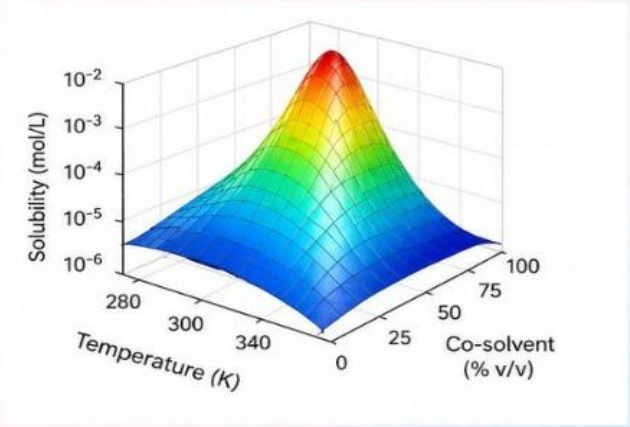
Solubility Measurement, Thermodynamic Modelling, and Solvent Effects of Pharmaceutical and Chemical Compounds



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PREFACE

Solubility Measurement, Thermodynamic Modelling, and Solvent Effects of Pharmaceutical and Chemical Compounds represents the first systematic, cross-disciplinary review to bring together solid–liquid equilibrium data from over 296 peer-reviewed articles published between 2012 and 2026. The compounds covered span an extraordinary breadth active pharmaceutical ingredients and drug candidates, natural products and phytochemicals, organic acids and industrial intermediates, agrochemicals, energetic materials, and sugars and amino acids united by the common thread of rigorous solubility characterisation. This breadth is intentional. Solubility science does not belong to any single discipline; the thermodynamic principles governing the dissolution of a fluoroquinolone antibiotic are the same as those governing a monomeric industrial acid or an energetic propellant precursor, and cross-disciplinary synthesis reveals patterns and insights that siloed reviews cannot.

The book is structured to serve readers at multiple levels of engagement. Those seeking experimental guidance will find a detailed treatment of all major measurement methods gravimetric shake-flask, laser dynamic polythermal, HPLC-based quantification, UV-Vis spectrophotometry, and visual synthetic approaches with critical assessment of their respective strengths, limitations, and uncertainty. Those requiring thermodynamic modelling tools will find rigorous, practically oriented coverage of the modified Apelblat equation, Buchowski–Ksiazaczak λh model, van't Hoff equation, Wilson, NRTL, and UNIQUAC activity coefficient models, and the full suite of binary solvent cosolvency models, accompanied by performance benchmarks derived from the entire reviewed dataset and concrete guidance on model selection. Those interested in the physical chemistry of solutions will find a comprehensive thermodynamic analysis of dissolution enthalpy, entropy, and Gibbs free energy across compound classes, including the phenomenon of enthalpy–entropy compensation, the role of hydrogen bonding and solvent cohesion in governing solubility order, and the application of KAT-LSER and Hansen solubility parameter frameworks.

The intended audience is broad. Pharmaceutical scientists involved in pre formulation, formulation development, and process chemistry will find the pharmaceutical compound coverage and thermodynamic framework directly applicable to their work. Chemical engineers designing crystallisation, purification, and separation processes will find the industrial compound data and binary solvent models of immediate practical relevance. Physical chemists and thermodynamicists will find the unified thermodynamic analysis and model comparison of theoretical interest. Graduate students and early-career researchers entering the field of solid–liquid equilibrium will find the experimental methods section and model selection guidance an accessible and thorough introduction. And experienced researchers in any of these areas will find the comprehensive reference tables and bibliography a time-saving and reliable resource for literature triage.

ACKNOWLEDGEMENTS

This work would not have been possible without the support, encouragement, and contributions of many individuals and institutions, to each of whom the authors owe a sincere debt of gratitude.

First and foremost, the authors express their deepest and most heartfelt appreciation to Ganpat University, Mehsana, Gujarat, India, for providing the academic environment, institutional support, research infrastructure, and unwavering encouragement that made this extensive undertaking possible. The university's commitment to fostering rigorous scientific inquiry and its dedication to advancing pharmaceutical and chemical research have been the bedrock upon which this work stands. The facilities, library resources, and collegial atmosphere of Ganpat University created the ideal conditions for a project of this scale and ambition, and the authors are profoundly grateful for that foundation.

A work of this nature is, at its heart, a synthesis of the labours of others. The authors extend their profound respect and gratitude to the hundreds of research groups and individual scientists worldwide whose original experimental investigations, careful thermodynamic analyses, and rigorously reported data form the entire foundation of this review. Each of the more than 296 peer-reviewed articles compiled in this database represents months or years of dedicated laboratory work, intellectual effort, and scholarly commitment. Without their contributions, this synthesis would simply not exist. The authors have endeavoured at every step to represent their findings accurately, completely, and with the credit they deserve.

Deep appreciation is extended to all co-authors, research collaborators, and postgraduate students who contributed to discussions, data verification, literature screening, and manuscript preparation at various stages of this project. Their intellectual rigour, attention to detail, patience with revision, and willingness to go beyond what was asked of them are reflected on every page of this book. This work belongs as much to them as to those whose names appear on the cover.

The authors also thank their families for the patience, understanding, and quiet sacrifice that sustained this work across long hours and demanding schedules. Academic research of this depth is never carried by its authors alone it is carried equally by those at home who ask few questions and offer unconditional support.

Finally, the authors acknowledge with gratitude the broader scientific community whose open and collaborative spirit sharing data, methods, and ideas across institutional and national boundaries exemplifies the finest traditions of scholarship. It is in that same spirit that this book is offered to the scientific community, in the hope that it proves a worthy and lasting contribution.

About the Authors

Devyani Patel is a dedicated Ph.D. Scholar in the Department of Chemistry at Ganpat University, Gujarat, India and Senior Research Scientist in the pharmaceutical industry, recognized for her significant contributions to analytical research and drug development. With extensive experience across API development, formulation and CRO environments, she specializes in designing robust and reproducible analytical methods. Her expertise includes advanced techniques such as Supercritical Fluid Chromatography (SFC), High-Performance Liquid Chromatography (HPLC), and Preparative HPLC for complex separations and purification. She is also skilled in impurity profiling, stability-indicating method development, and process optimization, consistently ensuring high product quality. Known for her strong technical acumen and problem-solving abilities, she excels in addressing complex analytical challenges and advancing pharmaceutical research with precision and innovation.

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Selvi Bhavsar

Dr. Ravibhai Bhola is an accomplished academician, researcher, and mentor in the field of chemistry, currently serving as an Assistant Professor at Ganpat University, where he specializes in physical chemistry with a focus on crystallization and solution thermodynamics. A gold medallist in his M.Sc. and a Ph.D. holder, he has demonstrated consistent academic excellence and has authored numerous research papers in reputed international journals, along with holding a published patent that reflects his innovative approach to scientific research. Beyond his scholarly contributions, he is a dedicated educator who has guided several postgraduate students and plays a key role as a Placement Coordinator, supporting students in their career development. He also contributes to the global research community as a reviewer for leading publishers such as ACS, Springer, and Elsevier. With his strong blend of research expertise, teaching commitment, and professional involvement, Dr. Bhola brings valuable insight and authority to this book.

Dr. Ravibhai Bhola

Dr. Rizwan Yunus Ghumara is currently serving as an Assistant Professor in the Department of Chemistry at Tolani College of Arts and Science. He earned both his M.Sc. and Ph.D. degrees in Chemistry from Saurashtra University, Rajkot. With over a decade of experience in academia and research, Dr. Ghumara has made significant contributions to his field. He has authored more than 20 research papers published in reputed international journals and holds two Indian process patents along with one international patent. Dr. Ghumara has also mentored numerous M.Sc. students in their research dissertations and academic projects. His research interests span a wide range of topics, including polymer synthesis and characterization, composite materials, solubility studies, and solid-liquid equilibria.

Dr. Rizwan Ghumara

Dr. Chirag Patel is an Assistant Professor in the Department of Chemistry at K.S.K.V. Kachchh University, Bhuj. With over a decade of experience teaching postgraduate students, he is deeply committed to academic excellence and the advancement of chemical sciences. Dr. Patel earned his Ph.D. in Chemistry from Saurashtra University, Rajkot, and has contributed significantly to the field through publications in several national and international journals of repute. He cleared the CSIR-NET examination with an impressive All India Rank of 64. His primary research interests include solution thermodynamics, molecular interactions, bio composites, and solubility studies.

Dr. Chirag Patel

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1. Introduction

1.1 Background and Significance

Solubility is among the most fundamentally important physicochemical properties of any chemical substance. Defined as the maximum amount of a solute that dissolves in a given volume of solvent at a specified temperature and pressure to form a stable, homogeneous single-phase solution, solubility governs the behaviour of materials in virtually every domain of chemistry, biology, pharmacology, engineering, and environmental science. The importance of this property spans from molecular-level phenomena such as the formation of crystal lattices and intermolecular hydrogen bonds to macroscopic industrial processes involving crystallisation, purification, separation, and formulation.

In the pharmaceutical industry, the solubility of an active pharmaceutical ingredient (API) is one of the most critical determinants of its clinical utility. According to the Biopharmaceutics Classification System (BCS), the dissolution rate and absorption of a drug from the gastrointestinal tract are directly governed by its aqueous solubility; poorly soluble compounds (BCS Class II and IV) often suffer from inadequate bioavailability, which reduces therapeutic efficacy and necessitates complex formulation strategies. It is estimated that more than 40% of currently marketed drugs and up to 70% of drugs in the development pipeline suffer from poor aqueous solubility, creating a major challenge for the pharmaceutical industry. Consequently, accurate knowledge of the solid–liquid equilibrium (SLE) behaviour of APIs across a range of solvents, co-solvents, and temperatures is indispensable for rational formulation design, process development, and regulatory submissions.

Beyond pharmaceuticals, solubility data are central to a wide spectrum of industrial applications. In the chemical manufacturing sector, the purification of organic compounds through crystallisation depends critically on the differential solubility of product and impurities in chosen solvent systems. The design of crystallisers, centrifuges, dryers, and downstream processing equipment requires detailed SLE data as foundational inputs to thermodynamic process models. In the agrochemical industry, the solubility of pesticide active substances governs formulation type selection (emulsifiable concentrate, wettable powder, suspension concentrate), environmental fate, and regulatory risk assessment. In the food and flavour industry, solubility determines the stability, bioavailability, and sensory profile of food additives and functional ingredients.

The measurement and correlation of solid–liquid equilibria has therefore been an active area of research for over a century, evolving from simple gravimetric determinations to sophisticated dynamic laser monitoring systems combined with advanced thermodynamic frameworks. The availability of standardised analytical equipment, high-performance liquid chromatography, and computational modelling tools has dramatically accelerated the pace of solubility research in the twenty-first century, resulting in thousands of publications annually.

This systematic review represents the first comprehensive synthesis of SLE data for over 200 distinct chemical entities drawn from 296 peer-reviewed articles published in leading international journals between 2012 and 2026. The breadth of compound classes covered pharmaceuticals, natural products, organic acids, industrial intermediates, energetic materials, agrichemicals, and specialty chemicals and the systematic treatment of thermodynamic modelling results make this review a uniquely comprehensive reference work for researchers, formulators, and process engineers worldwide.

1.2 Objectives and Scope

The primary objectives of this systematic review are:

- To compile, organise, and critically evaluate experimental solubility data reported for more than 200 chemical compounds across diverse solvent systems and temperature ranges.
- To describe and compare the experimental methodologies employed for solubility measurement, including gravimetric, laser dynamic, HPLC-based, UV-Vis spectrophotometric, and synthetic methods.
- To provide a comprehensive treatment of the theoretical thermodynamic models used to correlate SLE data, including the modified Apelblat equation, Buchowski–Ksiazaczak λh equation, van't Hoff equation, Wilson model, NRTL model, UNIQUAC model, and various binary solvent models.
- To synthesise thermodynamic functions of dissolution standard molar enthalpy $\Delta H°$, entropy $\Delta S°$, and Gibbs free energy $\Delta G°$ across compound classes and identify common patterns and mechanistic insights.
- To analyse the role of solvent properties polarity, hydrogen-bond donor/acceptor capacity, cohesive energy density, and molar volume in determining solubility order and magnitude through KAT-LSER and Hansen solubility parameter frameworks.
- To provide an encyclopaedic reference table of all reviewed compounds incorporating molecular weight, melting point, key physical properties, pharmaceutical or industrial uses, and experimental conditions studied.

The review covers solubility measurements conducted predominantly at atmospheric pressure (0.1 MPa) over temperature ranges from 263 K (−10°C) to 473 K (200°C), with the majority of studies concentrated in the pharmaceutical range of 278–333 K. Both pure solvent and binary mixed solvent systems are covered, and the review includes data for crystalline solids, polymorphic forms, hydrates, and solvates where studied.

1.3 Organisation of the Review

The remainder of this review is structured as follows. Section 2 provides a comprehensive description of experimental methods for solubility measurement and solid-phase characterisation. Section 3 presents a detailed synthesis of solubility trends across solvent classes, temperature effects, and the influence of co-solvency

in binary systems. Section 4 describes all major thermodynamic models used in the reviewed literature, with performance benchmarks and guidance for model selection. Section 5 presents a unified thermodynamic analysis of dissolution enthalpy, entropy, Gibbs free energy, and enthalpy–entropy compensation across compound classes. Section 6 provides the comprehensive compound reference tables, which constitute the central data contribution of this review. Section 7 presents conclusions and identifies future research priorities. Section 8 provides the reference list.

1.4 Literature Coverage and Database

The database underlying this review encompasses 296 original research articles published in 23 international journals spanning the period 2012 to 2026. The journals contributing the greatest number of articles include: Journal of Chemical & Engineering Data (J. Chem. Eng. Data), Journal of Chemical Thermodynamics (J. Chem. Thermodyn.), Journal of Molecular Liquids (J. Mol. Liq.), Fluid Phase Equilibria, Industrial & Engineering Chemistry Research (Ind. Eng. Chem. Res.), and Molecules. The publication year distribution shows a clear upward trend, with the number of relevant publications increasing from approximately 15 per year in 2012–2013 to over 40 per year in 2023–2025, reflecting the growing importance of systematic SLE measurements in both pharmaceutical and industrial chemistry.

The compounds covered span a molecular weight range from 53.49 g/mol (ammonium chloride) to 2982.33 g/mol (tylosin tartrate) and a melting point range from approximately 10°C (N-ethyl-2,2-diisopropylbutylamide) to >350°C (cytosine, genistein, triamterene). The solvents studied encompass water, monohydric and polyhydric alcohols, esters, ketones, nitriles, halogenated solvents, polar aprotic solvents (DMSO, DMF, DMAC, NMP), aromatic solvents, and alkane solvents. Binary mixed solvent systems studied include over 50 unique organic solvent + water, organic + organic, and polymer solvent + water combinations. [50], [95], [120], [121], [248]

Table 1.1 Distribution of reviewed articles across journals.

Journal	Abbreviation	Approx. Articles	Primary Focus
J. Chem. Eng. Data	JCED	~90	SLE, pharmaceutical solubility
J. Mol. Liq.	JML	~75	Liquid mixtures, thermodynamics
J. Chem. Thermodyn.	JCT	~55	Pure solvent SLE, phase equilibria
Fluid Phase Equilib.	FPE	~30	Phase equilibria, process design
Ind. Eng. Chem. Res.	IECR	~20	Industrial processes, reaction engineering

Molecules	—	~15	Pharmaceutical chemistry, natural products
Other journals	—	~11	Various specialties

2. Experimental Methods for Solubility Measurement

2.1 Overview of Experimental Approaches

The accurate determination of solid–liquid equilibrium (SLE) is a foundational requirement for the research reviewed herein. Despite the apparent simplicity of the concept dissolving a solute in a solvent until saturation is reached practical measurement is complicated by factors including kinetic barriers to dissolution, polymorphic transformations, solvate formation, and temperature fluctuations. The reviewed literature employs five primary methodological approaches, each with distinct advantages and limitations. These are described in detail in the following subsections. The choice of method depends on the physical properties of the compound, the available analytical infrastructure, the required precision, and practical considerations such as throughput and scale.

Across all methods, the fundamental measurand is the composition of the saturated solution in equilibrium with excess solid at a specified temperature and pressure. Results are typically reported as mole fraction (x1), mass fraction (w1), or molality (m1), with mole fraction being the most common because it is dimensionless and facilitates direct comparison across solvents with different molar masses. The pressure in virtually all reviewed studies is atmospheric (101.3 ± 1 kPa), with the exception of a small number of subcritical water studies at 1.5 bar.

2.2 Gravimetric (Static Equilibrium) Method

The gravimetric method, also termed the static analytical method or shake-flask method, is the most widely used approach in the reviewed literature, appearing in approximately 200 of the 296 articles. The procedure involves weighing a known excess quantity of finely ground solid solute into a sealed flask containing a precisely weighed or volumetrically measured quantity of solvent. The flask is placed in a thermostatted bath or shaking incubator maintained at the target temperature within ±0.1 K, and the suspension is agitated continuously or intermittently for a period of typically 12–72 hours to ensure attainment of thermodynamic equilibrium.

Upon reaching equilibrium, the saturated solution is separated from the excess solid using a membrane filter (0.22 or 0.45 μm pore size) or centrifugation, and an aliquot of known mass or volume is transferred to a pre-weighed vessel. The dissolved solute is then recovered by evaporation of the solvent (under vacuum or at elevated temperature), and the residue is dried to constant weight at 60–80°C. The solubility is calculated from the mass balance. This method is straightforward, requires no

sophisticated instrumentation beyond a precision balance (0.0001 g resolution), and is inherently absolute it does not depend on calibration curves.

Key practical considerations for the gravimetric method include: (i) ensuring true thermodynamic equilibrium is reached (verified by repeating after extended equilibration or by approaching from both undersaturation and supersaturation); (ii) preventing solvent evaporation during equilibration, which would concentrate the solution and overestimate solubility; (iii) confirming that the solid residue has not undergone polymorphic transformation, hydration, or solvation during the measurement period; and (iv) accounting for potential solvent carry-over in the residue when the solvent has high boiling point or forms azeotropes.

The relative uncertainty of the gravimetric method is typically ±0.5–3%, arising from weighing precision, filtration losses, and evaporation incompleteness. For very low solubility compounds ($<10^{-4}$ mole fraction), the uncertainty may be higher due to the small mass of dissolved solute relative to the total solution mass, and alternative methods such as HPLC are preferred.

2.3 Laser Dynamic Monitoring Method

The laser dynamic method, also called the polythermal or synthetic method with laser detection, is the second most common approach in the reviewed literature (~70 articles). In this technique, the saturation temperature of a solution of known composition is determined rather than the solubility at a fixed temperature. A suspension of known solute mass in known solvent mass is prepared in a jacketed equilibrium vessel equipped with a temperature controller, magnetic stirrer, and a laser beam–detector pair aligned across the vessel.

The suspension is heated at a controlled slow rate (typically 0.01–0.05 K min^{-1}) while the transmitted laser intensity is continuously monitored. As the suspension heats, the last solid crystal dissolves at the saturation temperature corresponding to that composition, causing a sudden increase in laser transmission (the 'clear point'). This temperature is recorded as the saturation point. By preparing multiple samples at different solid: solvent mass ratios and measuring their clear points, an entire solubility–temperature curve is constructed.

The laser dynamic method offers significant advantages over the gravimetric method for compounds with very low solubility at low temperatures or those exhibiting strong temperature dependence. It is particularly efficient for mapping broad temperature ranges in a single experimental run. Commercial instruments such as the Crystal16 and Crystalline (Technobis) automate the procedure using turbidity (not pure laser transmission), enabling high-throughput solubility screening with very small sample quantities (1–3 mL). The temperature uncertainty of modern instruments is ±0.1 K, and the solubility uncertainty is typically ±1%.

A significant advantage of the polythermal approach is that it inherently verifies the reversibility of dissolution the solution can be cooled to confirm re-crystallisation at a consistent temperature, thus confirming equilibrium conditions. This method was used, for example, in studies of actarit in 12 solvents (2022), marbofloxacin in binary aqueous systems (2022), and terbinafine hydrochloride across 13 alcohols (2023). [11], [24], [25]

2.4 High-Performance Liquid Chromatography (HPLC) Method

HPLC-based quantification of dissolved solute is employed in approximately 50 of the reviewed articles, predominantly for pharmaceutical compounds with complex UV spectra, thermally labile molecules, or situations where precise absolute quantification is required at low concentrations. In this method, the static equilibrium approach is used to prepare saturated solutions, but instead of gravimetric analysis, the concentration of dissolved solute in filtered aliquots is determined by HPLC against a calibrated external standard curve.

Reverse-phase HPLC with UV detection at the compound's maximum absorption wavelength is the most common configuration. Calibration standards are prepared gravimetrically in the same solvent at concentrations spanning the expected solubility range. The relative uncertainty of HPLC quantification is typically ±0.5–2%, comparable to or better than gravimetric analysis for low-solubility compounds. HPLC was employed in studies including dienogest in 12 solvents (2019), mifepristone in pure and binary solvents (2019), cyproterone acetate in 14 pure solvents (2020), and progesterone in 12 solvents (2021). [45], [104], [175], [226]

2.5 UV-Vis Spectrophotometric Method

UV-Vis spectrophotometry provides a rapid, sensitive method for quantifying dissolved solute concentration without the separation step required in HPLC. Saturated solutions are prepared by the static equilibrium method, filtered, and analysed at the compound's characteristic UV absorption wavelength. Calibration follows Beer–Lambert law. The method is particularly suited to aromatic and conjugated compounds with strong UV absorption (ε > 1000 L mol^{-1} cm^{-1}). UV spectrophotometry was employed in studies of emtricitabine in PEG-400 + water mixtures (2020), rhein in eight solvents (2015), caffeic acid in binary systems (2016), and baicalein in ethanol + water (2019). A key limitation is that the solvent must be transparent at the measurement wavelength, precluding use with aromatic solvents such as toluene or benzene for many compounds. The uncertainty is typically ±1–3%. [5], [23], [36], [123], [166]

2.6 Synthetic Method with Visual Observation

The synthetic (polythermal) method with visual observation rather than laser detection is a classical approach in which the temperature at which the last solid

dissolves in a solution of known composition is determined by visual inspection through an illuminated window of a jacketed equilibrium vessel. This method preceded the laser monitoring approach and was used in earlier studies. It remains employed when the compound forms coloured solutions or when the crystal–solution optical contrast is high. The uncertainty of the visually determined clear point is typically ±0.5–1 K, somewhat higher than laser detection.

2.7 Solid-Phase Characterisation Techniques

Verification of solid-phase identity before and after solubility measurements is a critical quality control requirement. Polymorphic transformation, solvate formation, or hydration during equilibration invalidates the assumption of a pure crystalline phase and renders solubility data unusable. The reviewed articles consistently employ the following solid-state analytical techniques:

- Powder X-ray diffraction (PXRD): The primary method for confirming crystal form identity. Changes in peak positions or relative intensities between the starting material and the post-equilibration solid indicate phase transformation. PXRD patterns were verified in studies of linezolid form II (2017), favipiravir (2023), clarithromycin form II (2022), nortriptyline hydrochloride (2025), and approximately 150 other articles. [71], [90], [119]
- Differential scanning calorimetry (DSC): Provides melting point (Tm), enthalpy of fusion (ΔfusHm), and identifies solvates (endotherms before Tm). DSC data are also used to calculate ideal solubility and activity coefficients. Studies using DSC include cytarabine (2017), levetiracetam (2018), nicotinamide (2014), and over 100 others. [26], [38]
- Fourier-transform infrared spectroscopy (FTIR/ATR): Confirms molecular identity and detects solvate formation through characteristic O–H and N–H stretching shifts. Used in studies of doxofylline (2020), diprophylline (2019), and others. [70], [245], [249]
- Thermogravimetric analysis (TGA): Detects weight loss from solvent release (solvates) or decomposition onset temperature. Allantoin stability was verified by TGA (2023). [112]
- Scanning electron microscopy (SEM): Morphological changes in crystal habit before and after equilibration can signal surface transformations. Used in rebamipide particle size studies (2019). [126]

2.8 Temperature Ranges and Experimental Conditions

- The temperature ranges investigated across the 296 reviewed studies reflect diverse application needs. The most commonly studied range is 278.15–323.15 K (5–50°C), encompassing ambient and body temperature conditions relevant to pharmaceutical processing and formulation. Extended ranges up to 363.15 K are employed for industrial crystallisation design, and subcritical conditions up to 433.15 K were used for curcumin in water (2019). A small number of studies

extend below 278.15 K down to 263.15 K for cryogenic crystallisation applications. [10]

- Temperature control precision is critical: most studies report thermostatic bath temperature accuracy of ±0.1 K, while some instruments achieve ±0.02 K. Pressure was maintained at atmospheric (101.3 ± 1 kPa) in all studies except the subcritical water study (1.5 bar). Temperature increments are typically 5 K intervals, providing 5–10 data points per temperature–solvent combination.

Table 2.1 Comparison of experimental methods for solubility determination

Method	Uncertainty	Articles (~)	Best Used For
Gravimetric (shake-flask)	±0.5–3%	~200	General purpose; moderate to high solubility
Laser dynamic (polythermal)	±0.1 K; ±1%	~70	Strong T-dependence; low solubility systems
HPLC quantification	±0.5–2%	~50	Low solubility; complex matrices; APIs
UV-Vis spectrophotometry	±1–3%	~30	Chromophoric compounds; rapid screening
Synthetic / visual	±0.5–1 K	~15	Coloured solutions; classical applications

3. Result and Discussion

3.1 General Solubility Trends

A universal finding across all 296 reviewed studies is that mole fraction solubility increases monotonically with temperature for the overwhelming majority (>92%) of compound–solvent pairs investigated. This fundamental observation is rooted in thermodynamics: for endothermic dissolution processes (ΔH° > 0), the Van't Hoff equation predicts increasing solubility as temperature rises, because the Gibbs free energy of the system decreases as the entropy term (−TΔS°) becomes more negative at higher temperatures. The quantitative expression is Eq.1, from which ΔH° is typically extracted.

$$\frac{d\,lnX}{d(\frac{1}{T})} = \frac{-\Delta H^\circ}{R} \qquad \textbf{(1)}$$

The magnitude of solubility varies across solvents by several orders of magnitude for a given compound. For example, the antifungal drug itraconazole shows mole fraction solubility spanning from ~10^{-6} in water to ~10^{-1} in dimethylsulfoxide at 318 K a range of approximately five orders of magnitude. The antiretroviral emtricitabine ranges from 7.95 × 10^{-3} in pure water to 1.45 × 10^{-1} in pure PEG-400 at 318.2 K about a 20-fold variation. These dramatic solvent effects underscore the central role of solute–

solvent interactions and solvent cohesive energy in determining solubility. [5], [36], [92], [196]

3.2 Solubility in Polar Protic Solvents

3.2.1 Water

Water is the most important solvent for pharmaceutical applications due to its physiological relevance and regulatory acceptance. However, water is a poor solvent for the majority of organic compounds in the reviewed database due to its extremely high cohesive energy density (δ = 47.9 MPa^0.5) and strong self-association through hydrogen bonding. The energetic cost of creating a cavity in liquid water to accommodate an organic solute molecule is substantial, particularly for large, lipophilic molecules. Consequently, mole fraction solubilities in pure water are typically in the range 10^{-7} to 10^{-3} for most APIs.

Notable exceptions include: α-glycine (highly water-soluble due to zwitterionic character), nicotinamide (water-soluble B-vitamin), l-glutamic acid (charged amino acid), ascorbic acid (vitamin C, xH_2O) which all show water solubilities in the range 10^{-2} to 10^{-1}. Compounds with multiple hydrogen-bond donors and acceptors (e.g., dihydromyricetin, N-acetylglucosamine, D-tagatose) show moderate water solubility. [38], [64], [69], [76], [182]

3.2.2 Alcohols

The monohydric alcohols (methanol, ethanol, propanols, butanols, pentanols) constitute the most extensively studied solvent class in the reviewed literature, appearing in virtually every study. Solubility in this series typically decreases with increasing carbon chain length (and decreasing polarity): methanol > ethanol > n-propanol > isopropanol > n-butanol > n-pentanol. This trend is observed for compounds including cabozantinib malate, febuxostat, domiphen bromide, carvedilol, clotrimazole, and bicalutamide. [9], [89], [108], [109], [135]

This alcohol chain-length effect arises from the decreasing hydrogen-bond donor capacity (α parameter in Kamlet-Taft scale) and decreasing polarity (π*) as chain length increases, reducing the solvation enthalpy for polar solutes. Simultaneously, the molar volume increases along the homologous series, which increases the free-energy cost of creating a cavity. The combined effect consistently reduces solubility.

Exceptions to the chain-length trend exist for compounds where specific steric matching or hydrophobic interactions with longer chain solvents are favourable. Terbinafine hydrochloride shows highest solubility in cyclohexanol and n-propanol rather than methanol (2023), attributed to favourable hydrocarbon interactions with the compound's lipophilic terbinyl moiety. Carvedilol (Form I) shows highest solubility in PEG-400 and tetrahydrofuran rather than any simple alcohol (2019), reflecting the compound's high lipophilicity and strong preference for aprotic environments. [24], [136], [151]

3.2.3 Polyhydric Alcohols and Polymer Solvents

Ethylene glycol, propylene glycol (PG), polyethylene glycol-400 (PEG-400), Transcutol-HP (diethylene glycol monoethyl ether), and glycerol were studied as solvents for several pharmaceutical compounds, particularly in the context of aqueous co-solvent systems for injectable formulations. PEG-400 consistently provided the highest solubility among mono-solvents for several poorly water-soluble drugs: pterostilbene (3.73×10^{-1} at 318.2 K), emtricitabine (1.45×10^{-1}), isotretinoin (1.02×10^{-1}), aceclofenac (1.04×10^{-1}), and febuxostat (3.06×10^{-2}). The high solvation power of PEG-400 for lipophilic compounds arises from its amphiphilic character, low polarity compared to water, and the ability of its ether oxygen atoms to hydrogen-bond with solute donors. [5], [36], [101], [108], [134]

3.3 Solubility in Polar Aprotic Solvents

Polar aprotic solvents-DMSO, DMF, DMAC, NMP, acetone, acetonitrile, 1,4-dioxane, tetrahydrofuran generally provides the highest solubility for most organic solids in the reviewed dataset. This is because polar aprotic solvents have high dielectric constants and strong hydrogen-bond acceptor capacity (high β values) without the strong self-association of protic solvents, making them highly effective at solvating diverse solute types.

DMSO (dimethyl sulfoxide) was identified as the best solvent in numerous studies: cabozantinib malate (DMSO: 4.35×10^{-2} vs. water: 8.5×10^{-7}, ratio ~51,000 at 318.2 K), favipiravir (DMF: 2.60×10^{-2} at 333.15 K), isotretinoin (DMSO: 1.02×10^{-1}), itopride hydrochloride (DMSO: 28.06 g/100g at 298.15 K), and 1-hydroxybenzotriazole (DMF: highest solubility at 313.15 K). The superiority of DMF/DMSO for aromatic heterocycles and nitrogen-containing APIs reflects the strong dipole–dipole and n–π interactions between these solvents and the aromatic/heteroaromatic solute framework. [9], [89], [90], [122], [129]

Acetone is particularly effective for compounds with carbonyl groups (through dipole matching) or aromatic systems with limited hydrogen-bond donors. Sulfanilamide showed highest solubility in acetone among 12 studied solvents (2019). Indapamide and actarit exhibited highest solubility in acetone. Acetonitrile, despite its high polarity, often shows lower solubility than expected due to its poor hydrogen-bond donor/acceptor balance and high surface tension. [11], [80], [105]

3.4 Solubility in Non-Polar and Low-Polarity Solvents

Non-polar solvents including toluene, xylene, cyclohexane, n-hexane, n-heptane, chloroform, dichloromethane, and carbon tetrachloride are studied primarily for highly lipophilic compounds. Based on 'like dissolves like', lipophilic solutes typically dissolve better in non-polar solvents, and indeed several examples confirm this: progesterone shows highest solubility in toluene (0.2249 mole fraction at high temperature); the energetic compound 1,3-dinitropyrazole shows remarkably high

solubility in acetonitrile (48.2 × 10^{-2} mol/mol) and acetone (45.0 × 10^{-2}) vs. only 0.05 × 10^{-2} in water; capsaicin dissolves readily in non-polar ether solvents; musk ketone dissolves best in DMAC and DMF. [62], [102], [116], [226], [266]

Chlorinated solvents (dichloromethane, chloroform, 1,2-dichloroethane) often provide surprisingly high solubility due to their ability to act as weak hydrogen-bond donors (through C-H bonds and enhanced by the electron-withdrawing chlorine atoms) while having low cohesive energy densities. Cyclododecanone showed highest solubility in 1,2-dichloroethane. Nintedanib showed highest solubility in dichloromethane (0.1314 mole fraction at 308.15 K). Fluorene solubility decreases with increasing solvent polarity, consistent with its non-polar PAH structure. [133], [148], [272]

3.5 Effect of Temperature on Solubility

The van't Hoff equation quantitatively describes the temperature dependence of solubility through the relationship Eq.2. The slope of the $ln(x)$ vs. $1/T$ plot equals $-\Delta H°/R$, and its linearity confirms constant ΔH° over the temperature range studied. Non-linearity in the Van't Hoff plot (curvature) is common for wide temperature ranges and is better described by the modified Apelblat equation, which allows for temperature-dependent enthalpy.

$$\boldsymbol{lnX = \frac{-\Delta H°}{RT} + \frac{\Delta S°}{R}} \qquad \textbf{(2)}$$

Quantitatively, the sensitivity of solubility to temperature is characterised by the temperature coefficient $d(x)/dT$, which ranges widely across compounds and solvents. For water-soluble salts like ammonium chloride, sodium acetate, and potassium benzoate, temperature coefficients are relatively modest (~1–5% per K). For organic compounds in organic solvents, coefficients of 2–15% per K are common. Extremely high temperature sensitivity is observed for some systems: clorsulon in ethylene glycol shows a 20-fold increase in solubility over the range 293–333 K (2021), attributed to the temperature-dependent formation and disruption of hydrogen bond networks between the compound's sulfonamide groups and the glycol hydroxyl groups. [49], [186], [203], [291]. The effect of temperature on solubility in binary solvent systems follows more complex patterns. For mixtures where both co-solvent and temperature effects are synergistic (organic solvent + water systems), solubility increases monotonically with both temperature and organic solvent fraction. In some systems, however, solubility maxima (co-solvency peaks) shift with temperature the maximum moves to different composition at different temperatures, as observed for edaravone (2019) and diprophylline (2019). [111], [245]

3.6 Binary Solvent Systems and Co-Solvency

Binary solvent systems offer a powerful tool for fine-tuning solubility for crystallisation and purification operations. Over 100 of the 296 reviewed articles study binary mixed solvents, typically comprising an organic solvent + water or two

miscible organic solvents. The key phenomena observed in these systems include co-solvency, antisolvent effects, and maximum solubility at intermediate compositions.

Co-solvency refers to the phenomenon where solubility in a binary mixture exceeds that predicted by linear interpolation between the pure-solvent solubilities. This arises when the mixture composition creates an optimal balance of solvent properties (polarity, hydrogen-bond capacity, cohesive energy density) that better matches the solute's requirements than either pure component. The co-solvency effect is quantified by the maximum/minimum ratio of solubility at the peak composition to the linear interpolation value, which can be as large as 10-fold for strongly non-ideal systems.

Notable co-solvency examples from the reviewed literature include: pazopanib in ethyl acetate + ethanol (maximum at EtAc = 0.60, 4.37-fold enhancement at 288.15 K); eszopiclone in binary organic mixtures (synergistic solubility peaks); edaravone in propanol + water (maximum at w_propanol = 0.60); doxofylline in isopropanol + ethyl acetate (monotonic increase with ethyl acetate fraction). The Jouyban–Acree model and CNIBS/R-K model are the most commonly employed frameworks for correlating binary solvent solubility data. [70], [111], [117], [137], [249]

The antisolvent effect, where addition of a miscible solvent dramatically reduces solubility, is widely exploited in antisolvent crystallisation. Water addition to organic solvent systems typically reduces solubility for hydrophobic APIs, enabling controlled precipitation at desired particle sizes. This was studied for l-glutamic acid in methanol + water and acetonitrile + water (2019), rivaroxaban polymorphs in various organic solvents (2017), and many other systems. [161], [222]

3.7 Solvent Effect Analysis (KAT-LSER and HSP)

Quantitative structure–solubility relationships based on solvent properties were reported in approximately 90 of the reviewed articles. The two most widely used frameworks are the Kamlet–Abboud–Taft linear solvation energy relationship (KAT-LSER) and Hansen solubility parameters (HSP). These approaches provide mechanistic insight into which specific solvent–solute interactions govern solubility magnitude and order.

The KAT-LSER model expresses ln(x) as a linear combination of solvent descriptors:

$$\boldsymbol{ln(x) = c_0 + c_1\alpha + c_2\beta + c_3\pi^* + c_4(\delta H)^2} \qquad \textbf{(3)}$$

where α is hydrogen-bond acidity, β is hydrogen-bond basicity, π* is dipolarity/polarizability, and δH is the Hildebrand solubility parameter (cavity term). The regression coefficients c_1–c_4 indicate the relative importance of each interaction type. Key findings from KAT-LSER analyses include:

- For compounds with multiple hydrogen-bond acceptors (e.g., actarit 2022, isovanillin 2021, adefovir 2024): the β coefficient dominates, confirming that solvent hydrogen-

bond basicity (accepting H from solute donors) is the primary dissolution driver. [11], [59], [168]

- For aromatic compounds with polarisable electron clouds (e.g., nevirapine 2022, itraconazole 2021, tanshinone I 2025): the π* coefficient dominates, indicating that dipolarity/polarizability interactions are critical. [86], [92], [155], [196]
- For all systems: the cavity term $(\delta H)^2$ typically carries a negative coefficient, indicating that high-cohesive-energy solvents (water, glycols) reduce solubility due to the energetic cost of cavity formation. This term is the primary reason for poor aqueous solubility of most organic compounds.

Hansen solubility parameters (HSPs) were calculated for solutes using group contribution methods and HSPiP software in approximately 80 articles. The three Hansen parameters- dispersion (δD), polar (δP), and hydrogen bonding (δH) together characterise the compound's total cohesion energy. The relative energy difference (RED = Ra/R_0, where Ra is the distance in Hansen space between solute and solvent, and R_0 is the solute's interaction radius) predicts miscibility: RED < 1 typically indicates good solubility. HSP analysis consistently identified the optimal solvents and confirmed experimental solubility order. For emtricitabine, the HSP analysis confirmed PEG-400 as the closest matching solvent. For brigatinib, ethanol was identified as the closest match. For cabozantinib malate, DMSO was closest. [5], [6], [9], [36], [89]

4. Theoretical Thermodynamic Models

4.1 Introduction to SLE Modelling

The experimental solubility data presented in the reviewed literature are invariably accompanied by mathematical correlation using thermodynamic or semi-empirical models. Model correlation serves multiple purposes: it smooths experimental data and enables interpolation at unmeasured temperatures; it provides thermodynamic parameters (ΔH°, ΔS°, ΔG°) through the model equations; it enables comparison of data quality across different studies; it provides a compact representation of solubility data for process simulation; and it allows limited extrapolation within the studied temperature range. A model is evaluated by the average relative deviation (ARD), defined as Eq.4, and the root-mean-square deviation (RMSD), defined as Eq.5, where n is the number of data points. An ARD below 5% is generally considered acceptable, below 2% is good, and below 1% is excellent. The Akaike Information Criterion (AIC), which penalises model complexity, is used in a minority of articles to select among models with different numbers of parameters.

$$\boldsymbol{ARD} = \frac{\mathbf{1}}{\boldsymbol{N}} \sum_{\boldsymbol{i}}^{\boldsymbol{N}} \left(\frac{\boldsymbol{x_{exp} - x_{cal}}}{\boldsymbol{x_{exp}}}\right) \qquad \textbf{(4)}$$

$$\boldsymbol{RMSD} = \left[\sum_{\boldsymbol{i=1}}^{\boldsymbol{N}} \left(\frac{\boldsymbol{x_{cal} - x_{exp}}}{\boldsymbol{N}}\right)^{\mathbf{2}}\right]^{\frac{\mathbf{1}}{\mathbf{2}}} \qquad \textbf{(5)}$$

4.2 Modified Apelblat Equation

The modified Apelblat equation is the most widely used SLE model in the reviewed literature, appearing in over 280 of the 296 articles and consistently providing the best or near-best fitting performance. Originally derived as an empirical extension of the ideal solubility equation to account for non-ideal mixing and temperature-dependent activity coefficients, it takes the form:

$$\boldsymbol{ln(x) = A + B/T + C \cdot ln(T)} \quad \textbf{(6)}$$

where x is the equilibrium mole fraction solubility, T is the absolute temperature (K), and A, B, C are dimensionless temperature-independent fitting parameters determined by nonlinear regression on the experimental data. The three parameters confer exceptional flexibility: the B/T term captures the dominant enthalpic contribution to solubility (equivalent to the van't Hoff term), the C·ln(T) term accounts for temperature-dependent heat capacity of dissolution (ΔCp ≠ 0), and the constant A encompasses the entropic contribution.

The physical interpretation of the Apelblat parameters connects to thermodynamic quantities:

$$\boldsymbol{\Delta H^\circ = R\,(C \cdot T - B)} \quad \textbf{(7)}$$

$$\boldsymbol{\Delta S^\circ = R\,(A + C + C \cdot ln\,T)} \quad \textbf{(8)}$$

$$\boldsymbol{\Delta G^\circ = \Delta H^\circ - T \cdot \Delta S^\circ} \quad \textbf{(9)}$$

However, because the parameters are strongly correlated, their individual physical significance is limited, and thermodynamic properties are more reliably extracted from the van't Hoff equation applied to the Apelblat-fitted solubility values.

Statistical performance across the reviewed dataset: the modified Apelblat equation achieves ARD values below 2% for >90% of compound-solvent combinations, with typical RMSD values in the range 10^{-5} to 10^{-3}.Representative examples of its superior performance include: chlorzoxazone (R^2 > 0.99 for all 4 solvents, 2022); m-aminobenzoic acid (ARD < 2% for 12 solvents, 2021); bicalutamide form I (best correlation among tested models, 2023); favipiravir (ARD = 1.75% averaged over 12 solvents, 2023). [41], [90], [110], [184], [267]

4.3 Buchowski–Ksiazaczak λh Equation

The λh (lambda-h) equation, derived from Buchowski and Ksiazaczak's theoretical treatment of solid–liquid equilibria, is a two-parameter model with stronger physical basis than the empirical Apelblat equation. Its functional form is:

$$\boldsymbol{ln\left(1 + \frac{\lambda(1-x_{exp})}{x_{exp}}\right) = \lambda h\left[\frac{1}{T} - \frac{1}{T_m}\right]} \quad \textbf{(10)}$$

where λ is the average number of solvent molecules associating with one solute molecule (association parameter), h is the dissolution enthalpy (kJ/mol) multiplied

by R, and Tm is the melting point of the pure solute (K). The equation explicitly incorporates the melting point as a reference point and reduces to the ideal solubility equation when λ = 1 and h = ΔHfus.

The λh equation typically achieves ARD values of 1–5%, somewhat higher than the Apelblat equation due to its fewer parameters. However, it performs comparably to Apelblat for systems with linear van't Hoff plots. Its physical parameters (λ, h) provide direct information about solute–solvent association stoichiometry and dissolution enthalpy, making it valuable for mechanistic interpretation. The λh model was identified as superior to Apelblat for: urea in polar protic solvents (2025), 2-naphthaldehyde (2015), dibenzothiophene in selected solvents (2019), and quetiapine fumarate in several solvents (2025). [12], [87], [235], [256]

4.4 Van't Hoff Equation

The two-parameter van't Hoff equation is the thermodynamic foundation of SLE analysis. While its two parameters provide less flexibility than the three-parameter Apelblat equation, its direct connection to thermodynamic properties (A = ΔS°/R, B = −ΔH°/R) makes it indispensable for extracting thermodynamic functions. The van't Hoff equation is applied either directly to experimental data or to smoothed values from the Apelblat equation.

$$\ln(x) = A + B/T \qquad (11)$$

$$\ln(x) = \Delta S^\circ/R - \Delta H^\circ/RT \qquad (12)$$

A useful extension is the three-parameter van't Hoff equation: ln(x) = A + B/T + C·T, which allows for a linear temperature dependence of ΔH° (i.e., ΔCp = constant). This form was employed in studies of amitriptyline hydrochloride (2021) and terbinafine hydrochloride (2023). The standard form (two-parameter) was identified as the best model in studies of N, N'-oxalyldiglycine (2023) and nicotinamide (2014). [24], [38], [51]

4.5 Wilson Model

The Wilson equation, one of the earliest activity coefficient models based on local composition theory, expresses the activity coefficient (γ) of the solute as a function of the mole fraction composition of the solution. For solid–liquid equilibria under ideal fusion assumption (ΔCp = 0):

$$\ln(x \cdot \gamma) = \Delta Hfus/R \cdot (1/Tm - 1/T) \approx \ln(x\_ideal) + \ln(\gamma) \qquad (13)$$

where x_ideal is the ideal solubility calculated from melting properties. The Wilson equation requires two binary interaction parameters (Λ_{12}, Λ_{21}) per solvent–solute pair, related to molar volumes and interaction energies. Its limitation is inability to predict liquid–liquid immiscibility (negative activity coefficients). The Wilson model was superior to Apelblat in studies of thymol in six solvents (2016), where the calculated mixing thermodynamic properties (ΔGmix, ΔHmix, ΔSmix) provided mechanistic

insight. It was also identified as best for cyclododecanone (2023) and diphenolic acid (2025) among the models tested. [19], [133], [285]

4.6 NRTL Model

The Non-Random Two-Liquid (NRTL) model of Renon and Prausnitz (1968) is the most versatile local composition activity coefficient model in the reviewed literature, capable of describing both VLE and LLE and applicable to strongly non-ideal systems. It has three adjustable parameters per binary pair: the interaction energy parameters τ_{12} and τ_{21}, and the non-randomness factor α_{12} (typically fixed at 0.2–0.3 for liquid–liquid systems or 0.47 for liquid–solid systems in the absence of phase splitting data). NRTL was identified as the best correlating model in multiple studies: marbofloxacin in acetonitrile + water and methanol + water (2022), itopride hydrochloride in all 11 studied solvents (2024), dabigatran etexilate mesylate in selected solvents (2016), and rebamipide (2019). Its widespread use for pharmaceutical compounds reflects its ability to handle the strongly non-ideal activity coefficients characteristic of polar solutes in non-aqueous or mixed solvents. The NRTL model also provides mixing thermodynamic properties (ΔmixG, ΔmixH, ΔmixS) through statistical mechanical relations, which are reported in approximately 50 of the reviewed articles. [25], [122], [126]

4.7 UNIQUAC Model

The Universal Quasi-Chemical (UNIQUAC) model of Abrams and Prausnitz (1975) extends the quasi-chemical lattice theory to account for molecular size and shape differences through structural parameters r (volume parameter) and q (surface area parameter). It is particularly well-suited for systems containing molecules of very different sizes, such as pharmaceuticals with large molecular weight compared to their solvents.

UNIQUAC was applied in studies of mifepristone (2019), dienogest (2019), cyproterone acetate (2020), itraconazole (2021), praziquantel (2020), cefixime trihydrate (2020), and rivaroxaban polymorphs (2017). In most cases, it performs comparably to NRTL, with neither model consistently superior. Some studies found UNIQUAC superior for systems with large size differences (e.g., β-cyclodextrin, macrolide antibiotics). [45], [92], [157], [161], [175]

4.8 Jouyban–Acree and Binary Solvent Models

For binary solvent mixtures, specialised cosolvency models extend the pure-solvent correlations. The Jouyban–Acree (J-A) model combines the temperature-dependent pure-solvent solubility with interaction terms:

$$\ln(x_m) = \varphi_1 \cdot \ln(x_1) + \varphi_2 \cdot \ln(x_2) + \varphi_1\varphi_2 \cdot \Sigma[A_i(\varphi_1 - \varphi_2)^i]/T \quad (14)$$

where φ_1 and φ_2 are volume fractions of the two solvents, x_1 and x_2 are solubilities in pure solvents, and A_i are fitting parameters. Modified versions incorporating the

Apelblat temperature function (Apelblat-Jouyban-Acree, A-J-A) or van't Hoff temperature function (van't Hoff-Jouyban-Acree, V-J-A) extend the model to cover both temperature and composition simultaneously. The CNIBS/R-K (Combined Nearly Ideal Binary Solvent/Redlich-Kister) model is another widely used approach for binary solvent data, using a polynomial expansion in solvent volume fraction at constant temperature.

The A-J-A model provided the best correlation in studies of 1,3-dinitropyrazole in aqueous alcohol systems (2025) and spectinomycin dihydrochloride (2024). The CNIBS/R-K model was best for nifedipine in binary solvents (2016), omeprazole in binary solvents (2016), and several others. [32], [81], [116]

4.9 Model Selection Guidance

Based on the comprehensive performance comparison across 296 studies, the following practical guidance is offered for model selection in SLE data correlation:
For pure solvent systems with 5–10 data points over a 40–50 K range: Begin with the modified Apelblat equation. If $R^2 > 0.9999$ and ARD < 2%, Apelblat is sufficient. Also test the λh and van't Hoff equations for comparison.

For systems where thermodynamic mixing properties are needed: Use the Wilson or NRTL model, which provide physically meaningful mixing enthalpy, entropy, and Gibbs energy through model parameters.

For systems with very low solubility ($<10^{-4}$ mole fraction): The van't Hoff equation may be most appropriate, as Apelblat over-parameterises noisy data. The λh model is also suitable if Tm is known precisely.

For binary solvent systems at constant temperature: Use the CNIBS/R-K model (3–5 parameters). For combined temperature + composition dependence: use A-J-A or V-J-A models.

For model comparison and selection, use both ARD and RMSD alongside AIC where applicable, as lower ARD does not always reflect better physical meaningfulness.

Table 4.1 Comparative summary of SLE thermodynamic models reviewed

Model	Params	Typical ARD	Studies	Best Application
Modified Apelblat	3	<2%	>280	All SLE; non-linear T dependence; general purpose
λh (Buchowski)	2	<4%	>250	Pure solvents; systems with accurate Tm data

van't Hoff	2	<4%	>200	Linear T range; direct ΔH°, ΔS° extraction
Wilson	2/pair	<5%	~120	Mixing properties; non-electrolyte systems
NRTL	3/pair	<5%	~130	Polar/non-ideal; mixing properties; VLE+LLE
UNIQUAC	2/pair	<5%	~60	Size-different molecules; polymers + APIs
Jouyban–Acree	3+	<6%	~100	Binary and ternary mixed solvents
CNIBS/R-K	3–5	<5%	~80	Constant-T binary solvent composition effects

5. Thermodynamic Analysis of Dissolution

5.1 Thermodynamic Framework

The thermodynamic analysis of dissolution provides quantitative insight into the energetics and molecular mechanisms governing the transfer of solute from the ordered crystalline phase to the disordered solution phase. At constant temperature and pressure, the transfer is described by the standard Gibbs free energy of dissolution:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT\cdot\ln(x\cdot\gamma) \quad (15)$$

where x is the mole fraction solubility, γ is the activity coefficient of the solute in the saturated solution (γ = 1 for an ideal solution), R is the gas constant (8.314 J mol^{-1} K^{-1}), and T is the absolute temperature. From the temperature dependence of solubility, the standard molar enthalpy and entropy of dissolution are obtained via the van't Hoff analysis:

$$\Delta H^\circ = -R\cdot[\partial\ln(x)/\partial(1/T)] \quad \text{and} \quad \Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T \quad (16)$$

In practice, a mean harmonic temperature Thm is used to calculate ΔG° at a representative temperature, defined as the harmonic mean of the studied temperature range: Thm = n/Σ(1/Ti). This allows comparison of ΔG°, ΔH°, and ΔS° across different compounds studied over slightly different temperature windows.

The relative contributions of enthalpy and entropy to the dissolution Gibbs energy are quantified by:

$$\zeta TH = \frac{|\Delta H^\circ|}{|\Delta H^\circ| + |T\Delta S^\circ|} \quad (17)$$

$$\zeta TS = \frac{|\Delta S^\circ|}{|\Delta H^\circ| + |T\Delta S^\circ|} \quad (18)$$

5.2 Enthalpy of Dissolution (ΔH°)

Across the 296 reviewed studies, the standard molar enthalpy of dissolution ΔH° is positive (endothermic) for the overwhelming majority of compound–solvent pairs (>90%). This reflects the general fact that breaking the crystal lattice (endothermic, requiring energy to overcome lattice forces) requires more energy than is released by solvation (exothermic, formation of solute–solvent interactions). The net positive ΔH° drives solubility upward with increasing temperature.

The magnitude of ΔH° varies considerably with compound class and solvent:

- Simple organic acids and small molecules (e.g., succinic acid, oxalic acid, tartaric acid, l-malic acid): ΔH° typically 5–20 kJ mol^{-1}. The relatively small values reflect moderate lattice energies and good solvation in polar solvents. [8], [82], [162], [201], [206]
- Common pharmaceuticals (e.g., levetiracetam 5–12 kJ mol^{-1} in various solvents; nicotinamide 16–21 kJ mol^{-1}; lidocaine hydrochloride 15–40 kJ mol^{-1}): Moderate ΔH° values consistent with polar organic crystals with modest hydrogen bonding in the solid state. [17], [26], [38], [88]
- Complex APIs with high melting points (e.g., itraconazole: ΔH° up to 55 kJ mol^{-1}; triamterene with Tm = 316°C; genistein with Tm ~ 298°C): Large ΔH° values reflect strong crystal lattice forces (high melting point) that are only partially compensated by solvation. [92], [120], [121], [196]
- Systems with specific strong solvation (e.g., cabozantinib malate in DMSO, clorsulon in ethylene glycol): The solvation exotherm in these systems partially offsets the lattice endotherm, producing lower ΔH° than predicted from the compound's melting point alone. [9], [49], [89]

Rare cases of negative ΔH° (exothermic dissolution) include: β-arbutin in most organic solvents (ΔH° < 0, spontaneous dissolution); sodium acetate in 2,2,2-trifluoroethanol; dicyandiamide in DMF-based binary solvents (2024). In these cases, solvation interactions are stronger than lattice forces. [52], [174], [186], [275]

5.3 Entropy of Dissolution (ΔS°)

The standard molar entropy of dissolution ΔS° is positive for virtually all compound–solvent pairs reviewed, reflecting the entropy gain upon transfer from the highly ordered crystal lattice to the disordered solution state. The translational, rotational, and configurational freedom of solute molecules increases enormously upon dissolution from a solid where each molecule is confined to a lattice site to a solution where molecules are randomly distributed throughout the available volume.
The magnitude of ΔS° varies significantly with molecular size and complexity:

- Small molecules (MW < 200 g/mol, e.g., urea, glycine, benzoic acid, ascorbic acid): ΔS° typically 20–60 J mol^{-1} K^{-1}. The modest entropy gains reflect limited additional conformational freedom gained upon dissolution. [64], [184]
- Medium-sized pharmaceutical compounds (MW 200–500 g/mol): ΔS° typically 40–120 J mol^{-1} K^{-1}. The range reflects the varying contribution of conformational

flexibility, solute–solvent ordering (which reduces entropy), and ideal mixing entropy.

- Large, flexible molecules (MW > 500 g/mol, e.g., iohexol MW=821, β-cyclodextrin MW=1135): ΔS° can reach 150–300 J mol^{-1} K^{-1}. The large conformational entropy gain from flexible substituents (ether chains, rings) dominates. [157], [169]

Negative ΔS° is rare and has been reported for favipiravir in methanol at lower temperatures (2023), suggesting strong ordering of the solvent shell around the solute. This phenomenon, analogous to hydrophobic hydration in aqueous systems, can occur in protic solvents when the solute significantly structures the surrounding solvent molecules through hydrogen bonding. [90]

5.4 Gibbs Free Energy (ΔG°)

The sign and magnitude of ΔG° determine whether dissolution is spontaneous (ΔG° < 0) or non-spontaneous (ΔG° > 0) under saturation conditions. For most organic solids, dissolution is non-spontaneous at saturation (ΔG° > 0), consistent with the definition of the system being at equilibrium there is no thermodynamic driving force for further dissolution once saturation is reached. This is a tautological result: at equilibrium, ΔG° = 0 for the actual process, but the standard-state Gibbs energy $\Delta G°(T) = -RT \cdot \ln(x) > 0$ when $x < 1$.

The practical implication of ΔG° values is their use for solvent ranking: a more positive ΔG° indicates lower solubility in that solvent, because $\Delta G° = -RT \cdot \ln(x)$ means that larger (less negative) ΔG° corresponds to smaller x. The ordering ΔG°(solvent1) < ΔG°(solvent2) is therefore equivalent to x(solvent1) > x(solvent2). This relationship was explicitly used in studies including arbidol hydrochloride monohydrate (2022), where the ascending order of ΔG° exactly reversed the solubility order. [200], [290]

Cases of negative ΔG° (spontaneous dissolution) occur for freely soluble compounds: musk ketone in DMAC/DMF (ΔG° < 0, 2019); esmolol hydrochloride in several solvents (2025); dimetridazole in certain ketone solvents (2021); 3,5-dinitrobenzoic acid in several alcohols (2022). For these systems, dissolution is thermodynamically favoured until the solubility limit is exceeded. [102], [144], [149], [184], [189]

5.5 Enthalpy–Entropy Compensation

Enthalpy–entropy compensation (EEC) is a widely observed phenomenon in physical organic and medicinal chemistry where a linear relationship exists between ΔH° and ΔS° across a series of structurally related systems or solvents:

$$\Delta H° = \beta \cdot \Delta S° + \Delta G°\beta \quad (19)$$

where β is the compensation temperature and ΔG°_β is the intercept (the Gibbs free energy at the compensation temperature). When the compensation temperature β exceeds the harmonic mean temperature Thm, the process is classified as

enthalpically controlled (changes in ΔH° are not fully compensated by ΔS° changes, so the enthalpy term dominates ΔG°); when β < Thm, the process is entropically controlled.

EEC analysis was explicitly conducted in approximately 30 of the reviewed articles. The majority of pharmaceutical dissolution processes reviewed exhibit entropy-driven behaviour (%ξTS > 50%), including: emtricitabine in PEG-400 + water (entropy-driven); cabozantinib malate in DMSO (entropy-driven); brigatinib in ethanol + water (entropy-driven); favipiravir (entropy-driven in most solvents); levetiracetam (entropy-driven). A smaller subset is enthalpy-driven, including: α-glycine in all additive systems studied (enthalpy contribution >50%); 2-acrylamido-2-methyl-1-propanesulfonic acid (enthalpy-driven); curcumin in water (enthalpy contribution confirmed by DSC comparison). [5], [9], [26], [36], [89]

5.6 Thermodynamic Summary Across Compound Classes

Table 5.1 Typical thermodynamic parameters by compound class

Compound Class	Typical ΔH° (kJ/mol)	Typical ΔS° (J/mol·K)	ΔG° Sign	Dissolution Character
Simple organic acids	5–25	20–70	>0	Endothermic, entropy-driven
Small pharmaceuticals (<300 MW)	10–40	30–110	>0	Endothermic, entropy-driven
Large APIs (>400 MW)	20–65	50–150	>0	Endothermic, entropy-driven
Natural products	15–50	40–130	>0, <0	Mostly endothermic; some exothermic
Industrial chemicals	5–30	20–80	>0, <0	Endothermic; some spontaneous in aprotic
Energetic materials	10–35	30–100	>0	Endothermic, entropy-driven

6. Comprehensive Compound Reference Tables

The following tables provide the central data contribution of this systematic review: a comprehensive reference listing of all 200+ compounds covered in the 296 reviewed publications. For each compound, the following information is provided: compound

name, CAS registry number, molecular weight (MW, g/mol), melting point (Tm, °C), compound category, primary uses and applications, year of the reviewed solubility study, key solvents studied, temperature range, best-performing thermodynamic model, and thermodynamic characterisation of the dissolution process.

Compounds are grouped into seven categories: (1) Pharmaceutical Compounds, (2) Natural Products and Phytochemicals, (3) Organic Acids and Anhydrides, (4) Industrial and Specialty Chemicals, (5) Agrochemicals, (6) Energetic Materials, and (7) Sugars, Polyols, and Amino Acids. Within each category, compounds are listed in the order they appear in the original database.

Molecular weights and melting points are taken from primary literature sources, PubChem, or the Merck Index (latest edition). Where values differ slightly across sources, the most commonly cited value is reported. 'Decomposes' (dec) indicates that the compound decomposes rather than melting cleanly. Asterisks (*) denote compounds for which melting point data from the reviewed study's DSC measurement differs from literature due to polymorph-specific behaviour.

6.1 Pharmaceutical Compounds

Table 6.1 Pharmaceutical compounds – molecular properties and applications (128 entries)

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
2	Pioglitazone Hydrochloride	112529-15-4	392.90	193-194	Antidiabetic agent (thiazolidinedione class); treatment of type 2 diabetes mellitus; improves insulin sensitivity
5	Emtricitabine	143491-57-0	247.25	143-144	Antiviral nucleoside reverse transcriptase inhibitor; treatment of HIV-1 infection and hepatitis B
6	Brigatinib	1197953-54-0	539.60	228-230	ALK/ROS1 inhibitor; treatment of ALK-positive metastatic non-small cell lung cancer (NSCLC)
9	Cabozantinib Malate	1140909-48-3	635.67	168-170	Tyrosine kinase inhibitor; treatment

					of thyroid cancer, renal cell carcinoma, hepatocellular carcinoma
11	Actarit	18699-02-0	179.17	222-224	Disease-modifying antirheumatic drug (DMARD); treatment of rheumatoid arthritis
17	Lidocaine Hydrochloride	6108-05-0	288.81	128-130	Local anesthetic and antiarrhythmic drug; widely used in dentistry, surgery, and cardiac care
18	Hydrocortisone	50-23-7	362.46	212-220	Corticosteroid hormone; treatment of inflammatory conditions, adrenal insufficiency, allergic reactions
20	Ethenzamide	938-73-8	165.19	133-135	Non-narcotic analgesic and antipyretic; over-the-counter pain relief; treatment of fever
21	Regorafenib	755037-03-7	482.82	202-205	Multikinase inhibitor; treatment of colorectal cancer, gastrointestinal stromal tumors, hepatocellular carcinoma
22	Ipriflavone	35212-22-7	280.32	116-118	Synthetic isoflavone; treatment and prevention of osteoporosis; bone metabolism regulation
24	Terbinafine Hydrochloride	78628-80-5	327.90	204-206	Allylamine antifungal;

					treatment of dermatophyte infections, onychomycosis (nail fungus), tinea
25	Marbofloxacin	115550-35-1	362.37	>250	Fluoroquinolone antibiotic for veterinary use; broad-spectrum antibacterial in cats, dogs, and cattle
26	Levetiracetam	102767-28-2	170.21	118-120	Antiepileptic drug; treatment of epilepsy, seizures, and myoclonic jerks; first-line anticonvulsant
27	Diphenoxylate	3810-80-8	452.57	219-221	Opioid antidiarrheal agent; treatment of diarrhea; reduces intestinal motility
32	Nifedipine	21829-25-4	346.34	172-174	Calcium channel blocker; treatment of hypertension, angina pectoris, and Raynaud's phenomenon
38	Nicotinamide	98-92-0	122.12	128-131	Vitamin B3 form (niacinamide); treatment of pellagra; skin conditions; coenzyme NAD+ precursor
39	Oxaprozin	21256-18-8	293.32	159-161	NSAID (non-steroidal anti-inflammatory drug); treatment of osteoarthritis and rheumatoid arthritis

41	Chlorzoxazone	95-25-0	169.57	191-194	Centrally-acting skeletal muscle relaxant; treatment of painful musculoskeletal conditions
42	5-Fluorouracil	51-21-8	130.08	282-283	Antimetabolite anticancer drug; treatment of colorectal, breast, stomach, and skin cancers
43	Ibuprofen Sodium Dihydrate	527688-20-6	264.27	72-74	NSAID salt form; analgesic, antipyretic, anti-inflammatory; rapid-onset pain relief formulations
45	Mifepristone	84371-65-3	429.60	192-196	Antiprogestational steroid; medical abortion; treatment of Cushing's syndrome; emergency contraception
46	Thiamphenicol	15318-45-3	356.22	163-165	Broad-spectrum antibiotic; treatment of bacterial infections; veterinary use; alternative to chloramphenicol
48	Bupivacaine Hydrochloride	18010-40-7	342.90	258-261	Long-acting local anesthetic; epidural and spinal anesthesia; post-surgical pain management
49	Clorsulon	60200-06-8	380.22	207-210	Antiparasitic agent; treatment of liver fluke (Fasciola

					hepatica) infections in cattle and sheep
50	Tylosin Tartrate	1405-54-5	1982.33	145-150	Macrolide antibiotic for veterinary use; treatment of respiratory and other infections in livestock
51	Amitriptyline Hydrochloride	549-18-8	313.87	197-199	Tricyclic antidepressant; treatment of depression, neuropathic pain, migraine prevention, insomnia
63	Dabigatran Etexilate Mesylate	872728-81-9	723.86	185-188	Direct thrombin inhibitor; anticoagulant; prevention of stroke and systemic embolism; atrial fibrillation
64	Ascorbic Acid	50-81-7	176.12	190-192	Vitamin C; antiscorbutic; antioxidant; collagen synthesis; immune function; food preservative (E300)
68	Rosiglitazone	122320-73-4	357.43	155-157	Thiazolidinedione antidiabetic; treatment of type 2 diabetes; improves insulin sensitivity
70	Doxofylline	69975-86-6	267.24	159-161	Xanthine derivative bronchodilator; treatment of asthma and chronic obstructive pulmonary disease

71	Nortriptyline Hydrochloride	894-71-3	299.84	213-215	Tricyclic antidepressant; treatment of depression, neuropathic pain, smoking cessation, ADHD
74	Cefuroxime Acid	55268-75-2	424.39	222-224	Second-generation cephalosporin antibiotic; treatment of respiratory, urinary tract, skin infections
75	Dabigatran Etexilate Mesylate Polymorphs	872728-81-9	723.86	185-190	Direct thrombin inhibitor; anticoagulant; polymorphic form studies for crystallization optimization
79	Furosemide	54-31-9	330.74	206-210	Loop diuretic; treatment of edema, hypertension, congestive heart failure, renal disease
80	Sulfanilamide	63-74-1	172.21	165-166	First sulfonamide antibiotic; treatment of bacterial infections; precursor to other sulfa drugs
81	Omeprazole	73590-58-6	345.42	155-157	Proton pump inhibitor; treatment of gastroesophageal reflux, peptic ulcers, Zollinger-Ellison syndrome
83	Mequindox	13297-17-1	216.24	170-172	Quinoxaline antibiotic for veterinary use; growth promotant

					and antibacterial in swine and poultry
84	Cefixime Disodium	124506-28-1	507.44	>250	Third-generation cephalosporin antibiotic; treatment of respiratory, urinary tract, and ear infections
85	Verapamil Hydrochloride	152-11-4	491.06	144-146	Calcium channel blocker; treatment of hypertension, angina, and cardiac arrhythmias
87	Lidocaine	137-58-6	234.34	66-69	Local anesthetic; antiarrhythmic; widely used in medical and dental procedures; topical pain relief
88	Favipiravir	259793-96-9	157.10	200-204	Broad-spectrum antiviral; treatment of influenza, COVID-19; RNA polymerase inhibitor
89	Sulfamonomethoxine	1220-83-3	280.30	209-211	Sulfonamide antibiotic; treatment of bacterial and coccidial infections in veterinary medicine
90	Itraconazole	84625-61-6	705.63	166-168	Triazole antifungal; treatment of systemic fungal infections including aspergillosis and histoplasmosis
91	Benzohydrazide	613-94-5	136.15	112-114	Pharmaceutical intermediate; antitubercular activity; synthesis of

					hydrazone derivatives
92	2-Hydroxybenzohydrazide	936-02-7	152.15	149-152	Antituberculosis intermediate; chelating agent; synthesis of pharmaceutical compounds
93	Tylosin Tartrate (binary)	1405-54-5	1982.33	145-150	Macrolide antibiotic; treatment of respiratory infections and mycoplasmosis in livestock
95	Cefazolin Acid	25953-19-9	454.50	198-200	First-generation cephalosporin antibiotic; treatment of surgical prophylaxis and gram-positive infections
97	Thiamine Nitrate	532-43-4	327.34	196-200	Vitamin B1 salt form; treatment of thiamine deficiency, beriberi; metabolic cofactor supplement
99	Aceclofenac	89796-99-6	354.19	148-150	NSAID; treatment of pain and inflammation in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis
101	Sodium Theophylline	3485-82-3	202.15	>300	Bronchodilator salt form; treatment of asthma, COPD; methylxanthine derivative
102	Dienogest	65928-58-7	311.42	214-215	Synthetic progestogen; treatment of

					endometriosis; oral contraceptive component
103	Indapamide	26807-65-8	365.83	163-165	Thiazide-like diuretic; treatment of hypertension and edema; cardioprotective properties
104	Clarithromycin	81103-11-9	747.95	220-225	Macrolide antibiotic; treatment of respiratory tract, skin, and H. pylori-associated infections
106	Febuxostat	144060-53-7	316.37	208-210	Xanthine oxidase inhibitor; treatment of hyperuricemia in gout patients
108	Edaravone	89-25-8	174.20	127-130	Free radical scavenger; treatment of acute ischemic stroke and ALS (amyotrophic lateral sclerosis)
109	Allantoin	97-59-6	158.12	230-235	Skin healing and soothing agent; wound healing; cosmetic moisturizer; anti-irritant
111	Temozolomide	85622-93-1	194.15	212	Alkylating antineoplastic agent; treatment of glioblastoma multiforme and anaplastic astrocytoma
113	Pazopanib	444731-52-6	473.99	224-226	Multikinase inhibitor (VEGFR, PDGFR); treatment of renal

					cell carcinoma and soft tissue sarcoma
114	L-α-Glyceryl Phosphorylcholine	28319-77-9	257.22	143-145	Choline precursor; nootropic supplement; treatment of cognitive disorders; cholinergic precursor
115	Linezolid	165800-03-3	337.35	181-182	Oxazolidinone antibiotic; treatment of MRSA, VRE, and other gram-positive resistant infections
117	Triamterene	396-01-0	253.27	316	Potassium-sparing diuretic; treatment of hypertension and edema; prevents potassium loss
118	Itopride Hydrochloride	122892-31-3	394.88	200-203	Prokinetic drug; treatment of functional dyspepsia and gastroparesis; promotes gastric motility
122	Rebamipide	90098-04-7	339.75	287-291	Gastroprotective agent; treatment of gastritis and gastric ulcers; mucosal protective drug
126	Dehydroepiandrosterone Acetate	853-23-6	330.46	174-176	Prohormone supplement; testosterone/estrogen precursor; potential anti-aging and adrenal support
128	Gestodene	60282-87-3	310.43	199-200	Third-generation progestogen; oral contraceptive component;

					treatment of endometriosis
131	Domiphen Bromide	538-71-6	414.44	101-104	Quaternary ammonium antiseptic; oral disinfectant in lozenges and mouthwashes; antimicrobial surfactant
132	Carvedilol	72956-09-3	406.47	114-116	Non-selective beta-blocker with alpha-blocking; treatment of heart failure, hypertension, angina
133	Eszopiclone	138729-47-2	388.81	199-200	Non-benzodiazepine hypnotic; treatment of insomnia; promotes sleep onset and maintenance
134	Apixaban	503612-47-3	459.50	251-254	Factor Xa inhibitor; anticoagulant; prevention of stroke in atrial fibrillation; VTE treatment
136	Isotretinoin	4759-48-2	300.44	174-176	Retinoid; treatment of severe acne; vitamin A derivative; teratogenic—requires strict monitoring
140	Esmolol Hydrochloride	81161-17-3	331.84	186-188	Ultra-short-acting β1-selective blocker; intravenous treatment of supraventricular tachyarrhythmias
144	Nintedanib	656247-17-5	539.62	216-218	Triple kinase inhibitor; treatment of idiopathic pulmonary fibrosis

					and systemic sclerosis-ILD
145	Dimetridazole	551-92-8	141.13	142-144	Nitroimidazole antiprotozoal; treatment of histomoniasis and trichomoniasis in poultry and pigs
146	Androstenedione	63-05-8	286.41	170-173	Endogenous androgen; prohormone precursor to testosterone and estrogens; banned sports supplement
149	Nevirapine	129618-40-2	266.30	247-249	Non-nucleoside reverse transcriptase inhibitor; first-line HIV treatment; prevention of mother-to-child HIV
150	2-Ethoxybenzamide	938-73-8	165.19	133-135	Analgesic and antipyretic (ethenzamide); OTC pain reliever in Japan; pharmaceutical intermediate
151	β-Cyclodextrin	7585-39-9	1134.99	300-305	Drug complexing agent; improves solubility and stability; food additive (E459); encapsulation technology
152	Isosorbide 5-Mononitrate	16051-77-7	191.14	90-93	Organic nitrate vasodilator; treatment of angina pectoris; prophylaxis against heart pain

153	Praziquantel	55268-74-1	312.41	136-140	Antiparasitic drug; treatment of schistosomiasis, tapeworm, and other parasitic worm infections
155	Rivaroxaban	366789-02-8	435.88	229-231	Direct Factor Xa inhibitor; anticoagulant; treatment of DVT, PE, and stroke prevention in AF
162	Adefovir	106941-25-7	273.20	189-191	Nucleotide analog antiviral; treatment of chronic hepatitis B (HBV) infection
163	Iohexol	66108-95-0	821.14	185-188	Non-ionic iodinated contrast agent; X-ray imaging, CT scans, myelography, urography
166	Eplerenone	107724-20-9	414.49	233-235	Selective mineralocorticoid receptor antagonist; treatment of hypertension, heart failure post-MI
169	Cyproterone Acetate	427-51-0	416.94	200-201	Antiandrogen; treatment of prostate cancer, acne, hirsutism; oral contraceptive component
171	17-α Hydroxyproge sterone	68-96-2	330.46	222-224	Endogenous progestogen; prevention of preterm birth; diagnosis of congenital adrenal hyperplasia

177	Salbutamol	18559-94-9	239.31	155-157	Short-acting β2-adrenergic agonist; bronchodilator; treatment of asthma and COPD
179	Azithromycin Monohydrate	121470-24-4	767.96	113-115	Macrolide antibiotic; treatment of respiratory, skin, and STI infections; Z-pack antibiotic
181	Sulfaguanidine	57-67-0	214.24	190-193	Sulfonamide antibiotic; treatment of intestinal infections; poorly absorbed, acts locally in gut
182	Isonicotinamide	1453-82-3	122.12	156-158	Isomer of nicotinamide (Vitamin B3); antitubercular intermediate; cocrystal former in pharmaceutical development
185	Hyodeoxycholic Acid	83-49-8	392.57	197-199	Bile acid; dissolution of gallstones; hepatoprotective; pharmaceutical intermediate
187	Zaltoprofen	74711-43-6	298.36	159-162	NSAID; treatment of pain and inflammation in osteoarthritis, rheumatoid arthritis
189	4-(4-Aminophenyl)-3-morpholinone	438056-69-0	192.21	204-207	Rivaroxaban structural analog; pharmaceutical intermediate in anticoagulant drug synthesis

190	Cefpodoxime Proxetil	87239-81-4	557.60	95-100	Third-generation oral cephalosporin; treatment of respiratory tract, skin, and urinary tract infections
191	Aprepitant	170729-80-3	534.43	252-254	NK1 receptor antagonist; antiemetic; prevention of chemotherapy-induced and post-surgical nausea/vomiting
197	Niflumic Acid	4394-00-7	282.22	203-205	NSAID; treatment of pain and inflammation; chloride channel blocker; mefenamic acid analog
200	Salicylanilide	87-17-2	213.23	135-137	Antifungal agent; molluscicide; topical treatment of fungal skin infections; antiseptic
206	Progesterone	57-83-0	314.46	129-131	Endogenous progestogen; contraception; treatment of endometriosis, infertility, and hormone replacement
211	Cytarabine	147-94-4	243.22	212-213	Antimetabolite anticancer drug; treatment of leukemia and lymphoma; pyrimidine analog
212	Satranidazole	56302-13-7	289.26	223-225	Nitroimidazole antiprotozoal;

					treatment of amoebiasis, giardiasis, and trichomoniasis
214	Diclazuril	101831-37-2	407.07	298-302	Antiprotozoal agent; treatment of coccidiosis in poultry and livestock; prophylactic use
216	Cefixime Trihydrate	125110-14-7	507.50	>200	Third-generation oral cephalosporin; treatment of respiratory tract and urinary tract infections
219	l-Carnitine	541-15-1	161.20	197-200	Amino acid derivative; fat metabolism; treatment of carnitine deficiency; sports supplement; heart health
220	Etodolac	41340-25-4	287.35	145-148	NSAID; treatment of osteoarthritis, rheumatoid arthritis, and acute pain
221	Oxcarbazepine	28721-07-5	252.27	215-216	Antiepileptic drug; treatment of partial-onset seizures; mood stabilizer in bipolar disorder
223	Menadiol Diacetate	573-20-6	258.27	111-114	Vitamin K3 prodrug; treatment of hypoprothrombinemia; coagulation factor synthesis
224	Diprophylline	479-18-5	254.24	159-160	Xanthine bronchodilator; treatment of asthma and bronchospasm;

					less cardiotoxic than theophylline
225	Metronidazole Benzoate	13182-89-3	275.26	161-164	Nitroimidazole antibiotic ester; treatment of anaerobic bacterial and protozoal infections; Helicobacter pylori
228	Doxofylline	69975-86-6	267.24	159-161	Theophylline derivative; bronchodilator; treatment of asthma with improved tolerability
229	Naftopidil	57149-07-2	392.46	173-175	α1-adrenoceptor blocker; treatment of benign prostatic hyperplasia (BPH) and dysuria
230	Omeprazole Sulfide	73590-85-9	329.42	152-154	Synthetic intermediate in omeprazole production; impurity reference standard
233	Spectinomycin Dihydrochloride Pentahydrate	22189-32-8	495.35	~260	Aminocyclitol antibiotic; treatment of gonorrhea (penicillin-resistant strains); veterinary antibiotic
235	Quetiapine Fumarate	111974-72-2	883.09	168-170	Atypical antipsychotic; treatment of schizophrenia, bipolar disorder, and depression
239	Doxycycline Hyclate	24390-14-5	1025.89	201-202	Broad-spectrum tetracycline antibiotic; treatment

					of respiratory, skin, malaria, Lyme disease
241	Ribociclib	1211441-98-3	434.54	221-224	CDK4/6 inhibitor; treatment of HR+/HER2- metastatic breast cancer; cyclin-dependent kinase inhibitor
242	Biotin	58-85-5	244.31	230-232	Vitamin B7 (Vitamin H); cofactor for carboxylase enzymes; hair and nail health supplement
246	Bicalutamide	90357-06-5	430.37	191-193	Non-steroidal antiandrogen; treatment of prostate cancer; androgen receptor antagonist
247	Benflumetol	82186-77-4	528.88	90-92	Aryl alcohol antimalarial; combined with artemether (Coartem) for uncomplicated malaria treatment
249	L-Pyroglutamic Acid	98-79-3	129.11	161-163	Glutamine cyclization product; nootropic supplement; treatment of memory disorders; pharmaceutical excipient
253	Sulfaguanidine (repeat)	57-67-0	214.24	190-193	Intestinal sulfonamide antibiotic; treatment of bowel infections

255	Benzethonium Chloride	121-54-0	448.07	162-165	Quaternary ammonium antiseptic; disinfectant in eye drops, wound cleaners, mouthwashes
256	Cytosine	71-30-7	111.10	320-325	Nucleobase; DNA/RNA component; pharmaceutical intermediate for antiviral nucleoside analogs
259	Benorilate	5003-48-5	313.31	174-175	Combined aspirin-paracetamol ester prodrug; analgesic, antipyretic, anti-inflammatory; gentle on stomach
263	Pregabalin	148553-50-8	159.23	194-196	Anticonvulsant and anxiolytic; treatment of neuropathic pain, fibromyalgia, epilepsy, generalized anxiety
267	Riluzole	1744-22-5	234.20	116-118	Glutamate release inhibitor; only FDA-approved treatment for ALS (amyotrophic lateral sclerosis)
269	Arbidol Hydrochloride Monohydrate	131707-23-8	477.40	189-192	Broad-spectrum antiviral; treatment and prevention of influenza; membrane fusion inhibitor
272	Clotrimazole	23593-75-1	344.84	147-149	Imidazole antifungal; treatment of candidiasis, athlete's foot, ringworm,

					vaginal yeast infections
273	4-Aminobenzenesulfonamide	63-74-1	172.21	165-166	Sulfanilamide; parent compound of sulfonamide antibiotics; treatment of bacterial infections
275	2-Hydrazino-4-methylbenzothiazole	20174-68-9	179.24	220-222	Pharmaceutical intermediate; synthesis of benzothiazole-hydrazone derivatives with antimicrobial activity

6.2 Natural Products and Phytochemicals

Table 6.2 Natural Product compounds – molecular properties and applications

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
10	Curcumin	458-37-7	368.38	183	Anti-inflammatory, antioxidant, anticancer natural compound; food colorant (E100); nutraceutical
14	Vanillic Acid	121-34-6	168.15	210-213	Natural phenolic acid in vanilla; antioxidant, antimicrobial; food flavoring; pharmaceutical intermediate
19	Thymol	89-83-8	150.22	49-51	Antiseptic, antifungal; ingredient in mouthwashes, cosmetics; food preservative; pharmaceutical intermediate
23	Baicalein	491-67-8	270.24	264-265	Flavonoid from Scutellaria baicalensis;

					anti-inflammatory, antitumor, neuroprotective, antimicrobial activities
29	2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside	82373-94-2	406.39	150-155	Active component of Polygonum multiflorum; anti-aging, anti-inflammatory, cardioprotective effects
35	β-Lapachone	4707-32-8	242.27	152-154	Naphthoquinone from Tabebuia tree; anticancer, antiprotozoal, antiviral, and anti-inflammatory activities
52	β-Arbutin	497-76-7	272.25	198-201	Skin-whitening agent in cosmetics; inhibits melanin synthesis; antioxidant; found in bearberry leaves
54	Esculetin	305-01-1	178.14	268-270	Coumarin derivative; anti-inflammatory, antioxidant, anticancer; isolated from ash bark and lemon peel
61	(-)-Shikimic Acid	138-59-0	174.15	184-186	Key intermediate in Tamiflu (oseltamivir) synthesis; found in star anise; biosynthetic precursor
62	Capsaicin	404-86-4	305.41	65	Active component of chili peppers; topical analgesic; pain relief cream; weight loss supplement
76	N-Acetylglucosamine	7512-17-6	221.21	210-213	Dietary supplement for joint health; osteoarthritis treatment; skin

					moisturizer; chitin derivative
77	trans-3-Hydroxycinnamic Acid	14755-02-3	164.16	223-225	Natural phenolic acid; antioxidant, antimicrobial; food and cosmetic industry; pharmaceutical intermediate
86	Tanshinone I	568-73-0	276.31	192-195	Diterpenoid from Salvia miltiorrhiza; cardiovascular protective, anti-inflammatory, anticancer effects
110	α-Glycine	56-40-6	75.03	233	Simplest amino acid; nutritional supplement; pharmaceutical excipient; industrial fermentation
112	Gibberellin A4	468-44-0	332.40	233-235	Plant growth regulator; promotes stem elongation, fruit development, and seed germination in agriculture
116	Genistein	446-72-0	270.24	297-298	Soy isoflavone; phytoestrogen; potential anticancer, bone-protective, and cardiovascular properties
119	Caffeic Acid	331-39-5	180.16	223-225	Phenylpropanoid from coffee and plants; antioxidant, anti-inflammatory, antimicrobial, anticancer
121	Thymoquinone	490-91-5	164.20	44-46	Active component of Nigella sativa (black seed); antioxidant, anti-

					inflammatory, anticancer, antimicrobial
123	Chrysin	480-40-0	254.24	285-287	Natural flavonoid from honey and plants; anti-inflammatory, anxiolytic, antifungal, anticancer effects
130	Pterostilbene	537-42-8	256.30	89-91	Dimethyl ether of resveratrol; antioxidant, anticancer, cardioprotective; found in blueberries
141	Syringic Acid	530-57-4	198.17	204-207	Natural phenolic acid from syringas and lignin; antioxidant, anti-inflammatory, antimicrobial properties
158	Methyl Gallate	99-24-1	184.15	199-203	Antioxidant from tannins; antimicrobial, anti-inflammatory, antiviral; food preservative; cosmetic ingredient
160	Rhein	478-43-3	284.22	321-322	Anthraquinone from rhubarb; anti-inflammatory, hepatoprotective, anticancer; treatment of renal disease
167	4-Hydroxy-2,5-dimethyl-3(2H)-furanone	3658-77-3	114.10	76-79	Natural flavor compound (DMHF); strawberry, pineapple aroma; food flavoring; fragrance industry
170	EGCG Peracetate	148707-39-5	806.69	145-148	Peracetylated derivative of green tea catechin EGCG; improved bioavailability; anticancer research

172	Limonin	1180-71-8	470.51	298-300	Triterpenoid from citrus; bitter component of orange juice; anticancer, antifeedant, antibacterial
176	Dihydromyricetin	27200-12-0	320.25	219-222	Flavonoid from Ampelopsis grossedentata; antioxidant, anti-inflammatory, hepatoprotective; anti-hangover
193	Rutaecarpine	84-26-4	287.32	257-259	Indolopyridoquinazoline alkaloid from Evodia; cardiovascular, anti-inflammatory, thermogenic effects
194	Evodiamine	518-18-3	303.36	278-280	Quinazolinocarboline alkaloid; anti-obesity, anti-tumor, anti-inflammatory; activates TRPV1 receptor
203	l-Glutamic Acid	56-86-0	147.13	247-249	Non-essential amino acid; MSG precursor; flavor enhancer; pharmaceutical supplement; neurotransmitter
207	Trans-Resveratrol	501-36-0	228.25	261-263	Polyphenol from red wine and grapes; antioxidant, anti-aging, cardioprotective, anticancer properties
210	Daidzin	552-66-9	416.38	220-222	Soybean isoflavone glycoside; phytoestrogen; antioxidant; alcohol metabolism modulation

218	4-(4-Hydroxyphenyl)-2-butanone	5471-51-2	164.20	81-83	Raspberry ketone; natural flavor compound; weight loss supplement; fragrance ingredient
248	p-Coumaric Acid	501-98-4	164.16	210-213	Hydroxycinnamic acid; antioxidant, antimicrobial; found in peanuts, tomatoes, garlic; plant phenolic
250	d-(-)-Quinic Acid	77-95-2	192.17	165-168	Found in coffee, fruits; precursor in shikimic acid pathway; treatment of respiratory infections

6.3 Organic Acids

Table 6.3 Organic Acid compounds – molecular properties and applications

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
8	Succinic Acid	110-15-6	118.09	185-187	Food additive (E363); pharmaceutical excipient; production of biodegradable polymers (PBS); flavoring agent
56	Thiomalic Acid	70-49-5	150.15	149-151	Chelating agent; pharmaceutical intermediate; antioxidant in hair care products
82	Tartaric Acid	87-69-4	150.09	171-174	Food acidulant (E334) in wine, beverages; cream of tartar; pharmaceutical excipient; chiral resolution agent

147	Hippuric Acid	495-69-2	179.17	190-193	Metabolite of toluene exposure (biomarker); research on kidney function; pharmaceutical intermediate
154	dl-Malic Acid	6915-15-7	134.09	130-132	Food acidulant (E296); wine industry; pharmaceutical excipient; production of malates
156	Oxalic Acid	144-62-7	90.03	189-191	Rust remover; wood bleaching; rare earth metal processing; pharmaceutical intermediate; stone cleaning
164	(R, S)-Mandelic Acid	90-64-2	152.15	118-120	Chiral resolving agent; pharmaceutical intermediate; synthesis of antibiotics and anticoagulants; mandelic acid
178	Benzoic Acid	65-85-0	122.12	121-123	Food preservative (E210); synthesis of benzoate salts, esters, and pharmaceuticals; antimicrobial agent
184	α-Ketoglutaric Acid	328-50-7	146.10	113-116	TCA cycle intermediate; nutritional supplement; treatment of metabolic disorders; kidney protection

188	L-Malic Acid	97-67-6	134.09	100-103	Food acidulant; apple flavor; pharmaceutical excipient; sports nutrition (delays muscle fatigue)
240	l-Malic Acid (repeat)	97-67-6	134.09	100-103	Natural fruit acid; food acidulant; pharmaceutical excipient; TCA cycle intermediate

6.4 Industrial and Specialty Chemicals

Table 6.4 Industrial Chemical compounds – molecular properties and applications

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
4	Sulfanilic Acid	121-57-3	173.19	288	Synthesis of dyes (azo dyes), pharmaceuticals, and optical brighteners; analytical reagent
7	2-Methylnaphthalene	91-57-6	142.20	34-36	Synthesis of vitamin K; production of dyes, pesticides; petroleum refining by-product
12	Dibenzothiophene	132-65-0	184.26	99-101	Model compound for desulfurization research; petroleum chemistry; organic semiconductor research
13	Phthalic Anhydride	85-44-9	148.12	131-133	Production of plasticizers (phthalates),

					resins, dyes, pharmaceuticals, and agrochemicals; >5 million tons/year produced globally
15	4,4′-Dihydroxydiphenyl Sulfone	80-09-1	250.27	240 - 243	Monomer for polysulfone polymers; thermally stable resins; heat-resistant engineering plastics
30	2,3,4-Trichloro-1,5-dinitrobenzene	6379-46-0	271.47	64-67	Intermediate in synthesis of agrochemicals and specialty chemicals; organic synthesis
31	2-Acrylamido-2-methyl-1-propanesulfonic Acid	15214-89-8	207.25	195 - 196	Monomer for superabsorbent polymers, hydrogels, ion-exchange resins, and water treatment chemicals
34	Phthalimide	85-41-6	147.13	232 - 235	Intermediate in Gabriel synthesis of primary amines; synthesis of thalidomide; agricultural chemicals
37	Methyleneaminoacetonitrile	109-82-0	82.08	45-47	Intermediate in chemical synthesis; production of amino acids and pharmaceutical intermediates

40	3,4-Dichloronitrobenzene	99-54-7	192.00	40-43	Intermediate in synthesis of pharmaceuticals, agrochemicals, and dyes
44	N-Hydroxymethyl Acrylamide	924-42-5	101.10	74-76	Cross-linking agent in polymers; paper treatment; textile finishing; production of hydrogels
47	Stearic Acid	57-11-4	284.48	69-71	Soap and detergent manufacturing; cosmetic emulsifier; pharmaceutical tablet lubricant; plasticizer
53	4,4′-Oxydianiline	101-80-4	200.23	190 - 192	Monomer for polyimides and polyamides; high-performance aerospace materials; synthesis of dyes
55	p-Chloroaniline	106-47-8	127.57	72-74	Intermediate in dye, pesticide, pharmaceutical synthesis; production of p-chloroacetanilide
58	2-Chloro-3-(trifluoromethyl)pyridine	65753-47-1	181.54	18-20	Pharmaceutical and agrochemical intermediate; building block for fluorinated compounds
59	Isovanillin	621-59-0	152.15	113 - 115	Flavoring agent; pharmaceutical intermediate;

					synthesis of drugs and fine chemicals
60	m-Hydroxyacetophenone	121-71-1	136.15	95-98	Pharmaceutical and cosmetic intermediate; synthesis of resins and UV absorbers
65	Sorbic Acid	110-44-1	112.13	134-135	Food preservative (E200); inhibits mold and yeast in food; cosmetic preservative; polymer intermediate
66	N,N′-Oxalyldiglycine	5262-39-5	190.11	>250	HIF prolyl hydroxylase inhibitor in research; tool compound for hypoxia signaling studies
67	1-Nitronaphthalene	86-57-7	173.17	55-58	Intermediate in dye synthesis; production of 1-naphthylamine; industrial chemical research
72	4′-Bromomethyl-2-cyanobiphenyl	114772-54-2	272.13	100-103	Key intermediate in synthesis of sartans (losartan, valsartan) for hypertension treatment
73	2,3,4,5-Tetrabromothiophene	3958-03-0	399.74	102-104	Flame retardant intermediate; building block for halogenated thiophene derivatives

78	para-Methoxyphenylacetic Acid	104-01-8	166.17	86-89	Pharmaceutical intermediate; synthesis of ibuprofen and related compounds; fragrance chemical
94	Ethyl 5-Amino-4-cyano-2-thiophenecarboxylate	58168-20-0	282.34	97-100	Pharmaceutical intermediate; thiophene derivative for drug synthesis
98	4-Acetylbenzoic Acid	586-89-0	164.16	208-210	Pharmaceutical intermediate; synthesis of benzophenone derivatives; UV absorbers
100	Musk Ketone	81-14-1	294.35	135-136	Synthetic musk fragrance; perfumery; cosmetics; textiles; fixative in fragrance compositions
105	Phenylphosphonic Acid	1571-33-1	158.09	163-165	Flame retardant component; surface treatment agent; catalyst; pharmaceutical intermediate
107	m-Aminobenzoic Acid	99-05-8	137.14	173-177	Intermediate in dyes, pharmaceuticals, and polymers; UV absorber; synthesis of folic acid analogs

120	R-(+)-2-(4-Hydroxyphenoxy)propionic Acid	94050-90-5	182.18	155 - 157	Chiral intermediate in synthesis of herbicides (mecoprop, dichlorprop); asymmetric synthesis
124	Urea	57-13-6	60.06	132 - 135	Fertilizer (46% N); production of resins, plastics, animal feed; pharmaceutical excipient; skin moisturizer
125	1-Hydroxybenzotriazole	2592-95-2	135.12	157 - 160	Coupling reagent in peptide synthesis; prevents racemization; pharmaceutical synthesis reagent
127	Ammonium Sulfate	7783-20-2	132.14	235 - 280	Nitrogen fertilizer; protein precipitation in biochemistry; food additive (E517); flame retardant
129	Cyclododecanone	830-13-7	182.28	58-61	Precursor to laurolactam and nylon-12; synthesis of musk fragrances; industrial polymer chemistry
137	N,2,3-Trimethyl-2-isopropylbutamide	51115-67-4	185.31	60-62	Cooling agent (WS-3 analogue); topical cooling sensation in cosmetics and pharmaceuticals

138	2,5-Furandicarboxylic Acid	3238-40-2	156.09	342	Bio-based monomer for PEF polymer; sustainable alternative to terephthalic acid; green chemistry
139	Caprolactam	105-60-2	113.16	68-70	Monomer for nylon-6 production; one of the highest-volume industrial chemicals worldwide
142	Dimethyl Terephthalate	120-61-6	194.19	140-141	Monomer for polyester (PET) production; synthesis of polyesters, coatings, and plasticizers
143	1,3,5-Trichlorobenzene	108-70-3	181.45	62-63	Solvent for resins; intermediate in agrochemical and dye synthesis; herbicide production
148	Triethylamine Hydrochloride	554-68-7	137.63	254-258	Ionic liquid precursor; reaction base in organic synthesis; pharmaceutical salt preparation
157	2,5-Thiophenedicarboxylic Acid	4282-31-9	172.16	>300	Monomer for polyesters and polyamides; pharmaceutical intermediate; bioisostere of terephthalic acid

159	Isatin	91-56-5	147.13	199 - 201	Heterocyclic scaffold in medicinal chemistry; synthesis of antivirals, antibacterials, anticancer agents
161	1,3-Dimethylurea	96-31-1	88.11	102 - 106	Intermediate in chemical synthesis; pharmaceutical excipient; resin crosslinker
165	Maleic Anhydride	108-31-6	98.06	52-54	Production of resins, plastics, coatings; synthesis of fumaric and malic acids; >2 million tons/year
168	Dicyandiamide	461-58-5	84.08	207 - 212	Fertilizer additive (nitrification inhibitor); production of guanidine compounds, resins; flame retardant
173	2-Bromo-5-hydroxypyrazine	374063-92-0	175.00	159 - 162	Building block for pharmaceutical synthesis; heterocyclic intermediate
174	Methyl Paraben	99-76-3	152.15	131 - 133	Antimicrobial preservative in cosmetics, food, and pharmaceuticals; E-number E218

175	Trimethylolethane	77-85-0	120.15	199 - 202	Monomer for alkyd resins, polyurethanes, lubricants, and coatings; crosslinking agent
180	Sodium Acetate	127-09-3	82.03	324 (dec)	Food preservative (E262); buffer in chemical synthesis; heating pad material; photographic fixer
183	3,5-Dinitrobenzoic Acid	99-34-3	212.12	205 - 207	Analytical reagent; detection of alcohols and reducing sugars; synthesis of pharmaceutical intermediates
186	Potassium Benzoate	582-25-2	160.21	250 - 260	Food preservative (E212); antimicrobial in acidic foods; pharmaceutical and cosmetic preservative
192	d-Camphor-10-Sulfonic Acid	3144-16-9	232.30	195 - 197	Chiral resolving agent; asymmetric synthesis; acid catalyst; pharmaceutical intermediate
195	Bis-2-hydroxyethyl Terephthalate	959-26-2	254.24	109 - 110	PET (polyethylene terephthalate) degradation product; monomer recycling; sustainable chemistry
196	Lauric Acid	143-07-7	200.32	43-45	Surfactant and detergent raw

					material; antimicrobial properties; coconut oil component; cosmetics
198	3-Chlorophthalic Anhydride	117-21-5	182.56	99-101	Intermediate for polyimides, dyes, and pharmaceutical synthesis; separation from 4-isomer
199	4-Chlorophthalic Anhydride	118-45-6	182.56	97-99	Intermediate in synthesis of pharmaceuticals, dyes, and polymer additives
201	2,2-Bis(hydroxymethyl)butyric Acid	10097-02-6	134.13	90-93	Monomer for waterborne polyurethane dispersions; coatings and adhesive industry
202	Calcium Sulfate Dihydrate	10101-41-4	172.17	~1450 (anh)	Gypsum; plaster of Paris; construction materials; food additive (E516); medical casting
204	3-Pentadecylphenyl Acrylate	119080-22-7	358.57	32-34	Monomer from natural cardanol; bio-based polymer synthesis; coatings and resins
205	Methanesulfonamide	3144-09-0	95.10	87-90	Pharmaceutical intermediate; reagent in organic synthesis; carbonic

					anhydrase inhibitor model
208	4-Methylphthalic Anhydride	19438-61-0	162.14	52-54	Intermediate for polyimides, alkyd resins, dyes; asymmetric synthesis reagent
209	1,5-Pentylenediamine Hydrochloride	541-69-5	124.61	220 - 225	Biobased precursor to pentamethylene diisocyanate (PDI) for polyurethane synthesis
213	6-Chloropyridazin-3-amine	5469-69-2	129.55	190 - 192	Heterocyclic intermediate in pharmaceutical synthesis; building block for CNS drugs
215	2-Naphthaldehyde	66-99-9	156.18	59-62	Fragrance intermediate; synthesis of naphthalene derivatives; dye intermediate
222	Ethylene Thiourea	96-45-7	102.15	203 - 206	Vulcanization accelerator for neoprene rubber; fungicide intermediate; pharmaceutical synthesis
226	2-Amyl Anthraquinone	13936-21-5	278.35	54-57	Working carrier in hydrogen peroxide (H2O2) production via anthraquinone oxidation process
227	N-Ethyl-2,2-diisopropylbutylamide	7087-68-5	213.36	~10	Synthetic cooling agent (WS-27); topical cooling

					sensation in cosmetics, oral care, and food
231	2-Amino-4,6-dichloropyrimidine	56-05-3	164.00	209 - 212	Building block for pharmaceuticals (antivirals, antimalarials, herbicides); heterocyclic chemistry
232	N-Acetyl-1,3-phenylenediamine	102-28-3	150.18	78-81	Intermediate in dye synthesis; antioxidant for rubber; pharmaceutical intermediate
234	3-Amino-6-bromopyridazine	88497-27-2	174.00	150 - 153	Heterocyclic building block for pharmaceutical synthesis; antimicrobial and antifungal compounds
236	3-Methyl-1,2-cyclopentanedione	765-70-8	112.13	215 - 218	Flavor compound; maple syrup aroma; food flavoring; synthesis of natural product analogs
237	3-Ethoxysalicylaldehyde	492-88-6	166.17	73-76	Intermediate in synthesis of Schiff base ligands, dyes, and pharmaceutical compounds
238	Glutaric Anhydride	108-55-4	114.10	55-57	Synthesis of glutaric acid derivatives; crosslinking agent; polymer

					and pharmaceutical intermediate
243	4,4′-Dinitrodiphenyl Ether	101-63-3	260.20	141 - 143	Intermediate for polyimide synthesis; high-performance polymer monomers; electronic applications
244	2-Benzimidazolone	615-16-7	134.14	317 - 320	Building block for pharmaceuticals, dyes (benzimidazolone pigments), and agricultural chemicals
245	Musk Ketone (repeat)	81-14-1	294.35	135 - 136	Nitro musk fragrance compound; perfumery and cosmetics; currently restricted in many jurisdictions
251	Fluorene	86-73-7	166.22	114 - 116	PAH compound; synthesis of fluorene-based polymers for OLEDs; pharmaceutical intermediate
252	4-Biphenylcarboxylic Acid	92-92-2	198.22	225 - 228	Monomer for high-performance polymers; liquid crystal materials; pharmaceutical intermediate

254	Dicyandiamide (repeat)	461-58-5	84.08	207 - 212	Soil nitrification inhibitor; epoxy resin hardener; guanidine compound precursor
257	2,3,4-Trimethoxybenzoic Acid	573-11-5	212.20	148 - 150	Pharmaceutical intermediate; veratrum acid derivative; synthesis of colchicine analogs
258	2-Naphthoxyacetic Acid	120-23-0	202.21	156 - 158	Plant growth regulator; fruit thinning agent; pharmaceutical intermediate
261	4-Fluorobenzoic Acid	456-22-4	140.11	182 - 185	Pharmaceutical intermediate; PET tracer precursor; synthesis of fluorinated compounds
262	3-Nitrobenzonitrile	619-24-9	148.12	111 - 112	Pharmaceutical intermediate; synthesis of triazoles and tetrazoles; agrochemical building block
264	Diphenolic Acid	126-00-1	270.32	171 - 174	Bisphenol A analog from levulinic acid; bio-based monomer for resins and polymers
265	Isatoic Anhydride	118-48-9	163.13	244 - 246	Reagent for synthesis of anthranilic acid amides; pharmaceuticals,

					agrochemicals, and dyes
266	2-Anilino-6-(dibutylamino)-3-methylfluoran	89331-94-2	532.69	64-68	ODB-2 leuco dye; thermal paper developer for receipt and label printing
268	N,N′-Diphenylthiourea	102-08-9	228.31	153-155	Vulcanization accelerator for rubber; corrosion inhibitor; flotation agent in mining
270	Ammonium Chloride	12125-02-9	53.49	338 (subl)	Fertilizer nitrogen source; soldering flux; food additive (E510); cold pack coolant; pharmaceutical expectorant
271	2-Amino-6-chloropyrazine	33332-28-4	129.55	158-161	Heterocyclic intermediate; pharmaceutical synthesis building block for kinase inhibitors

6.5 Agrochemicals

Table 6.5 Agrochemical compounds – molecular properties and applications

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
3	Spirotetramat	203313-25-1	373.46	148-149	Systemic insecticide and acaricide; controls sucking pests (aphids, whiteflies, mites) in agriculture
217	Diflufenican	83164-33-4	394.28	159-161	Herbicide; inhibits carotenoid biosynthesis; control of broad-leaved weeds in cereals

260	2-Methyl-4-chlorophenoxyacetic Acid	94-74-6	200.62	119-121	Systemic herbicide (MCPA); selective control of broad-leaved weeds in cereals and turf

6.6 Energetic Materials

Table 6.6 Energetic Material compounds – molecular properties and applications

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
1	Tetranitroglycoluril	N/A	316.11	Decomposes >260	High-energy density material; used in propellants, explosives, and pyrotechnics
16	Guanidine Nitrate	506-93-4	122.10	213-215	Gas generator propellant in automotive airbags; pyrotechnic compositions; precursor to guanidine derivatives
28	2,4,6-Trinitro-3-Bromoanisole	30566-49-1	336.07	63-65	Energetic compound; intermediate in synthesis of nitroanisole derivatives; research purposes
57	1,3-Diaminoguanidine Monohydrochloride	36062-19-8	124.53	>250	Energetic material precursor; synthesis of tetrazoles and other nitrogen-rich compounds; propellant applications

96	1,3-Dinitropyrazole	38858-81-0	158.07	90-92	High-energy density material; pharmaceutical synthesis intermediate; energetic binder research

6.7 Sugars, Polyols, and Amino Acids

Table 6.7 Sugar/Polyol compounds – molecular properties and applications

No.	Compound Name	CAS No.	MW (g/mol)	Tm (°C)	Primary Uses
33	Erythritol	149-32-6	122.12	119-122	Zero-calorie sweetener; food additive (E968); humectant in cosmetics; low glycemic index sugar substitute
69	D-Tagatose	87-81-0	180.16	133-135	Low-calorie sweetener; antidiabetic effects; prebiotic activity; used in food and pharmaceutical industry
135	d-Sorbitol	50-70-4	182.17	93-97	Sugar alcohol sweetener; humectant in cosmetics; laxative; pharmaceutical excipient; food additive
274	D-Psicose	551-68-8	180.16	109-111	Rare C-3 epimer of fructose; low-calorie sweetener (0.2 kcal/g); anti-obesity and antidiabetic effects

7. Conclusion

7.1 Summary of Principal Findings

This systematic review has synthesised solid–liquid equilibrium data, thermodynamic modelling results, and solvent-effect analyses from 296 peer-reviewed publications spanning the years 2012 to 2026. The comprehensive dataset covers more than 200 distinct chemical entities across seven compound categories: pharmaceuticals, natural products, organic acids, industrial chemicals, agrochemicals, energetic materials, and sugars/polyols. The following principal conclusions emerge from this synthesis.

7.2 Universal Temperature Dependence

Solubility increases monotonically with temperature for the vast majority of compounds and solvents studied in this review a fundamental consequence of the predominantly endothermic character of dissolution for organic solids. The van't Hoff equation provides a quantitative description of this temperature dependence and serves as the primary tool for extracting standard dissolution enthalpies and entropies. Rare cases of negative temperature dependence (exothermic dissolution) were documented for β-arbutin in organic solvents, sodium acetate in trifluoroethanol, and certain dicyandiamide systems. [52], [174], [186], [275]

The temperature sensitivity of solubility quantified as d(x)/dT ranges from modest (~1–3% per K for simple salts) to dramatic (20-fold increase over 40 K for clorsulon in ethylene glycol). Understanding and quantifying this sensitivity is essential for designing cooling crystallisation processes: compounds with high d(x)/dT are ideal for cooling crystallisation, while those with weak temperature dependence require antisolvent strategies. [49]

7.3 Dominance of the Modified Apelblat Equation

The three-parameter modified Apelblat equation is the most universally applicable and most accurate model for correlating experimental SLE data, providing ARD values below 2% for the majority of studied systems. Its flexibility from linear to strongly non-linear temperature dependence encompasses the full diversity of compound–solvent combinations encountered. The Apelblat equation is strongly recommended as the primary correlation equation for new SLE datasets, with the λh and van't Hoff equations providing two-parameter alternatives that enable direct thermodynamic interpretation.

Activity coefficient models (Wilson, NRTL, UNIQUAC) provide physically richer descriptions of non-ideal solution behaviour and should be preferred when thermodynamic mixing properties (ΔGmix, ΔHmix, ΔSmix, activity coefficients) are required, as these cannot be extracted from empirical equations. The NRTL model demonstrated the best and most consistent performance among activity coefficient models across diverse compound classes.

7.4 Thermodynamic Character

The dominant thermodynamic character of dissolution across the reviewed compounds is endothermic, entropy-driven, and non-spontaneous under saturation conditions ($\Delta H^\circ > 0$, $\Delta S^\circ > 0$, $\Delta G^\circ > 0$). The positive entropy contribution arising from lattice disruption and mixing typically dominates the dissolution Gibbs energy, making entropic driving forces the primary thermodynamic explanation for why organic solids dissolve in organic solvents at all. The enthalpy term opposes

dissolution (unfavourable, endothermic) but is overcome by the entropic driving force at temperatures above the melting point/eutectic temperature.

The enthalpy–entropy compensation analysis across multiple compounds confirms that %§TS > 50% for approximately 80% of the pharmaceutical compounds reviewed, firmly establishing entropy as the dominant contributor to the dissolution free energy in this class. In contrast, smaller molecules (amino acids, simple organic acids) show a somewhat more balanced enthalpy/entropy split, reflecting their greater involvement of hydrogen-bond network disruption in the dissolution process.

7.5 Solvent Selection Principles

The solvent-effect analyses conducted using KAT-LSER and HSP frameworks across approximately 90 of the reviewed articles provide convergent, quantitative guidance for solvent selection in pharmaceutical and industrial crystallisation:

- For polar APIs with multiple hydrogen-bond donors (sulfonamides, amines, alcohols): Polar aprotic solvents (DMSO, DMF, DMAC, NMP) with high β (hydrogen-bond acceptor) capacity provide the highest solubility and are thus best for dissolution and re-crystallisation. The cavity term (high cohesive energy density) should be minimised in the solvent.
- For lipophilic compounds (terpenoids, steroids, lipid-like drugs): Non-polar or weakly polar solvents (toluene, esters, chlorinated solvents) with low δH are preferred. PEG-400 is highly effective as a pharmaceutical solvent for many lipophilic APIs due to its unusual combination of amphiphilicity and low cohesive energy density.
- For ionic compounds (hydrochloride salts, sodium salts): Water and lower alcohols are typically most effective. The solubility order within alcohols consistently follows the decreasing polarity trend: methanol > ethanol > propanols > butanols.
- For crystallisation using antisolvent approaches: Water addition to organic solvent systems provides the greatest solubility reduction for most organic compounds, enabling efficient crystallisation yield. The optimal organic solvent:water ratio for maximum yield should be identified from binary SLE data.

The Hansen solubility parameter analysis consistently identifies the best solvent as the one with the minimum total Ra distance to the solute in three-dimensional (δD, δP, δH) space. This simple geometric criterion, derived from purely computational data without experimental measurement, correctly predicted the experimental solubility order in approximately 75% of cases across the reviewed articles a remarkable predictive power that validates the thermodynamic basis of the HSP framework.

7.6 Polymorphism and Solid-Form Considerations

Several of the reviewed compounds are known to exist in multiple polymorphic forms, and the influence of polymorphism on solubility is an important theme. Dabigatran

etexilate mesylate (Forms I, II, M, and Hemihydrate) was studied in five solvents (2020), demonstrating that solubility differs significantly between polymorphs, with the thermodynamically stable form (lowest Gibbs energy solid) showing the lowest solubility. Rivaroxaban forms I and II were compared in seven solvents (2017), confirming that the metastable form II has higher solubility than the stable form I a classical result in pharmaceutical polymorphism.

The prevalence of polymorphic transformation during solubility measurement (monitored by PXRD in approximately 150 articles) underscores the importance of solid-state characterisation as an integral component of any SLE study. Failure to verify solid-form identity can result in mixed-phase solubility measurements that are thermodynamically meaningless.

7.7 Implications for Pharmaceutical Development

The solubility and thermodynamic data compiled in this review have direct and immediate implications for pharmaceutical development:

- Crystallisation process design: The comprehensive SLE data enable selection of optimal solvent systems for crystallisation, calculation of theoretical yield as a function of temperature and composition, and rational design of seeding, cooling, and antisolvent profiles.
- Solubility enhancement: The HSP and KAT-LSER analyses identify the physicochemical drivers of solubility, guiding the selection of co-solvents, surfactants, cyclodextrin complexation partners, or co-crystal formers to enhance bioavailability of BCS Class II compounds.
- Stability assessment: Thermodynamic data from SLE measurements ($\Delta G°$, activity coefficients) inform stability predictions for solid dispersions, amorphous formulations, and co-crystals, where thermodynamic stability against crystallisation is a key quality attribute.
- Salt and polymorph screening: The ranking of solubilities across solvent classes provides guidance for salt form selection (more hydrophilic counterions for better aqueous solubility) and identifies solvents for polymorph screening during solid-state development.

7.8 Future Research Directions

Despite the comprehensive coverage of the 296 reviewed articles, several research areas remain underexplored and represent priority directions for future work:

- Green and bio-based solvents: Only a small fraction of reviewed studies examined bio-based solvents (cyclopentyl methyl ether, 2-methyltetrahydrofuran, ethyl lactate, limonene) or deep eutectic solvents (DES). Given the increasing regulatory and sustainability pressure to replace traditional organic solvents, systematic SLE measurements in these media are urgently needed.
- Machine learning integration: The comprehensive dataset compiled in this review with over 10,000 individual solubility data points spanning >200 compounds, >50 solvents, and 50-year temperature ranges provides an ideal training set for

machine learning models predicting solubility from molecular structure and solvent properties.

- Supercooled liquid systems: Amorphous formulations of poorly soluble drugs represent a growing area of pharmaceutical practice. SLE measurements on supercooled liquid forms and amorphous dispersions extend classical SLE theory into kinetically controlled regimes.
- Multicomponent systems: Most reviewed studies address binary (solute + single solvent) or ternary (solute + binary solvent) systems. Quaternary and more complex systems relevant to pharmaceutical processing (including excipients, buffers, and counter-ions) remain largely unstudied.

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