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The Evolution of Pharmaceutical Solids: From Early Polymorphism to Cutting-Edge Drug Development

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Abstract: The pharmaceutical industry has a significant impact on society, and this influence does not need much explanation. The process of discovering, developing, and offering new drug products to patients is complex, demanding, and time-consuming. It includes many stages of research and development, using different scientific concepts. Most active pharmaceutical ingredients, especially synthetic and semi-synthetic drugs, are in solid form during preparation and use. Therefore, the solid-state properties of these substances play an important role in the performance of the final product. This review describes the development of research in this field. In the early stages, studies of solid-state properties were rare and often conducted only when a specific problem was identified. Over time, research into solid-state properties has become essential and is now an important part of drug discovery and development. To illustrate this progress, three case studies are discussed: chloramphenicol palmitate, torasemide, and azithromycin. Knowledge maps are also included to show how the research focus has changed over time. Finally, the paper provides a short overview of future trends in this field.

Keywords: polymorphism, drug formulation, polymorphic screening, torasemide, azithromycin, hydrates, solvates, pharmaceutical solids.

INTRODUCTION

IDENTIFYING a single area of science or technology as the most influential in the development of humanity is a challenging task. However, if we were to select a few key fields, drug research, development, and production would undoubtedly be among the foremost.[1] The immense impact of these activities on global health is reflected in the daily involvement of millions of professionals worldwide.[2] This sector is not only focused on improving individual health but also on addressing global health challenges.[3] While it is difficult to quantify the exact number of potential drug candidates currently under investigation by pharmaceutical companies and academic institutions, it is estimated that hundreds of thousands of molecules are being explored.[4] However, only a small fraction of these candidates progress to clinical trials, and even fewer are approved and registered as drugs.[5] Table 1 illustrates the current number of approved drugs and those in various stages of clinical trials.

Drug discovery, research, and development is a multifaceted and complex process that typically spans over

Table 1. Total number of drug according DrugBank[6] based on search from August 2024.

Category	Number of drug
Total Number of Small Molecule Drugs	13,117
Total Number of Approved Small Molecule Drugs	2,781
Total Number of Biotech Drugs	4,228
Total Number of Nutraceutical Drugs	135
Total Number of Experimental Drugs	6,722
Total Number of Illicit Drugs	205
Total Number of Approved Drugs	4,435
Total Number of Withdrawn Drugs	318
Total Number of Drugs	17,345

a decade and demands significant financial investment (as illustrated in Table 2).[7,8] The process begins with hit identification, where researchers screen numerous compounds over several months to a year to identify 'hits' that exhibit potential therapeutic effects,[9] based on different approaches, such as target-oriented synthesis or diversity-oriented synthesis.[10] Once hits are identified, the process moves into the lead identification phase, which can take 6 months to 2 years.[11] During this phase, the most promising compounds are selected and validated as potential drug candidates. This is followed by the lead optimization phase, lasting 1 to 2 years, where the selected leads undergo chemical modifications to optimize their efficacy, safety, and pharmacokinetics.[12] After these initial stages, the process advances to preclinical testing, where the safety and efficacy of the optimized compounds are rigorously evaluated both in vitro (in laboratory settings) and in vivo (using animal models).[13–15]

Only a small fraction of compounds pass these rigorous preclinical tests and move on to clinical trials, which are conducted in multiple phases.[8,16] Phase I trials involve a small number of predominantly healthy volunteers (and sometimes patients, based on indication) to assess the drug's safety and dosage.[17] Phase II trials expand the testing to a larger group of patients to evaluate the drug's efficacy and side effects.[18] Phase III trials involve an even larger patient population and compare the new drug to existing treatments (eg. Standard of Care, SoC) or a placebo. Successful Phase III trials can lead to regulatory approval, but even then, post-marketing Phase IV studies continue to monitor the drug's long-term effects and safety.[19]

The journey from drug discovery to market approval is fraught with challenges.[20] Many promising candidates fail at various stages due to unforeseen toxicity, lack of efficacy, or unfavourable pharmacokinetics.[8] Despite these hurdles, the successful development of a new drug can have a transformative impact on public health.[21,22] For instance, the development of antibiotics[23] revolutionized the treatment of bacterial infections, saving countless lives. Similarly, advances in oncology have led to targeted therapies that significantly improve the survival rates for various cancers.[24]

The economic impact of drug R&D is also profound.[5] The pharmaceutical industry is one of major contributors to the global economy,[1] generating billions of dollars in revenue[21] and providing employment to millions of people.[2] Investments in drug R&D drive technological advancements and foster innovation across various sectors, including biotechnology, chemistry, and data science, to name just few. Furthermore, the development of effective drugs reduces healthcare costs in the long run by preventing disease complications and reducing the need for more expensive treatments and hospitalizations.[25]

In addition to the tangible benefits, drug R&D also contributes to scientific knowledge and understanding.[26] Each step in the development process, from basic research to clinical trials, generates valuable data and insights that advance our understanding of human biology and disease mechanisms. This knowledge can lead to the discovery of new therapeutic targets and inform the development of future treatments.[27]

Despite the progress made, there are still significant challenges that need to be addressed.[3] One of the major issues is the high cost of drug development,[5,28] which can limit access to new treatments for many patients, especially in Low- and Middle-Income Countries (LMIC). There is also a need for more efficient and predictive models in preclinical testing to reduce the high attrition rates of drug candidates.[29] Additionally, the increasing complexity of diseases such as cancer and neurodegenerative disorders requires innovative approaches and technologies to develop effective therapies.[30]

Progress in the approach and methodology aimed at increasing the number of drugs for more effective treatments cannot be achieved by developing only one

Table 2. Timeline and Milestones in the Drug Development Process.

Phase	Average Duration	Description
Hit Identification	Several months to 1 year	Researchers screen numerous compounds to identify "hits" that show potential therapeutic effects.
Lead Identification	6 months to 2 years	After hits are identified, the lead identification phase involves selecting and validating the most promising compounds.
Lead Optimization	1 to 2 years	Leads are chemically modified and optimized for efficacy, safety, and pharmacokinetics.
Preclinical Studies	1 to 3 years	Laboratory and animal studies are conducted to assess the safety and biological activity of the drug before it is tested in humans.
Clinical Studies Phase I	1 to 2 years	Phase I trials test the safety, dosage, and side effects of the drug in a small group of healthy volunteers or patients.
Clinical Studies Phase II	2 to 3 years	Phase II trials evaluate the efficacy and further assess the safety of the drug in a larger group of patients.
Clinical Studies Phase III	3 to 5 years	Phase III trials involve large-scale testing to confirm the drug's efficacy, monitor side effects, and compare it to commonly used treatments.

area due to the complexity mentioned earlier.[31] It is certain that understanding biological disorders in the body at the molecular level, the application of artificial intelligence, data science, and automation will aid in this endeavour. However, on the other hand, progress in approach and more efficient research with timely decision-making regarding the suitability of candidates for the continuation of research phases can be enhanced through rational and timely use of fields that seemingly are not on the front lines of discovering new drugs or improving existing ones, such as new formulations.[32]

One such area is the research and optimization of solid-state properties of drugs and formulations.[33,34] A synonym for this field is associated with the word polymorphism, although today, when we talk about the properties of the solid state of drugs, we include significantly more concepts and phenomena in research and understanding.[35]

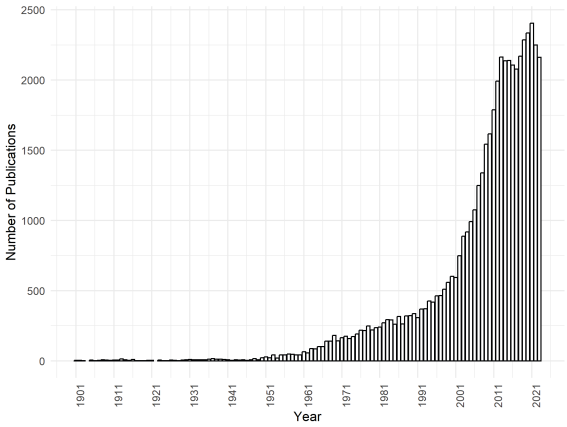


Figure 1. Total number of publications related to crystal polymorphism based on SciFinder search from 1990 to 2023. Publications prior to 1900 were excluded to enhance the clarity of the histogram.

From Polymorphism to Solid State Properties of Drug: The Evolution of Pharmaceutical Solids

The incorporation of polymorphism into pharmaceutical science provides an intriguing example of how certain phenomena transition into specialized fields.[36–38] To understand how polymorphism in crystals became relevant to pharmaceutical science, it is essential to begin with the basic definition of polymorphism. According to the Merriam-Webster dictionary, polymorphism is defined as the quality or state of existing in or assuming different forms. This concept includes various contexts: (1) the existence of a species in several forms independent of sexual variation; (2) the existence of a gene in several allelic forms or variations in a specific DNA sequence; and (3) the existence of a molecule, such as an enzyme, in several forms within a single species, as well as the property of crystallizing in two or more forms with distinct structures.

Polymorphism in crystalline forms was first identified in the early 19th century, with observations made in both inorganic and organic compounds. However, the study of polymorphism initially focused much more on inorganic compounds, particularly minerals, as well elements.[39,40] This focus is evident in the comprehensive monograph by Verma,[41] which extensively summarized the knowledge of polymorphism, primarily concentrating on inorganic substances. The systematic approach to studying polymorphism in inorganic materials was driven by the significantly different physical and chemical properties exhibited by various polymorphs, necessitating detailed analysis.

In contrast, while polymorphism was also recognized in organic compounds, it did not initially receive the same systematic attention. This divergence in research focus can be attributed to the scientific priorities of the 19th and early 20th centuries, when organic chemists were primarily concerned with exploring the reactivity of organic molecules in solution and identifying their structures through specific reactions.

Techniques such as melting point determination, refractive index measurements, and elemental analysis were traditionally the primary tools for organic analysis, with limited attention given to the solid-state properties of these materials. This is exemplified in a study where the authors describe a reaction involving acetylsalicylic acid (Aspirin®)[42] as well it is very interesting to see comparison of microscopy study[43] of Bayer Aspirin® and producer of acetylsalicylic acid and discussion about replacement of Bayer product with Heyden compound[44] as well study of difference in melting point.[45] The crystal and molecular structure of acetylsalicylic acid was published in 1964,[46] despite numerous earlier attempts[47,48] to resolve the structure of this important drug.

Research into the solid-state properties of organic compounds, including polymorphism, was sporadic and primarily driven by the interests of individual researchers.[49] The significance of polymorphism in organic compounds only gained broader recognition in the mid-20th century, coinciding with the rise of the pharmaceutical industry. This shift was further facilitated by the advancements in the X-ray diffraction techniques, which provided essential tools for solving crystal structures and advancing the study of solid-state properties.

In the context of drug research, the focus during this period was predominantly on the synthesis and structural elucidation of new drug molecules, with relatively little attention given to how variations in crystal structure could influence a drug's properties. This limited interest in

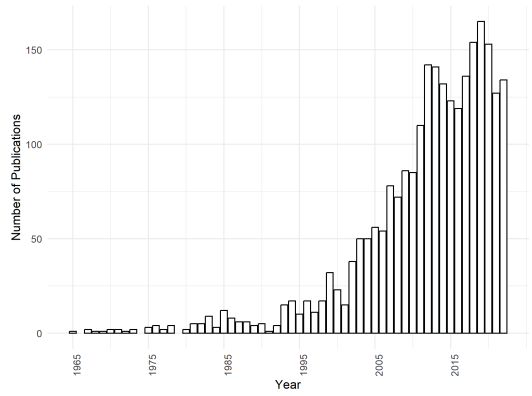


Figure 2. Total number of publications related to drug polymorphism based on SciFinder search from 1965 to 2023.

polymorphism within drug research is evident from a SciFinder search, which reveals over 2,700 publications (including journal articles, patents, reviews, and technical documents) related to polymorphism and drugs, highlighting the gradual yet growing awareness of its importance.

The Growth of Pharmaceutical Solid-State Technology

From the mid-1960s to the mid-1980s, research on the solid-state properties of pharmaceuticals was sporadic and largely dependent on the interest of specific research groups or companies.[50,51] During this period, several review articles and monographs were published, summarizing data on studies related to active pharmaceutical ingredients.[52–54] A notable example is the work by Kuhnert-Brandstätter, who published a comprehensive review and monograph in 1965 with a focus on barbiturates,[41] followed by additional significant publications in 1970s.[55] These works compiled extensive data on the polymorphic properties of pharmaceutical compounds, primarily using thermomicroscopy and IR spectroscopy.[56] Despite the development of methods for determining crystal structures during that time, the focus of crystallographers was more directed towards elucidating the crystalline and molecular structures of systems that had not yet been described crystallographically. Pharmaceutical solids were more often investigated using thermal, spectroscopic, and microscopic techniques. The integration of microscopy with thermal properties hinted at the future emphasis on a holistic approach to the study of pharmaceutical solids.

The Innsbruck school, based on legacy of Kofler, under Kuhnert-Brandstätter's leadership, made significant contributions to the understanding of pharmaceutical polymorphism.[41,57] Their research focused on the identification and characterization of different polymorphic forms, which can significantly influence the physical and chemical properties of drug substances, such as solubility, stability, and bioavailability.[58] The techniques developed and refined during this period laid the groundwork for the modern study of pharmaceutical solids.[59]

Borka and Haleblian's compilation in 1990 listed over 500 references to reports of polymorphism in more than 470 pharmaceutically important compounds. This exhaustive compilation underscored the prevalence of polymorphism in pharmaceutical substances and its critical role in drug development. Following this, Borka's 1991 review of polymorphic substances included in Fasciculae 1–12 of the European Pharmacopoeia provided a detailed account of the regulatory and practical implications of polymorphism in the pharmaceutical industry.[60]

As in any other field, the most significant breakthroughs and interest in research typically arise when a major challenge is overcome or when experimental measurements reveal substantial differences in properties due to a specific phenomenon. In the case of polymorphism, which gradually made its way into the realm of pharmaceutical research and development, a pivotal moment occurred with the discovery of polymorphic forms of chloramphenicol palmitate. The observed differences in the properties of these polymorphic modifications—such as solubility and bioavailability—highlighted how polymorphism could drastically influence the performance of a drug. This realization sparked a more serious interest in this area within the pharmaceutical industry.[37]

The recognition that different polymorphic forms of a drug could lead to variations in its effectiveness and stability marked a turning point. It became evident that understanding and controlling polymorphism was essential not only for ensuring consistent drug performance but also for optimizing therapeutic efficacy and securing patent protection.[61] This realization drove a surge in research focused on solid-state chemistry and crystallography, ultimately leading to more sophisticated drug development strategies that account for the impact of polymorphic variations.[33]

The Development of Polymorph Screening and Experimental Methods Used in the Last Three Decades

The last three decades have witnessed remarkable advancements in polymorph screening methodologies, fundamentally transforming pharmaceutical solid-state research. The transition from traditional empirical approaches to high-throughput and predictive methods reflects a significant evolution driven by technological innovations and an increased understanding of crystallization mechanisms.

Early polymorph screening predominantly relied on classical crystallization techniques such as solvent

evaporation, cooling crystallization, and slurry methods. These methods, while effective, were limited by their low throughput, lack of automation, and significant manual labor involved. Additionally, they provided limited insight into the crystallization pathways and the thermodynamics behind polymorph formation. The 1990s marked the initial phase of integrating systematic approaches into polymorph screening. Techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and hot-stage microscopy became standard practices. These allowed researchers to characterize the thermal properties of polymorphs, thereby providing crucial data on their stability and transitions. Simultaneously, advancements in X-ray diffraction (XRD),[62] particularly powder X-ray diffraction (PXRD), greatly enhanced the identification and characterization capabilities, establishing PXRD as an indispensable analytical method in pharmaceutical research.[63]

The turn of the century heralded the advent of automated high-throughput screening (HTS) methods.[64] Robotic platforms equipped with parallel reactors enabled rapid screening of hundreds to thousands of crystallization conditions simultaneously. These high-throughput crystallization techniques[65] significantly reduced the time required to identify and characterize polymorphs, leading to an increased understanding of polymorph landscapes and the thermodynamic and kinetic factors governing their formation. Moreover, advances in analytical techniques, including Raman spectroscopy and solid-state Nuclear Magnetic Resonance (ssNMR), provided complementary data to XRD,[66] particularly useful for distinguishing subtle differences between polymorphs or identifying amorphous phases. Raman microscopy, for instance, allowed in situ monitoring of crystal formation, offering unprecedented insight into real-time polymorph transitions and crystallization mechanisms.[67] Furthermore, the modern focus extends beyond merely identifying polymorphs to understanding and controlling crystallization processes at a molecular level.[68] Advanced microscopy techniques, such as Atomic Force Microscopy (AFM)[69] and Transmission Electron Microscopy (TEM),[70] and 3D electron diffraction (3DED)[71] now enable researchers to visualize crystal nucleation[72] and growth events in real-time at unprecedented resolutions.[73]

Mechanochemistry, Grinding, and Slurry Methods are key aspects of modern investigations and development of polymorphic systems, where mechanochemical techniques, grinding, and refined slurry mixing methods are increasingly being used as a supplement or alternative to classic solution-based crystallization processes.[74] Mechanochemistry—where chemical transformations, including transitions between polymorphic forms, are prompted by mechanical force (e.g., through ball milling or mortar grinding)—has become an indispensable tool in the exploration and discovery of new polymorphic forms.[75] Compared to conventional solution-based methods, mechanochemistry requires little or no solvent, making it both an attractive and sustainable approach. It also enables the production of polymorphic forms or cocrystals[76] that are difficult or practically impossible to achieve through solution-based crystallization.[77]

For example, dry (so-called “neat”) grinding involves milling the active pharmaceutical ingredient (API) without any solvent, often in a ball mill, to induce polymorphic transformation or cocrystal formation. This can lead to high-energy states and the discovery of metastable polymorphic forms. In the variant with added solvent (LAG, Liquid-Assisted Grinding), a small amount of solvent catalytically assists the grinding process, increasing molecular mobility and guiding crystallization toward specific polymorphic or cocrystal forms. Mechanochemical methods offer rapid screening and can yield metastable forms that might be overlooked by conventional approaches. They can also be carried out with minimal solvent use in line with green chemistry principles. Furthermore, in situ monitoring (e.g., via Raman spectroscopy or PXRD) during milling provides insights into mechanochemical transformation pathways, helping researchers better understand the kinetics and thermodynamics of such processes.[78] On the other hand, slurry-based screening—where an API is suspended in a solvent or solvent mixture—remains a mainstay in pharmaceutical development, enabling the identification of stable polymorphic forms and revealing the conditions under which one form transitions to another. Among recent innovations in this area are automated screenings (utilizing robotic platforms) that can prepare experiments in various solvents, at different temperatures, or at specific pH values, greatly increasing the speed and scope of research. Systematically varying solvent composition, temperature, and stirring rates helps clarify the stability relationships between different polymorphic forms, which is particularly important for determining process conditions and ensuring consistent production of the desired polymorph.[79] Additionally, combined approaches—such as initial screening by grinding to discover high-energy or metastable forms, followed by slurry-based stabilization to determine long-term stability under process-relevant conditions—represent an extremely effective strategy for comprehensive mapping of polymorphic landscapes.[80]

Polymorphisms of Single-Component Solids and Polymorphisms of Co-crystals and Salts

Thus far, the importance of polymorphism has been extensively discussed, including the methodologies developed to study it and its significant impact on the advancement of

pharmaceutical solid-state science. However, beyond single-component active pharmaceutical ingredients (APIs), there exists a broad range of salts and increasingly prevalent co-crystals. These multicomponent systems exhibit polymorphism analogous to single-component solids, making it a critical area of study due to its implications on drug performance and stability.[81] Polymorphism in salts and co-crystals introduces additional complexity due to the presence of multiple molecular entities. Salts, formed by ionic interactions between the API and a suitable counterion, often exhibit diverse polymorphic forms.[82] These different polymorphs can have dramatically varied physical and chemical properties, including solubility, dissolution rates, stability, and bioavailability. Given the common practice of salt formation in drug development to improve pharmacokinetic profiles, understanding salt polymorphism is crucial for successful pharmaceutical formulation.[83]

Similarly, co-crystals, defined as crystalline materials composed of two or more different molecules in a defined stoichiometric ratio stabilized predominantly by hydrogen bonds or other non-ionic interactions, have gained significant attention recently.[84] Like salts, co-crystals exhibit polymorphism, which arises from variations in their crystalline arrangement. Different polymorphic forms of co-crystals can lead to significant variations in physicochemical properties, necessitating thorough investigation during drug development.[85] The past two decades have seen substantial advancements in the characterization and screening techniques for multicomponent systems.[86]

Seeds, Seeding and Disappearing Polymorphs

Crystallization represents a critical unit operation in pharmaceutical manufacturing due to its direct influence on the physicochemical properties of active pharmaceutical ingredients (APIs), notably solubility, bioavailability, and stability. An essential method utilized to manage crystallization processes involves the intentional introduction of seed crystals, a technique commonly termed "seeding." Seed crystals provide pre-structured lattices onto which molecules preferentially attach, guiding crystal growth toward the desired polymorphic form while suppressing the formation of unwanted variants. Although seeding as a technique has been established in crystallization science for several decades, contemporary advancements in analytical methodologies and process control strategies have significantly enhanced its precision, making it indispensable for consistent polymorph selection and morphological control in pharmaceutical development.

Effective seeding strategies require careful consideration of multiple factors, including the timing, quantity, quality, and specific polymorphic form of the seed crystals. The preparation of high-quality seed crystals typically involves meticulous purification steps, controlled crystallization conditions, and precise characterization to ensure the seeds exhibit the desired polymorph, size distribution, and morphology. The timing of seed addition is equally critical; seeds must be introduced when the solution reaches an appropriate supersaturation level. Early or premature seeding may lead to inadequate crystal growth or uncontrolled nucleation, whereas delayed seeding might result in the spontaneous crystallization of undesired polymorphic forms. Moreover, the amount of seed introduced directly influences the kinetics of crystallization and the subsequent size distribution and purity of the resultant crystals. Too few seed crystals can cause heterogeneous nucleation and uncontrolled polymorph formation, while an excessive amount may lead to overly rapid crystallization and compromised product quality.

A notable and challenging phenomenon associated with polymorphism is the occurrence of "disappearing polymorphs".[87,88] This describes situations in which a previously accessible metastable polymorph ceases to crystallize following the introduction—often accidental—of a thermodynamically more stable form. Once introduced, the stable polymorph may persist as microscopic residues on equipment surfaces or within laboratory environments, inadvertently serving as nuclei for subsequent crystallizations. Consequently, the more stable polymorph dominates subsequent batches due to its lower free energy, effectively eliminating the previously observed metastable form. The well-documented case of ritonavir exemplifies the profound impact of disappearing polymorphs, wherein the unexpected emergence of a more stable crystalline form led to substantial production disruptions, necessitating urgent reformulation and regulatory interventions. This case underscores the critical importance of comprehensive polymorph screening and meticulous environmental and process controls during pharmaceutical product development. The investigations of pharmaceutical compounds such as ritonavir and rotigotine[89] have further highlighted the complexity and significance of polymorphic phenomena. Detailed studies of these compounds illustrate how subtle differences in polymorphic structures can dramatically influence therapeutic efficacy, stability, and manufacturing reproducibility. Such examples emphasize the necessity of advanced characterization techniques, stringent process control, and proactive risk management strategies in contemporary pharmaceutical crystallization research.[90,91]

Crystal Structure Prediction in Polymorph Screening

The prediction of crystal structures has been an aspiration in scientific research since the very beginning of modern

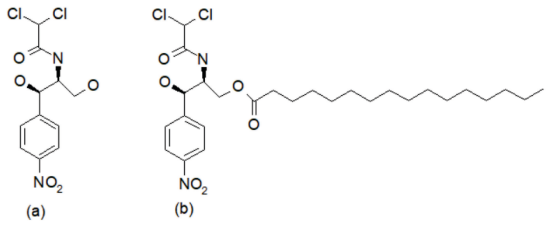
structural understanding.[92–94] Significant strides have been made in this area, particularly within the pharmaceutical industry, driven by the necessity for companies involved in drug discovery to rapidly identify, characterize, and protect all polymorphic forms of active pharmaceutical ingredients. Due to patent implications and regulatory requirements, it is essential to uncover and describe as many polymorphic forms as possible early in the drug development process.

A significant innovation during this period was the integration of computational methods into polymorph screening. Crystal structure prediction (CSP), employing molecular modeling and quantum chemical calculations, began to complement experimental techniques. CSP provided a theoretical framework for predicting possible crystal forms based solely on molecular structure, drastically reducing experimental uncertainty. Although computational predictions initially faced skepticism due to limited accuracy, continuous refinements and increased computational power over the past decade have substantially improved the reliability and acceptance of CSP methodologies.[95] In recent years, machine learning (ML) and artificial intelligence (AI) have further revolutionized polymorph screening.[96] By leveraging large datasets accumulated from decades of experimentation, ML models now effectively predict polymorphic forms and guide experimental designs.[97] These approaches enhance decision-making processes and optimize screening efficiency, significantly reducing drug development timelines and associated costs.

Case Study I: Polymorphism of Chloramphenicol Palmitate

Early studies on the physical and physiological properties of chloramphenicol palmitate were summarized by Aguiar.[98] and later reviewed by Mishra.[99] Chloramphenicol palmitate exists in three polymorphic forms (A, B, and C), as well as an amorphous form. Characterizing these forms using melting point and infrared (IR) analyses proved challenging and often inconclusive due to polymorphic transitions that occurred during sample preparation.[60]

Among these forms, the Form A is the most stable. However, it is the Form B and amorphous forms that are biologically active. Aguiar et al. investigated the physiological absorption rates of the A and B polymorphs of chloramphenicol palmitate. Their findings indicated that suspensions containing only the metastable Form B resulted in significantly higher blood levels following oral administration compared to those containing only the Form A, by nearly an order of magnitude. Since particle size had minimal effect on blood levels, it was concluded that the solid-state structure plays a crucial role in determining the physiological absorption rate.[98]



Scheme 1. Molecular structure of (a) chloramphenicol and (b) chloramphenicol palmitate (CAPP).

Further investigation into the absorption mechanism and its relation to polymorphism revealed that CAPP is almost insoluble in water, necessitating hydrolysis by enzymes in the small intestine before absorption can occur.[100,101] One proposed mechanism, as suggested by Aguiar[98] posits that the initial and rate-determining step in the absorption process involves the hydrolysis of CAPP in the intestine. These findings underscore the significant influence that polymorphic forms can have on the bioavailability of a drug, highlighting the importance of thorough polymorphic characterization in the pharmaceutical development process. Such studies have laid the foundation for future advancements in the field.

The sporadic nature of early research in this field gradually gave way to more organized and systematic investigations as the pharmaceutical industry recognized the impact of solid-state properties on drug performance. The development of advanced analytical techniques, such as X-ray diffraction (XRD), differential scanning calorimetry (DSC), and solid-state nuclear magnetic resonance (ssNMR), further propelled the field.[102–104] These

Table 3. Crystallographic data for polymorphic forms of chloramphenicol palmitate (CAPP) and chloramphenicol.

	CAPP Form A or α	CAPP Form B or β	CAPP Form C or γ	Chloramphenicol
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	*C* 2 (No. 5)	$P\,2_12_12_1$ (No.19)	$P\,2_1$ (No. 4)	$C\,2\,2\,2_1$ (No. 20)
	Unit cell parameters			
a / Å	34.11(2)	7.805(3)	35.53(2)	7.335(3)
b / Å	4.897(3)	52.503(15)	16.45(1)	17.552(8)
c / Å	39.45(2)	7.414(2)	5.185(6)	22.159(6)
α / °	90	90.0	90	90
β / °	110.17(4)	90.0	90.15(8)	90
γ / °	90	90.0	90	90
CCDC code	CLAMPL02 [109]	CLAMPL;[110] CLAMPL01[111]	CLAMPL03,[109] CLAMPL04 [110]	CLMPCL;[112] CLMPCL01;[113] CLMPCL02;[114] CLMPCL03;[115] CLMPCL04;[116]

techniques allowed for more precise and comprehensive characterization of polymorphic forms and other solid-state phenomena, such as solvatomorphism[105] and co-crystallization.[106–108]

Chloramphenicol and its derivative, chloramphenicol palmitate, were among the first drugs for which solid-state properties were studied in detail. These investigations began with the determination of their crystal structures and extended to the exploration of thermodynamic properties and polymorphic transformations, particularly under the application of mechanical stress. Various techniques, such as X-ray powder diffraction (XRD), differential scanning calorimetry (DSC), and infrared spectroscopy (IR), were employed to monitor polymorphic conversions and assess the thermodynamic stability of each form. These studies have provided a comprehensive understanding of chloramphenicol palmitate as an active pharmaceutical ingredient (API), highlighting the impact of polymorphism on its solubility, stability, and bioavailability.[117] This extensive body of research, reflected in numerous publications, not only ensured the drug's efficacy and stability in various formulations but also inspired researchers and

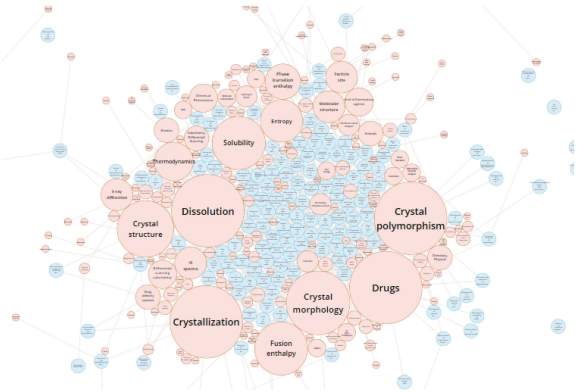


Figure 3. Knowledge graph for the most significant concept extracted from the publication publish in period from 1950 until 1985 based on Sci Finder search.

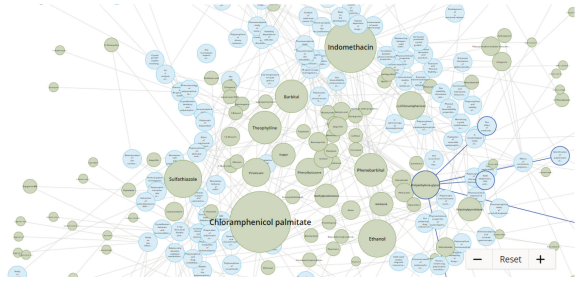


Figure 4. Knowledge graph for the compound which is subject of publication related to polymorphism and drug extracted from the publication from 1950 until 1985 based on Sci Finder search.

pharmaceutical companies to adopt systematic approaches in studying pharmaceutical solids. The detailed examination of chloramphenicol's polymorphs underscores the critical role of solid-state chemistry in drug formulation, directly influencing the efficacy, safety, and manufacturability of pharmaceuticals. Through understanding and controlling polymorphism, chemists and engineers can optimize drug formulations to meet necessary therapeutic standards, making this area of study essential for both academic research and industrial application.

Following the success in explaining how different forms of chloramphenicol palmitate affect bioavailability, and alongside the opportunities opened by instrumental analysis methods, an increasing number of researchers began to explore the solid state of drugs. An analysis of scientific papers from that period reveals that fundamental concepts of solid-state chemistry predominated (Figure 3). This shift in focus is clearly illustrated by the interconnectedness of key concepts within the field, as well connect research with specific molecule (Figure 4).

The figure highlights the central role of chloramphenicol palmitate in this research area, with the molecule standing out prominently within the network. This indicates its significance as a case study that demonstrated the critical impact of polymorphism on drug properties such as solubility and bioavailability. The network also shows how this research extended to other important molecules like indomethacin, which similarly drew attention due to the influence of polymorphic forms on its therapeutic performance.

In this network, significant emphasis is placed on concepts such as dissolution, crystallization, solubility, and crystal polymorphism. These topics are central to understanding the impact of polymorphism on drug properties, with large nodes indicating areas of intense research interest. For instance, the prominence of "Dissolution" and "Crystal Polymorphism" in the network suggests that these were critical areas where polymorphism was seen to have substantial effects on drug efficacy and performance.

Moreover, the figure highlights the importance of related areas such as "Crystal Structure" and "Crystal Morphology," which are essential for characterizing different polymorphic forms and understanding their behaviour in various conditions. The term "Drugs" is also highly connected, indicating a growing recognition of the need to consider solid-state properties during drug development.

In addition to chloramphenicol palmitate and indomethacin, the network map also includes other compounds such as sulfacetamide and barbitals, further illustrating the breadth of research during this time. These molecules, connected by their shared relevance to

polymorphism and solid-state chemistry, underline the growing recognition that controlling the crystalline form of a drug could lead to significant improvements in its efficacy, stability, and overall therapeutic profile.

The figure also reveals how these early studies laid the groundwork for broader applications of solid-state principles in drug development. By visualizing the relationships between different drugs and key concepts like crystallization, dissolution, and crystal structure, the network underscores the expanding interest in how polymorphism could be leveraged to optimize drug formulations. This interconnected research effort marked a pivotal moment in pharmaceutical science, where the focus began shifting from merely synthesizing new drugs to also understanding and controlling their solid-state properties to enhance therapeutic outcomes.

Cutting-Edge Progress in Pharmaceutical Solids

The 1990s witnessed the foundational development of utilizing solid-state properties for drug formulation. Researchers began to explore the solidification of drugs to enhance stability, solubility, and bioavailability. This era saw the advent of techniques such as solid dispersion, where drugs were dispersed in inert carriers in a solid state to improve dissolution rates. The primary goal was to address the poor solubility and bioavailability of many pharmaceutical compounds.

One of the early breakthroughs in this period was the introduction of solid-state characterization techniques such as X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). These techniques allowed for the identification and characterization of different polymorphic forms of drugs, which are crucial for understanding their physical and chemical stability.

For instance, the development of the HIV protease inhibitor ritonavir highlighted the significance of polymorphism in drug development. Initially, ritonavir was launched in a crystalline form that was later found to convert to a less soluble polymorph, leading to bioavailability issues. This case underscored the importance of thorough solid-state characterization during the early stages of drug development.

The ritonavir case has since become a standard reference in the field of pharmaceutical sciences, emphasizing the need for a comprehensive understanding of polymorphism in drug design and manufacturing. It has led to the development of more rigorous guidelines and best practices within the industry to ensure that all potential polymorphic forms of a drug are identified and characterized early in the development process. The case of ritonavir, while initially a significant challenge for Abbott Laboratories, ultimately became a powerful example of transparency and responsibility in pharmaceutical research. Following the unexpected polymorphic transformation of ritonavir, which jeopardized the drug's efficacy, Abbott Laboratories conducted an extensive internal investigation to understand the root causes of this issue.[90,118]

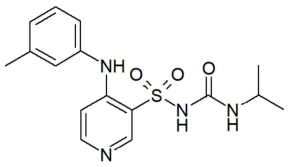
Recognizing the broader implications of their findings, Abbott Laboratories chose to share their research outcomes with the scientific community through a series of important publications. This decision to publish was not merely an act of transparency but also a strategic move to raise awareness about the challenges posed by polymorphism in drug development. By disseminating their results, Abbott Laboratories provided valuable insights that could help other pharmaceutical companies anticipate and mitigate similar risks in their own drug development processes.

Two examples that are exceptionally important and that have significantly contributed to the understanding of the importance of polymorphism in drug development are chloramphenicol palmitate and ritonavir, primarily because the differences in their properties are remarkably pronounced. These cases vividly illustrate how polymorphism can dramatically affect the efficacy, stability, and overall performance of a drug, leading to considerable attention from researchers and regulatory bodies alike. However, in addition to these well-known examples that are frequently cited in all relevant literature related to the solid-state of drugs, there are several other cases that may not be as widely recognized but are worth highlighting. These lesser-known examples have nonetheless played a crucial role in the development and registration of pharmaceutical products, demonstrating the broader impact of polymorphism on the successful formulation and commercialization of medications, ultimately benefiting patients by ensuring the availability of safe and effective therapies.

Case Study II: Polymorph of Torasemide

A particularly interesting example of polymorphism is that of torasemide, a drug that belongs to the class of highly soluble and highly permeable medications (as per the Biopharmaceutical classification - BCS Class I drug). In the case of this molecule, during the 1990s, new forms were discovered based on research predominantly conducted by pharmaceutical companies. These findings highlighted the potential for polymorphic variations even in compounds that were previously considered to be well-characterized, underscoring the ongoing importance of solid-state studies in optimizing drug formulations and improving therapeutic outcomes.

Torasemide, a loop diuretic, is primarily utilized for the treatment of oedema associated with conditions such as congestive heart failure, chronic kidney disease, and liver cirrhosis. Additionally, it plays a significant role in managing



Sheme 2. Molecular structure of torasemide.

hypertension. By promoting the excretion of sodium, chloride, and water through urine, torasemide effectively alleviates fluid overload. Its mechanism of action involves inhibition of the sodium-potassium-chloride co-transporter in the thick ascending limb of the loop of Henle, resulting in increased urine production and subsequent reduction in blood pressure.

With no significant effect on the drug's therapeutic efficacy, the polymorphism of torasemide has nonetheless garnered interest from several pharmaceutical companies due to its potential for enabling the filing of additional intellectual property (IP) claims that could enable earlier market entry with more affordable generic market penetration. This interest has led to investigations into its polymorphic forms, primarily to explore opportunities for innovation in drug formulation and lifecycle management.[119]

For instance, some polymorphs may be metastable, meaning they are not the most stable form under certain conditions but can still be isolated and formulated as stable materials. The ability to identify and control these forms is vital for producing generic versions of torasemide that meet bioequivalence requirements with the original branded product. This understanding allows pharmaceutical companies to optimize the formulation performance of torasemide, ensuring that the drug maintains its therapeutic effectiveness throughout its shelf life.

A thorough understanding of the crystal structure of a particular polymorph allows for its clear identification, which is extremely important in studies where product performance depends on solid-state properties[121] and claim is any significant between. It was precisely this detailed knowledge of the polymorphism of torasemide that enabled the design of research into the biopharmaceutical behaviour of torasemide, where any differences could not be attributed to different solid-state properties. Based on this study it was point out that there is not significant difference between dissolution profile of two polymorphic forma od torasemide, as it is BCS Class I drug.[119] This example contrasts sharply with the case of chloramphenicol palmitate. For chloramphenicol palmitate (BCS Class IV – poorly soluble and poorly permeable), the primary motivation for studying and controlling solid-state properties was the significant challenge of enhancing its solubility, as it directly impacted its bioavailability and therapeutic efficacy. Achieving better solubility through polymorph control was essential to optimizing its pharmacokinetics and patient outcomes. In the case of torasemide, however, the exploration of polymorphism was driven primarily by the strategic objective of circumventing existing patents and enabling earlier entry and generic market formation. The ability to identify and develop alternative polymorphic forms of torasemide provided a potential pathway to market access, bypassing the patent restrictions on the existing form. Once the polymorphism space was thoroughly mapped and understood, the knowledge gained was not only used for intellectual property advantages but also for improving the control and design of the final pharmaceutical product. This allowed for a more robust formulation that ensured consistent performance, stability, and manufacturability, ultimately benefiting both the pharmaceutical industry and the patients.

Table 4. Crystallographic data for polymorphic forms of torasemide.

Polymorphic form	Form T-I	Form T-II	Form T-N
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P* $2_1/c$ (No. 14)	*P* $2/n$ (No. 13)	*P* $2_1/c$ (No. 14)
Unit cell parameters			
a / Å	13.308	20.446(4)	11.430(3)
b / Å	8.223	11.615(3)	19.090(6)
c / Å	31.970	16.877(4)	16.695(6)
β / ∘	107.01	108.9	93.90(2)
CCDC code	TORSEM[120]	TORSEM01[120]	TORSEM02[119]

Understanding the crystal structure of a drug is essential because it affects how the drug dissolves in various media, which in turn influences its bioavailability in the body. The fact that one form of the drug failed to meet bioequivalence criteria highlights the importance of selecting the appropriate crystal form during drug development to ensure consistent therapeutic outcomes. Additionally, the study's findings suggest that regulatory guidelines, like those from the FDA, could be refined to better account for the impact of crystal structure on drug performance, particularly in the context of biowaivers for generic drugs.[121]

Solvate and Hydrate of Drug Substance

In the literature related to the solid-state properties of drugs, one often encounters the term "pseudopolymorph" or "pseudopolymorphism." It is important to note that these crystal forms do not meet the fundamental definition of polymorphism, which requires differences in crystal structure for the same chemical composition. However, to highlight that the observed differences arise from variations in composition due to the incorporation of solvents or

water molecules during crystal growth, the concept of pseudopolymorphism was introduced. This term serves to differentiate between true polymorphs, where the chemical composition is identical, but the structures differ, and cases where the differences are due to the inclusion of solvent or water molecules within the crystal lattice.

The study of pseudopolymorphism provides valuable insights into how these additional components influence the physical properties and stability of crystalline forms, which is crucial for the development and optimization of pharmaceutical formulations. The concept of pseudopolymorphism was first explored in the context of mineralogy by Freeman and Frazer, who studied the transformation of amphibole to pyroxene. They observed that in cases of pseudopolymorphism, the transformation reaction is not reversible, and there is a change in overall stoichiometry during the phase transition.

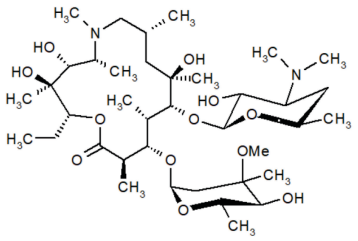
In the pharmaceutical field, one of the earliest studies related to pseudopolymorphism was published by Kuhnert-Brandstätter and Grimm, who investigated the crystallization of several drugs from different solvent systems. Their work highlighted how solvents could significantly alter the crystallization process, leading to the formation of different pseudopolymorphic forms.

In contrast, the concept of hydrates has been well-known since the early days of drug research and discovery. However, the specific role of water within the crystal structure was fully understood only after the introduction of diffraction experiments for crystal structure determination. These studies revealed how the incorporation of water molecules could influence not only the stability and solubility of a drug but also its overall bioavailability and therapeutic efficacy. This understanding has since become integral to the rational design and development of pharmaceutical products.

Case Study III: Azithromycin Hydrates and Solvates

Azithromycin, the first 15-membered macrolide antibiotic to reach the market, represents a significant milestone in the field of antibiotic therapy. Distinguished by the incorporation of a basic nitrogen atom into its macrocyclic ring, this innovation marked a major advancement in the development of macrolides.[122,123] The synthesis of azithromycin was the result of over 20 years of dedicated research aimed at transforming erythromycin into a more effective and improved drug. This breakthrough was achieved in 1980 by a talented team of researchers at PLIVA laboratories: Gabrijela Kobrehel, Gorjana Radobolja-Lazarevski, Zrinka Tamburašev, and Slobodan Djokić.[124–127]

Azithromycin's ability to form hydrates and solvates has made it a subject of extensive study, particularly in the context of pharmaceutical formulation. The hydrate forms



Scheme 3. Molecular structure of azithromycin.

of azithromycin have played a crucial role in the development of generic drug alternatives, underscoring their importance in pharmaceutical research. The most stable form of azithromycin is its dihydrate, which retains its water content up to temperatures exceeding 100 °C. The crystal structure of azithromycin dihydrate has been well-characterized since 1986. providing a solid foundation for further exploration of its physical properties.[128]

Azithromycin is also known for its versatility in forming a variety of hydrates and solvates,[129] which can lead to the creation of isostructural crystals.[130] These isostructural crystals share an identical crystal lattice framework, which allows for the inclusion of different solvent molecules or hydrates while maintaining the overall structure. This unique property of azithromycin enables the formation of crystals with identical cavities, which can be utilized for the design of additional pharmaceutical systems, potentially enhancing the drug's stability and bioavailability. The ability to manipulate these cavities by introducing various solvent molecules opens new avenues in drug formulation and delivery.

The patent US 7569549, titled "Isostructural pseudopolymorphs of azithromycin,"[131] along with US 6,936,591, titled "Amorphous 9-deoxo-9a-aza-9a-methyl-9a-homo-erythromycin A,[132] process for preparing the same, and uses thereof," represent significant advancements in the field of pharmaceutical solids derived from azithromycin. These patents detail the development of substantially pure isostructural hydrate and solvate forms of azithromycin, characterized by precise unit cell parameters—a novel approach at the time for the description of pharmaceutical solids. Traditionally, the identification of new solid-state forms relied primarily on characteristic XRPD (X-ray powder diffraction) peaks. The incorporation of precise unit cell parameters in these patents marked a significant advancement in the identification and characterization of pharmaceutical solids, offering a robust and detailed approach to distinguishing between polymorphic forms.

In the table below, typical representatives of the monoclinic and orthorhombic class of hydrates and solvates are shown, alongside the well-known azithromycin dihydrate form.

Table 5. Crystallographic data for hydrate and solvate of azithromycin.

	Dihydrate	Monoclinic class of hydrate and solvate	Orthorhombic class of solvates
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P\,2_12_12_1$ (No. 19)	$P\,2_1$ (No. 4)	$P\,2_12_12_1$ (No. 19)
Range of unit cell parameters*			
a (min - max) /Å	14.6540(12)	16.1578(4)	8.8290(20) 8.92080(10)
b /Å	16.7825(13)	16.1144(5)	12.167(2) 12.520(7)
c / Å	17.7640(16)	18.3107(4)	45.624(11) 45.853(8)
α / ◦	90	90.0	90
β / ◦	90	109,4360(12)	90
γ / ◦	90	90.0	90
CCDC code	GEGJAD[128] GEGJAD01[133] GEGJAD02[133] PILQIN[133] PILQUZ[133]	BENDUU[130] FISNIF[130] JIXXAQ[129] Data from S 6,936,549[131]	Data from US 6,936,591[132]

The Perspective for Future

Looking ahead, the future of solid-state drug formulation holds promising advancements and challenges. The integration of computational methods and machine learning in solid-state chemistry is expected to revolutionize the field. Predictive models can facilitate the rational design of solid forms, optimizing drug properties and accelerating the development process. These technologies can analyse vast amounts of data to identify patterns and predict the behaviour of drug molecules. This will facilitate the design of optimal solid forms and accelerate the development process.[134]

The role of solid-state chemistry in the generic drug industry has become increasingly significant as manufacturers strive to produce bioequivalent products that match the performance of branded drugs. Solid-state properties such as polymorphism, crystallinity, and solubility are crucial in ensuring that generic formulations are therapeutically equivalent to their brand-name counterparts. The following sections delve into the specific ways in which advancements in solid-state chemistry have impacted the development, regulation, and market success of generic drugs.

One of the critical requirements for generic drugs is to demonstrate bioequivalence to the branded counterpart. Solid-state characterization techniques, such as XRPD, DSC and spectroscopy, have enabled generic manufacturers to precisely reproduce the polymorphic forms of the original drug. This ensures that the generic version has the same solubility, stability, and bioavailability as the branded product.[135]

For instance, the development of amorphous solid dispersions (ASDs) has allowed generic manufacturers to produce formulations with improved bioavailability. By using techniques like hot-melt extrusion and spray drying, generics can achieve similar dissolution rates and bioavailability profiles, ensuring that they meet regulatory requirements for bioequivalence.

The scalability and reproducibility of solid-state formulation techniques have made it possible for generic manufacturers to produce high-quality products at a lower cost. Techniques such as hot-melt extrusion and spray drying are not only efficient but also cost-effective, allowing manufacturers to produce large quantities of generic drugs without compromising on quality.

For example, the use of hot-melt extrusion to produce amorphous solid dispersions (ASDs) has been widely adopted in the generic drug industry. This technique allows for the continuous production of ASDs, reducing manufacturing costs and ensuring consistent product quality.

The comparison of these two knowledge graphs underscores the significant evolution of research focus on polymorphism within the pharmaceutical industry over time. Figure 5, which represents the initial 150 publications in the field, highlights the foundational concepts of polymorphism, emphasizing broad and essential connections between crystallographic properties and drug behaviour. This early body of work was instrumental in establishing the scientific importance of polymorphism, yet during this phase, pharmaceutical companies and regulatory bodies

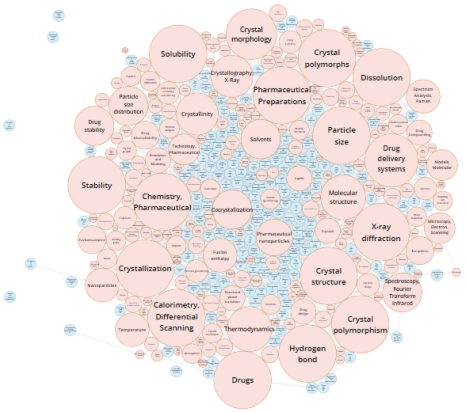


Figure 5. Knowledge map for the 150 most cited publications covering polymorphism in the pharmaceutical science.

largely overlooked the relevance of solid-state properties in drug development. At the time, the focus remained predominantly on molecular synthesis and solution-based properties, with limited recognition of how variations in crystal structure could impact key factors such as solubility, stability, and bioavailability. This lack of acknowledgment marked a critical gap, underscoring the nascent stage of understanding regarding the influence of solid-state chemistry on drug performance and manufacturability.

The knowledge map constructed from the most recent 150 publications (Figure 6) highlight the current focus of research, showcasing advancements and a deeper understanding of polymorphism and solid-state chemistry. Researchers have transitioned from foundational explorations to more sophisticated investigations into specific molecular interactions, such as hydrogen bonding, and their direct influence on the stability, solubility, and therapeutic efficacy of pharmaceutical formulations. This evolution reflects a broader application of solid-state knowledge, particularly in the context of tailoring drug properties for enhanced performance.

Notably, the inclusion of specialized concepts such as "antitumor agents" in the knowledge map underscores the increasing application of these principles in developing more effective and targeted drug therapies. This shift demonstrates the integration of solid-state chemistry into cutting-edge areas such as oncology, where precise control over solid state forms can significantly impact drug delivery, bioavailability, and patient outcomes. The focus on these advanced applications indicates a maturing field, where the interplay between crystallography, material science, and pharmaceutical innovation is driving the development of highly optimized and specialized therapeutics.

Overall, the progression from the first to the latest research highlights how the pharmaceutical industry has evolved from laying the groundwork of polymorphism to applying this knowledge in sophisticated and practical ways, optimizing drug design, and ensuring consistent therapeutic outcomes. This evolution underscores the importance of both foundational research and ongoing innovation in the field of drug development.

CONCLUSION

The field of pharmaceutical solid-state chemistry has evolved significantly over the past century, from the early recognition of polymorphism to the sophisticated understanding, manipulation of solid-state properties we have today. This evolution has been driven by the development of advanced analytical techniques, such as X-ray diffraction (XRD), solid-state NMR (ssNMR), and differential scanning calorimetry (DSC), FTIR and Raman spectroscopy which have enabled precise characterization and control of drug polymorphs, hydrates, solvates, and amorphous forms as well patent protection.[136]

The impact of these advancements is profound, as solid-state properties directly influence the solubility, stability, bioavailability, and overall therapeutic efficacy of pharmaceutical compounds. The case studies of chloramphenicol palmitate, torasemide and azithromycin demonstrate how a deep understanding of these properties can lead to significant improvements in drug performance and patient outcomes. Furthermore, the introduction of new methodologies, such as co-crystallization,mechanochemistry[137] and amorphous solid dispersions,[138] has provided powerful tools for overcoming the challenges of poor solubility and stability in drug development.[139]

Looking forward, the integration of computational methods,[140] machine learning,[141] and predictive modelling[95] is expected to further revolutionize the field.[142] These technologies will enable more efficient drug development processes, allowing for the rapid identification[143] and quality[144] of optimal solid forms and the design[145] of personalized medicines tailored to individual patient needs. Additionally, the continued exploration of novel materials, such as solid lipid nanoparticles and biodegradable polymers, will open new avenues for drug delivery and therapeutic innovation.[146]

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