These general

guidelines guarantee that analytical techniques are exact, accurate, and appropriate for the purposes for which they are designed for both small and large molecules [59].

Regulatory and Quality Considerations:

ICH and USFDA Guidance on Analytical Validation:

Noncompendial Analytical Procedures: Validation of analytical methods ensures the process is reliable and fit for its intended use. Clear scientific understanding of the method's purpose and approach is essential before starting validation. Method development and optimization typically establish this clarity.

Validation must be performed using qualified instruments and following cGMP-compliant procedures. The protocol should define justified acceptance criteria for each validation parameter, covering both drug substances and products in relevant matrices [60].

Validation Characteristic: Analytical method validation focuses on key parameters like specificity, linearity, accuracy, precision, range, and sensitivity, guided primarily by ICH Q2(R1) and FDA recommendations. Stability-indicating methods must detect changes over time using spiked, stressed, and aged samples to ensure specificity. NDA, ANDA, or BLA holders must provide data confirming method reliability and notify the FDA of significant changes [60].

Compendial Analytical Procedures: Analytical procedures from USP/NF or AOAC must be verified under actual conditions using a protocol that includes the method, acceptance criteria, and detailed parameters. Verification identifies necessary validation characteristics like specificity, LOD, LOQ, accuracy, and precision, which may vary with internal specs or formulation changes. Robustness testing is not needed if the compendial method is unchanged. Verification data must be included in regulatory submissions [60].

GMP/GLP Compliance in Analytical Procedures:

Regulatory Foundation: Governed under 21 CFR parts 210 and 211 in the U.S., GMP requires documented procedures, qualified instruments, and validated analytical methods to ensure reproducibility and accuracy [61].

Documentation and Records: Analytical test methods must be well-documented with detailed SOPs covering scope, equipment, reagents, sample preparation, system suitability criteria, calculations, and data reporting to enable reproducibility and audit readiness

Method Validation: Analytical methods must be validated per ICH Q2(R1/R2) guidelines, demonstrating specificity, accuracy, precision, linearity, detection limits, robustness, and range suitable to the intended application [61].

Equipment Qualification: Instruments must undergo installation, operational, and performance qualification (IQ/OQ/PQ) to verify fitness for purpose and must be maintained and calibrated regularly [61].

Scope and Purpose: GLP regulations address nonclinical safety, toxicity, pharmacokinetic, and environmental impact studies, ensuring data reliability for regulatory decision-making [62].

Method Validation and Equipment Qualification: Analytical methods in GLP studies must be validated to be "fit for purpose," covering accuracy, precision, linearity, robustness, and system suitability. Instruments undergo qualification and routine maintenance to ensure consistent performance [62].

Recent Advances and Future Trends:

Integration of Nanotechnology with Chromatographic Evaluations:

Nanostructured Stationary Phases: Advanced nanomaterials such as carbon nanotubes, graphene oxide, and nonporous ceramics are significantly enhancing the performance of stationary phases in both liquid and gas chromatography.

Carbon Nanotubes (CNTs): Incorporating CNTs into silica-based columns enhances the evaluation of molecular interactions, such as affinity and dispersion, through retention time analysis. Their exceptional surface area and chemical reactivity contribute to improved selectivity, particularly for small organic compounds and biomolecules [63].

Graphene Oxide: Due to its extremely high surface area (~2600 m²/g), graphene oxide-based phases significantly improve the retention and detection of peptides and proteins, making them ideal for high-sensitivity proteomic applications [63].

Nano porous Silica/Zirconia: These materials, offering surface areas up to approximately 1000 m²/g, enable efficient mass transfer and minimized peak broadening, thereby enhancing chromatographic resolution in liquid chromatography.

Miniature chromatographic Technique: Nano-Liquid Chromatography (Nano-LC): Nano-LC employs columns with internal diameters ranging from 10 to 100 micrometers and utilizes particles typically sized between 3 and 5 micrometers. This setup enables extremely low flow rates, typically measured in nanoliters per minute. Key advantages include significantly enhanced sensitivity, with detection limits reaching approximately 1 nanogram as well as minimal solvent usage, owing to the reduced dilution of analytes during separation [64].

Chromatographic Techniques: High-resolution examination of the form and surface characteristics of nanomaterials inside column structures is done using transmission electron microscopy (TEM). Fourier Transform Infrared Spectroscopy (FTIR): Identifies and examines interactions and chemical bonds between target analytes and nanomaterials. X-ray diffraction (XRD): Confirms that after being incorporated into the system, the crystalline structure of nanomaterials is preserved [65].

Use of AI in HPLC Method Development:

Artificial Neural Networks (ANN): In order to accurately predict retention duration and peak area, artificial neural networks (ANNs) are frequently utilized to represent nonlinear interactions between experimental inputs and HPLC outputs. ANN architectures outperform conventional linear modes by imitating the human brain and learning from big examples [66].

Adaptive Neuro-Fuzzy Inference System (ANFIS): Integrates fuzzy logic with neural networks to handle complexity in data and deliver precise predictions of chromatographic parameters, such as peak quantification [66].

Support Vector Machines (SVM): SVM models improve retention time prediction by capturing nonlinear data patterns through kernel functions like radial basis functions, balancing complexity and generalization [66].

Quantitative Structure-Retention Relationships (QSRR): Combining molecular descriptors derived from chemical structures with AI algorithms allows prediction of retention factors without new experiments, accelerating method development and reducing solvent consumption [66].

3D Printing and Personalized Chromatography: 3D printing is revolutionizing personalized chromatography by enabling the fabrication of highly customized chromatography columns and devices with precise geometries, tailored surface chemistries and bespoke flow channels [67]. This technology allows researchers to design and produce chromatography media that meet specific analytical or preparative needs, overcoming limitations of traditional manufacturing methods. 3D printing enables the fabrication of chromatography columns with diverse dimensions and complex geometries that are challenging to produce using traditional methods, allowing for highly specific designs [67]. The technology supports the creation of ordered porous structures and intricate stationary phases, enhancing separation efficiency through uniform beds and optimized flow dynamics. Advanced methods like hybrid stereo lithography offer fine feature resolutions (as low as 10–50 µm), enabling precise control over porosity and surface area, which are critical for effective separations. It's rapid, automated nature allows for quick design iterations and on-site production, reducing dependence on third-party suppliers and enabling real-time customization innovative printable materials containing reactive monomers, such as glyceryl methacrylate, enable post-print chemical modification, allowing for tailored stationary phase chemistries suited to specific analytes [67].

Green Solvents Used in HPLC:

Ethanol (EtOH): Ethanol, a green solvent in RP-HPLC, is renewable, non-toxic, biodegradable, and cost effective. It has similar chromatographic properties to methanaol but with higher UV cutoff and viscosity, which may increase back pressure.

Using UHPLC or superficially porous columns helps manage this, making ethanol a popular eco-friendly choice in pharmaceutical analysis [68].

Propylene Carbonate: Propylene carbonate is a biodegradable, low-toxicity solvent with high boiling and flash points, improving lab safety. Often used in ternary mixtures with ethanol due to limited water miscibility, it provides selectivity like acetonitrile but requires lower flow rates because of its higher viscosity. It is effective in pharmaceutical and bioanalytical analyses [68].

Acetone: Acetone is a biodegradable solvent with polarity comparable to acetonitrile but has a high UV cut off around 340 nm, which restricts its use in UV detection. Though volatile, it performs effectively with mass spectrometry and corona aerosol detectors, making it a greener alternative for those applications [68].

Ethyl Acetate: Produced from ethanol and lactic acid, ethyl lactate is biodegradable, non-toxic, and miscible with water. Drawbacks like chemical instability under some pH conditions and higher viscosity limit its use. It has been applied for fast separations of pharmaceuticals but is less common due to these challenges [68].

CONCLUSION: This review critically evaluates new technologies and previous research in drug formulation, including solid particle techniques, prodrug approaches, micronization, solid dispersions, Nano sizing, cyclodextrin, solid lipid nanoparticles, drug conjugates, colloidal systems, nanoemulsions, and micelles. The majority of novel drug candidates have poor water solubility, which is a major factor in determining bioavailability, formulation choices, and therapeutic efficacy. Nanotechnology has drawn attention as a promising approach to improving medication solubility and offering simple yet effective drug delivery systems. Pharmaceutical development continues to rely heavily on High-Performance Liquid Chromatography (HPLC) due to its precision, sensitivity, and adaptability. HPLC facilitates drug identification, quantification, purity analysis, stability observation, and bioavailability determination, making it a sine qua non for quality control and regulatory compliance. With advancements in pharmaceutical research, HPLC will remain the foundation for developments through guaranteeing product efficacy and safety. The way to the future of drug discovery is the combination of improved formulation methodologies with analytical technologies, allowing online monitoring and accelerating optimization.

Through this collaboration, drug behavior will be better understood, development accelerated, cost reduced, and drug performance predictability enhanced. Ultimately, this synergistic approach has the goal of generating safer, more effective, and tailored therapies for patients.

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REFERENCES:

1. Coltescu AR, Butnariu M and Sarac I: The Importance of Solubility for New Drug Molecules. Biomed. Pharmacol. J 2020; 13(02): 577–583. https://doi.org/10.13005/bpj/1920.
2. Bao Z, Tom G, Cheng A, Watchorn J, Aspuru-Guzik A and Allen C: Towards the Prediction of Drug Solubility in Binary Solvent Mixtures at Various Temperatures Using Machine Learning. J Cheminformatics 2024; 16(1): 117. https://doi.org/10.1186/s13321-024-00911-3.
3. Pogodina VV: Elizaveta Nilolaevna Levkovich-75th Birthday. Acta Virol 1975; 19(6): 509.
4. Patil R, Patil S and Mali S: Unlocking Potential: Cocrystals as Catalyst for Heightened Solubility and Dissolution of Low Solubility Pharmaceuticals. Int J Res Pharm Allied Sci 2024; 3(4): 73–88.
5. Maurya R, Vikal A, Patel P, Narang RK and Kurmi BD: "Enhancing oral drug absorption: overcoming physiological and pharmaceutical barriers for improved bioavailability." AAPS Pharm Sci Tech 2024; 25(7): 228. https://doi.org/10.1208/s12249-024-02940-5.
6. Guedes NM, Silva JG, Mesquita LLGDM, Castro WVD, Lima EDSP, Santana DPD and Bedor DCG: Review of the Dissolution Tests in the Brazilian Pharmacopeia. Braz. J. Pharm. Sci 2024; 60: e23633. https://doi.org/10.1590/s2175-97902024e23633.
7. BioRender. https://app.biorender.com/illustrations/67a95ffca9469b9bc295ec08 (accessed 2025-06-18).
8. BučevićPopović V, KarahmetFarhat E, Banjari I, JeličićKadić A and Puljak L: Bioavailability of oral curcumin in systematic reviews: a methodological study. Pharmaceuticals 2024; 17(2): 164. https://doi.org/10.3390/ph17020164.
9. Shah VP, Amido, GL, Amidon GL, Lennernas H, Shah VP and Crison JR: A theoretical basis for a biopharmaceutic drug classification: the correlation of *in-vitro* drug product dissolution and *in-vivo* bioavailability. Pharm Res 1995; 12: 413–420,—Backstory of BCS. AAPS J 2014; 16(5), 894–898. https://doi.org/10.1208/s12248-014-9620-9.
10. Wu K, Kwon SH, Zhou X, Fuller C, Wang X, Vadgama J and Wu Y: Overcoming challenges in small-molecule drug bioavailability: a review of key factors and approaches. Int

J Mol Sci 2024; 25(23): 13121. https://doi.org/10.3390/ijms252313121.
11. Mushtaq I, Ahmad M, Saleem M and Ahmed A: Pharmaceutical significance of schiff bases: an overview. Future J Pharm Sci 2024; 10(1): 16. https://doi.org/10.1186/s43094-024-00594-5.
12. Godge GR, Garje MA, Dode AB and Tarkase KN: Nanosuspension technology for delivery of poorly soluble drugs and its applications: a review. Int J Pharm Sci Nanotechnol 2020; 13(4): 4965–4978. https://doi.org/10.37285/ijpsn.2020.13.4.1.
13. Nyamba I, Sombié CB, Yabré M, Zimé-Diawara H, Yaméogo J, Ouédraogo S, Lechanteur A, Semdé R and Evrard B: Pharmaceutical approaches for enhancing solubility and oral bioavailability of poorly soluble drugs. Eur J Pharm Biopharm 2024; 204: 114513. https://doi.org/10.1016/j.ejpb.2024.114513.
14. Krishnaiah YSR: Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequivalence Bioavailab 2010; 02(02). https://doi.org/10.4172/jbb.1000027.
15. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G and Lee J: Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci 2014; 9(6): 304–316. https://doi.org/10.1016/j.ajps.2014.05.005.
16. Sievers RE, Huang ETS, Villa JA, Engling G and Brauer PR: Micronization of water-soluble or alcohol-soluble pharmaceuticals and model compounds with a low-temperature bubble dryer®. J Supercrit Fluids 2003; 26(1): 9–16. https://doi.org/10.1016/S0896-8446(02)00188-2.
17. Yildiz N, Tuna Ş, Döker O and Çalimli A: Micronization of Salicylic Acid and Taxol (Paclitaxel) by Rapid Expansion of Supercritical Fluids (RESS). J Supercrit Fluids 2007; 41(3): 440–451. https://doi.org/10.1016/j.supflu.2006.12.012.
18. Lee SK, Ha ES, Park H, Kang KT, Jeong JS, Kim JS, Baek I and Kim MS: Preparation of Hot-Melt-Extruded Solid Dispersion Based on Pre-Formulation Strategies and Its Enhanced Therapeutic Efficacy. Pharmaceutics 2023; 15(12): 2704. https://doi.org/10.3390/pharmaceutics15122704.
19. Chiou WL and Riegelman S: Pharmaceutical Applications of Solid Dispersion Systems. J Pharm Sci 1971; 60(9): 1281–1302. https://doi.org/10.1002/jps.2600600902.
20. Janssens S, De Armas HN, Roberts CJ and Van Den Mooter G: Characterization of Ternary Solid Dispersions of Itraconazole, PEG 6000, and HPMC 2910 E5. J Pharm Sci 2008; 97(6): 2110–2120. https://doi.org/10.1002/jps.21128.
21. Abdul-Fattah AM and Bhargava HN: Preparation and in Vitro Evaluation of Solid Dispersions of Halofantrine. Int J Pharm 2002; 235(1–2): 17–33. https://doi.org/10.1016/S0378-5173(01)00941-3.
22. Gomaa E, Fathi HA, Eissa NG and Elsabahy M: Methods for Preparation of Nanostructured Lipid Carriers. Methods 2022; 199: 3–8. https://doi.org/10.1016/j.ymeth.2021.05.003.
23. Leuenberger H: [No Title Found]. J Nanoparticle Res 2002; 4(1/2): 111–119. https://doi.org/10.1023/A:1020135603052.
24. Farinha S, Sá JV, Lino PR, Galésio M, Pires J, Rodrigues MÂ and Henriques J: Spray freeze drying of biologics: a review and applications for inhalation delivery. Pharm Res 2023; 40(5): 1115–1140. https://doi.org/10.1007/s11095-022-03442-4.
25. Rogers TL, Hu J, Yu Z, Johnston KP and Williams RO: A novel particle engineering technology: spray-freezing into liquid. Int J Pharm 2002; 242(1–2): 93–100. https://doi.org/10.1016/S0378-5173(02)00154-0.
26. Zhu J, Dai Z, Wang Y, Wang M and Wang Z: Rapid Freezing process of static salt-containing droplets under salt exclusion. Int J Heat Mass Transf 2024; 220: 124927. https://doi.org/10.1016/j.ijheatmasstransfer.2023.124927.
27. Sarangi S, Remya PN and Damodharan N: Advances in solvent based cocrystallization: bridging the gap between theory and practice. J Drug Deliv Sci Technol 2024; 95: 105619. https://doi.org/10.1016/j.jddst.2024.105619.
28. Nasibullin I, Smirnov I, Ahmadi P, Vong K, Kurbangalieva A and Tanaka K: Synthetic prodrug design enables biocatalytic activation in mice to elicit tumor growth suppression. Nat Commun 2022; 13(1): 39. https://doi.org/10.1038/s41467-021-27804-5.
29. Shahriari M, Kesharwani P, Johnston TP and Sahebkar A: Anticancer potential of curcumin-cyclodextrin complexes and their pharmacokinetic properties. Int J Pharm 2023; 631: 122474. https://doi.org/10.1016/j.ijpharm.2022.122474.
30. Ali Q. Hatem and Wedad K. Ali: Preparation and characterization of carvedilol solid dispersion by kneading method. Al mustansiriyah J Pharm Sc 2023; 23(4): 367–377. https://doi.org/10.32947/ajps.v23i4.1092.
31. Parikh RK, Mansuri NS, Gohel MC and Sonlwala MM: Dissolution enhancement of nimesulide using complexation and salt formation techniques. Indian Drugs 2005; 42(3): 149–154.
32. Wen X, Tan F, Jing Z and Liu Z: Preparation and study the 1: 2 inclusion complex of carvedilol with β-cyclodextrin. J Pharm Biomed Anal 2004; 34(3): 517–523.
33. Opanasopit P, Ngawhirunpat T, Chaidedgumjorn A, Rojanarata T, Apirakaramwong A, Phongying S, Choochottiros C and Chirachanchai S: Incorporation of Camptothecin into N-Phthaloyl Chitosan-g-mPEG Self-Assembly Micellar System. Eur J Pharm Biopharm 2006; 64(3): 269–276.
34. Barreiro-Iglesias R, Bromberg L, Temchenko M, Hatton TA, Concheiro A and Alvarez-Lorenzo C: Solubilization and stabilization of camptothecin in micellar solutions of pluronic-g-poly (acrylic acid) copolymers. J Controlled Release 2004; 97(3): 537–549.
35. Nanjwade BK, Patel DJ, Udhani RA and Manvi FV: Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs. Sci Pharm 2011; 79(4): 705.
36. Rajesh BV, Reddy TK, Srikanth G, Mallikarjun V and Nivethithai P: Lipid Based Self-Emulsifying Drug Delivery System (SEDDS) for Poorly Water-Soluble Drugs: A Review. J Glob Pharma Tech 2010; 2(3): 47–55.
37. Porter CJ, Trevaskis NL and Charman WN: Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Disco 2007; 6(3): 231–248.
38. Kovalenko MV, Manna L, Cabot A, Hens Z, Talapin DV, Kagan CR, Klimov VI, Rogach AL, Reiss P, Milliron DJ, Guyot-Sionnnest P, Konstantatos G, Parak WJ, Hyeon T, Korgel BA, Murray CB and Heiss W: Prospects of Nanoscience with Nanocrystals. ACS Nano 2015; 9(2): 1012–1057. https://doi.org/10.1021/nn506223h.
39. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S and Shin HS: Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnology 2018; 16(1): 71. https://doi.org/10.1186/s12951-018-0392-8.

40. Dhaval M, Vaghela P, Patel K, Sojitra K, Patel M, Patel S, Dudhat K, Shah S, Manek R and Parmar R: Lipid-Based emulsion drug delivery systems — a comprehensive review. Drug Deliv Transl Res 2022; 12(7): 1616–1639. https://doi.org/10.1007/s13346-021-01071-9.
41. Sala M, Diab R, Elaissari A and Fessi H: Lipid nanocarriers as skin drug delivery systems: properties, mechanisms of skin interactions and medical applications. Int J Pharm 2018; 535(1–2): 1–17.
42. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK and Hua S: Advances and challenges of liposome assisted drug delivery. Front Pharmacol 2015; 6: 286.
43. Kompella UB: Drug Delivery Applications of Supercritical Fluid Technology. I drugs Investig Drugs J 1999; 2(1): 33–34.
44. Pavlova PL, Minakov AV, Platonov DV, Zhigarev VA and Guzei DV: Supercritical fluid application in the oil and gas industry: a comprehensive review. Sustainability 2022; 14(2): 698. https://doi.org/10.3390/su14020698.
45. Liu Y, Liang Y, Yuhong J, Xi, P, Han JL, Du Y, Yu X, Zhu R, Zhang M, Chen W and Ma Y: Advances in nanotechnology for enhancing the solubility and bioavailability of poorly soluble drugs. Drug Des Devel Ther 2024; 18: 1469–1495. https://doi.org/10.2147/DDDT.S447496.
46. Hussain A, Altamimi MA, Ramzan M and Khuroo T: Hansen Solubility Parameters and QbD-Oriented HPLC Method Development and Validation for Dermatokinetic Study of a Miconazole-Loaded Cationic Nanoemulsion in Rat Model. ACS Omega 2023; 8(38): 34746–34759. https://doi.org/10.1021/acsomega.3c03713.
47. Hussain A, Ramzan M, Altamimi MA and Khuroo T: HSPiP and QbD Program–Based Analytical Method Development and Validation to Quantify Ketoconazole in Dermatokinetic Study. AAPS PharmSciTech 2023; 24(8): 231. https://doi.org/10.1208/s12249-023-02675-9.
48. HPLC Chromatography Hints and Tips for Chromatographers [HPLC TRAINING ARTICLES] : Proper Wavelength Selection for HPLC Method Development (or Purity Determination). https://hplctips.blogspot.com/2013/08/wavelength-selection-for-method.html (accessed 2025-05-26).
49. Zhang D, Wang R, Wang X and Gogotsi Y: *In-situ* Monitoring Redox Processes in Energy Storage Using UV–Vis Spectroscopy. Nat Energy 2023; 8(6): 567–576. https://doi.org/10.1038/s41560-023-01240-9.
50. Rote AR, Kumbhoje PA and Bhambar RS: UV-Visible spectrophotometric simultaneous estimation of paracetamol and nabumetone by auc method in combined tablet dosage form. Pharm Methods 2012; 3(1): 40–43. https://doi.org/10.4103/2229-4708.97722.
51. Dhole SM, Khedekar PB and Amnerkar ND: Comparison of UV Spectrophotometry and High Performance Liquid Chromatography Methods for the Determination of Repaglinide in Tablets. Pharm Methods 2012; 3(2): 68–72. https://doi.org/10.4103/2229-4708.103875.
52. Bulduk I and Akbel E: A comparative study of hplc and uv spectrophotometric methods for remdesivir quantification in pharmaceutical formulations. J Taibah Univ Sci 2021; 15(1): 507–513. https://doi.org/10.1080/16583655.2021.1991737.
53. Karve T and Banga AK: Comparative evaluation of physical and chemical enhancement techniques for transdermal delivery of linagliptin. Int J Pharm 2024; 654: 123992. https://doi.org/10.1016/j.ijpharm.2024.123992.
54. Anurag K and Kumar S: Scalable preparation of high-quality graphene by electrochemical exfoliation: effect of hydrogen peroxide addition. Bull Mater Sci 2023; 46(1): 42. https://doi.org/10.1007/s12034-022-02876-1.
55. Hussain K, Qamar A, Bukhari NI, Hussain A, Shehzadi N, Qamar S and Parveen S: Impact of particle-size reduction on the solubility and antidiabetic activity of extracts of Leaves of VincaRosea. Turk J Pharm Sci 2019; 16(3): 335–339. https://doi.org/10.4274/tjps.galenos.2018.02419.
56. Tsunoda C, Hasegawa K, Hiroshige R, Kasai T, Yokoyama H and Goto S: Effect of cyclodextrin complex formation on solubility changes of each drug due to intermolecular interactions between acidic NSAIDs and Basic H2 Blockers. Mol Pharm 2023; 20(10): 5032–5042. https://doi.org/10.1021/acs.molpharmaceut.3c00291.
57. Hasanah U, Wahyuni L and Zaini E: Micronized eutectic mixture of fenofibric acid-saccharin formation for solubility and dissolution enhancement. Int J Appl Pharm 2023; 56–60.
58. Borman P and Elder D: Q2(R1) Validation of Analytical Procedures: Text and Methodology. In ICH Quality Guidelines; Teasdale, A., Elder, D., Nims, R. W., Eds.; Wiley 2017; 127–166. https://doi.org/10.1002/9781118971147.ch5.
59. Prajapati P, Patel A and Shah S: DoE-Based Analytical Quality Risk Management for Enhanced AQbD Approach to Economical and Eco-Friendly RP-HPLC Method for Synchronous Estimation of Multiple FDC Products of Antihypertensive Drugs. J Chromatogr Sci 2021; bmab123. https://doi.org/10.1093/chromsci/bmab123.
60. Mahr AG, Lourenço FR, Borman P, Weitzel J and Roussel JM: Analytical quality by design fundamentals and compendial and regulatory perspectives. in introduction to quality by design in pharmaceutical manufacturing and analytical development; breitkreitz, M. C., Goicoechea, H., Eds.; AAPS Introductions in the Pharmaceutical Sciences; Springer International Publishing: Cham 2023; 10: 163–198. https://doi.org/10.1007/978-3-031-31505-3_8.
61. Doneski L and Dong M: Pharmaceutical Regulations: An Overview for the Analytical Chemist. LCGC N Am 2023; 211–215. https://doi.org/10.56530/lcgc.na.ua3181v7.
62. Doneski L and Dong M: Current Good Manufacturing Practice (cGMP): An Overview for the Analytical Chemist 2023; 41: 416–421.
63. Drożdż W, Ciesielski A and Stefankiewicz AR: Dynamic Cages—Towards Nanostructured Smart Materials. Angew. Chem 2023; 135(43): e202307552. https://doi.org/10.1002/ange.202307552.
64. Hemida M, Ghiasvand A, Macka M, Gupta V, Haddad PR and Paull B: Recent advances in miniaturization of portable liquid chromatography with emphasis on detection. J Sep Sci 2023 46(15): 2300283. https://doi.org/10.1002/jssc.202300283.
65. Frontiers | Integrating engineered nanomaterials with extracellular vesicles: advancing targeted drug delivery and biomedical applications. https://www.frontiersin.org/journals/nanotechnology/articles/10.3389/fnano.2024.1513683/full (accessed 2025-05-27).
66. Singh YR, Shah DB, Maheshwari DG, Shah JS and Shah S: Advances in AI-Driven retention prediction for different chromatographic techniques: unraveling the complexity. Crit Rev Anal Chem 2024; 54(8): 3559–3569.
67. Moleirinho MG, Feast S, Moreira AS, Silva RJS, Alves PM, Carrondo MJT, Huber T, Fee C and Peixoto C: 3D-Printed ordered bed structures for chromatographic purification of enveloped and non-enveloped viral particles. Sep Purif Technol 2021; 254: 117681. https://doi.org/10.1016/j.seppur.2020.117681.

68. Habib T, Brämer C, Heuer C, Ebbecke J, Beutel S and Bahnemann J: 3D-Printed microfluidic device for protein purification in batch chromatography. Lab Chip 2022; 22(5): 986–993. https://doi.org/10.1039/D1LC01127H.

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