The Effect of Polymorphism on the Properties of Molecular Materials
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1. Introduction

Polymorphism is one of the most important phenomena in solid state chemistry and it has been studied for many decades. There is a great deal of interest in the relationship between polymorphism in molecular materials and their properties. In recent years, the study of polymorphism has enabled us to apply this knowledge to industrial fields such as food, medicine and photography. The primary purpose of this review is to discuss how polymorphism in molecular materials affects properties. The review will focus first on defining polymorphism and introduce historical developments. It will then highlight the applications of polymorphism for pharmaceuticals, pigments and explosives, and propellants with an emphasis on the connection between structure and properties. Finally, a brief description will be presented of how analytical techniques can be used to characterise polymorphic forms.

1.1. Definition

Polymorphism is the term used to describe the crystallisation of the same component in different crystalline forms. According to McCrone, a polymorph is defined as “a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state”. Polymorphism is also related to allotropy and pseudopolymorphism. Allotropy refers to an element adopting different solid-state structures. For example, carbon has four common allotropes: diamond, graphite, fullerenes and graphene. Pseudopolymorphism represents phenomenon such as solvate formation. Solvates contain molecules of solvent within the crystal structures. Removing or adding solvents will change the structure of materials such that they are termed called polymorphic solvates.

2. History and extent of polymorphism

Although interest in how structure influences properties has early origins, polymorphism is a relatively new field of study for solid state materials. In 1818 Mitscherlich found that phosphates and arsenates had the same crystal form and he defined this phenomenon as “isomorphism”. ¹ In 1822 Mitscherlich discovered a direct example of polymorphism in sulphur. ²

“Whilst I was still seeking a difference in chemical composition I succeeded several times, in the recrystallization of the phosphate, in obtaining crystals having the same form as the acid arsenate. Since I knew definitely that there was no difference between the two salts I proceed with the investigation of this phenomenon, and the whole solution of the acid phosphate crystallizes several times in the form of arsenate. Hence it is established that one and the same body, composed of the same substances in the same proportions, can assume two different forms.”
In the late 19th century, there were many important advances in polymorphism. Lehmann (1891) characterised two types of polymorphism: *monotropic* and *enantiotropic* in Fig 1. A monotropic material exists in a single stable form under all temperatures. Enantiontropic means that the order of stability of two forms change with temperature. In 1897 Ostwald proposed a principle to predict the relative stability of polymorphs. This is now known as Ostwald’s Rule which state that the least stable form is often crystallised first. 

![Gibbs free energy diagrams for the cases of monotropic and enantiotropic](image)

Fig 1 Gibbs free energy diagrams for the cases of monotropic and enantiotropic
The development of experimental techniques and analytical instruments in the 20th century improved our understanding of polymorphism. Both Lehman’s assertion about monotropic and enatiotropic systems and Ostwald’s rule of stages were validated. However, scientists became interested other phenomena in the 1930s and the study of polymorphism almost ceased after this period until the 1960s when interest in polymorphism was stimulated again by McCrone. He defined polymorphism and mentioned the importance of polymorphism in pharmaceutical compounds.

In short, we can say that the key historical developments in polymorphism were (i) the discovery of polymorphs, (ii) the hypothesis of polymorphism which characterised types of polymorphs and developed rules to predict crystal forms by the relative stability of materials, and (iii) the definition and importance of polymorphism. This research into polymorphism was closely associated with analysis methods such as vibrational spectroscopy, thermal methods, density measurement and optical microscopy. These analytical measurements helped scientists to understand structure and behaviour of polymorphs thereby informing researchers about the importance of polymorphism in pharmaceuticals, dyes, pigments, and explosives and propellants.

3. **Research on polymorphism**

3.1. **Pharmaceutical compounds**

In 1997, Henck showed that polymorphism has a major impact on pharmaceutical compounds and drug delivery. Polymorphism can influence the formation and properties of medicine both on active ingredients and excipients, fillers, stabilizers, coatings, drying agents, etc. The properties are related to use, efficacy and stability of the drugs. The key factors for preparation of drugs are dissolution rate and solubility, both of which determine the bioavailability of a drug. Dissolution rate and solubility will be influenced by the formation of hydrates, solvates, metastable forms and amorphous forms. Scientists use thermal analysis, microscopy and thermo-microscopy to characterise pharmaceutical compounds.

3.1.1. **Solubility and dissolution rate**

Dissolution is the rate determining step of physiological absorption, which includes the dissolution of the drug in the stomach. The solubility is related to polymorphism because different polymorphs have different lattice energies in order to enter solution, the lattice energy must be overcome. And different dissolution rates will affect bioavailability. Solubility defines by the amount of solid which can dissolve into solvent. It is thermodynamics controlled. Dissolution Rate is the speed of solid to dissolve into solvent and it is kinetics controlled. Tuladhar (1983) studied the solubility of phenylbutazone polymorphs which is affected by different solvents as shown in Fig 2. 5
3.1.2. Bioavailability

According to Zannikos “the rate and extent of the physiological absorption of an active drug substance are decisive factors in its overall efficacy”. This means that different crystal modifications will have different bioavailabilities. Yokoyama’s study of antileukemic mercaptopurine in 1980 showed that the form had greater bioavailability which had higher solubility. In 1998, Kachi found that the anti-nematode drug, PF1022A (compound I), had four modifications and the more effective one was the amorphous form.

The degree of hydration and solvation will also affect the bioavailability. This was shown by the study of 3-palmitate (CAPP) which is insoluble in water. It needs to be hydrolysed by enzymes to become bioavailable. The hydration rate determines the rate of dissolution and hence influences the bioavailability. In conclusion, decreasing solubility and dissolution will reduce the bioavailability and these two factors are related to polymorphism.

3.1.3. Processing

3.1.3.1. The importance of metastable forms
According to Byrn “the stable form is also the least soluble form” which means that the thermodynamically stable form is not always bioavailable. Chemburkar and Bauer mentioned “the lower solubility of stable forms may limit their pharmacological utility”, so that metastable forms may be required. In 1991, Weissbuch used interactions between solvents and crystals to determine the crystal form. In 1995, Weissbuch used inhibitor prevent formation of the stable form and hence obtain the metastable form.8 These show that stability and structure information can control the formation of polymorphic forms.

3.1.3.2. The importance of the amorphous forms
Amorphous materials have higher solubilities and dissolution rates and so they are often more suitable for drug delivery. There is therefore increasing interesting in the formation and analysis of amorphous forms. In 1999, Guillory used many ways to get amorphous medical materials by “employing crystallization procedures far from equilibrium such as solidification from the melt, freeze drying or spray drying, removal of solvent from a solvate, precipitation by changing pH, or by mechanical processing such as granulation, grinding or milling”.

3.1.4. Intellectual property and patents
The legal definition of intellectual property is “a property right that can be protected under federal and state law, including copyrightable works, ideas, discoveries, and inventions.” A Patent is an invention which needs to be novel and always related to intellectual property. One of the famous cases is Zantac, ranitidine hydrochloride, which can inhibit extra stomach acid to treat ulcers. It was developed by Allen & Hanburys Ltd. in the 1970’s. There are 658 patents to process ranitidine hydrochloride. These patents were granted by the USA in 1978.

3.1.5. Analytical methods
Scientists use microscopy, thermo-microscopy and thermal method to analyse pharmaceutical compounds. Microscopy is an efficient and simple way to characterise polymorphs and hot stage microscopy increases the accuracy of analysis. Thermal analysis techniques are also useful to study polymorphs. The combination of differential scanning calorimetry (DSC) and X-ray diffraction to do quantitative analysis is particularly powerful. DSC helps scientists to understand solid-solid transitions such as melting, crystallisation and glass transitions. It can determine the melting behaviour of polymorphs and qualify the formation of hydrates. Thermal methods also connect TGA with IR to do simultaneous quantitative analysis of weight changes. These analytical methods help to identify, characterise and assess sample purity of the crystal form used in medicines.

3.2. Applications to dyes and pigments
Interesting in colour has been continued for centuries and scientists are still fascinated with the applications for dyes and pigments. According to Evans the difference between dyes and pigments lies in their solubilities. “Most dyes are generally soluble, while pigments are regarded as insoluble in the medium”. The colour changes of dyes and pigments are related to the structure of the solids. Dissolution and solubility can also vary the uses of dyes and
pigments. From Herbst and Hunger’s studies, they discovered that the ability to absorb light and to scatter light can influence the colour of pigments. Degeneration ability for resisting light and weather can induce the colour changes. Another factor to cause colour changes is the sticking tendency of molecules. Nowadays, the most widely used polymorphic forms are quinacridones, phthalocyanines and perylenes.

3.2.1. Quinacridones
In 1955, Du Pont characterised quinacridones (compound II) and then identified the polymorphic behaviour and photochemical stability. According to Manger and Struve’s studies, they found that quinacridone has three polymorphic forms: α, β, γ. These three forms were distinguished by X-ray powder diffraction. The α and γ forms are red and β is violet.

![Quinacridones (compound II)](image)

3.2.2. Perylenes
Perylene (compound III) pigments are the derivatives from Pigment Red 224. In 1999, Ogawa found that Pigment Red 224 has two polymorphic forms. These forms were detected by electron crystallography on microcrystalline thin films. One of perylene’s widely used derivatives is Pigment Red 179 which is also called perylene red.

![Perylene (compound III)](image)

Another is Pigment Red 149 which is widely used in textile applications. It has three polymorphic forms: α, β, γ which have different shades of red. The β form shows a more yellow tint than the α form.

In 1989, Klebe found that the properties of perylenes are associated with R-substituents. Mizuguchi also found that the structure will change on contact with solvent vapours.
3.2.3. Phthalocyanines

Phthalocyanines (compound IV) can be used in inks, paints, plastics and etc. It was first found in 1907 by Braun and Tscherniak. They found the metal-free form which is a greenish residue. Disebach and von der Weid found another form- the Ni derivatives, which is blue. Copper phthalocyanine (CuPc) is one of the most wildly used phthalocyanine pigments. It has various polymorphic forms and the crystal structure changes in crystallisation process or synthetic procedures. Different polymorphic forms exist as different colour since they have different structure. It shows that solid state properties influence colour.

![Phthalocyanines (compound IV)](image)

3.3. Applications in explosives and propellants

Explosives and propellants produce light, heat and gas at high rates. Cooper and Kurowski categorised the explosives and propellants into three types: pyrotechnics; propellants; high explosives include primary and secondary explosives. The properties of explosives will change by polymorphism and transformations. There are two widely used explosives: HMX and RDX.

3.3.1. HMX

HMX is cyclotetramethylene tetranitramine (compound V) and it is a powerful explosive. HMX has four polymorphic forms: α, β, γ, δ. In 1950, McCrone discovered that β form was stable at room temperature and γ-form is hydrate. A key factor is impact sensitivity, which is affected by crystal shape and size. Cady and Smith found that the sensitivity of the β-form is independent of particle size and that the crystal structure influences sensitivity. So the order of sensitivity is δ > γ > α > β. HMX exhibits conformational polymorphism in which the β-form’s chair conformation is the most stable one.
3.3.2. RDX

RDX is cyclo-1, 3, 5-trimethylene-2, 4, 6-trinitramine (compound VI). RDX has four conformational polymorphs: α, β, γ and ε which exist over a range of pressure and temperature. The most stable form is the α-form; the β-form is obtained from high-boiling solvents and is very different from α. At high pressure RDX shows a third form γ, illustrating that pressure can cause polymorphic transition and pressure is that an important tool for studying polymorphism.

3.3.2.1. Pressure studies

Pressure will induce polymorphism and phase transition. In 1923 Ephraim found that [Co(NH$_3$)$_5$NO$_2$] I$_2$ has two polymorphic forms and they are all isotropic. However, Boldyreva (2000) found a new form of [Co(NH$_3$)$_5$NO$_2$] I$_2$ by applying different pressure. This new form appears at hydrostatic pressure and it is anisotropic. The third form is caused by structural distortion by hydrogen bonding and interactions between iodine.

3.4. Electrical conductivity

Molecular materials are usually considered to be insulators because their intermolecular interactions are too weak for effective electron transfer. However, planar molecules with
delocalised \( \pi \)-bonding have stronger interactions between neighbouring molecules and so can be semiconductors. They have a planar arrangement of \( \pi \)-stacked molecule, which narrows the band gap. Delocalised \( \pi \)-bonding allows electrons to move more freely in planar molecules. There are two types of packing structures of planar molecules: mixed stacks and segregated stacks. The former crystallises with alternating donors and acceptors, and the latter contains only one type of molecule in each stack. The complexes with mixed stack structures are thermodynamically stable and act as semiconductors. The complexes with segregated stack structures are kinetically stable and have metallic conductivity. They are called polymorphic charge-transfer complexes. Both temperature and pressure can cause polymorphic transitions.

3.5. **Organic magnetic materials**

Magnetic behaviour is related to polymorphic phase transitions. When the structure of the material is changed, the molecular environment will be changed and then the magnetic behaviour of the material will be changed resulting in a change in the behaviour, too. Miller showed this with the trimorphic system composed of decamethylferrocene with TCNQ.\(^{15}\) The thermodynamically stable form was prepared in solution at -35\(^\circ\)C. It crystallised as purple plates with a herring-bone structure. This form is a paramagnetic material. A second, kinetically stable form was prepared from a warm solution of acetonitrile. This form is green and behaves as a metamagnetic material. A third form was recrystallised from acetonitrile at -20\(^\circ\)C. This crystallised as purple parallelepiped crystals and behaves as a ferromagnetic material.

3.6. **Nonlinear optical activity**

If the direction of polarised light changes after passing through the material, it means it has optical activity. The optical activity of a crystal is related to the symmetry group of the crystal structure. When molecules lack any symmetry, they are optically active. This means that molecules with a centrosymmetric structure are optically inactive. Nonlinear optical activity (NLO) means that the relation between polarisation and electric field is not linear and the wavelength halves after passing through the crystal. Nonlinear optical materials crystallised in non-centrosymmetric space groups. Hence NLO is associated with packing, and so is therefore affected by polymorphism. Hall (1986) discovered that the rates of cooling or evaporation can affect nonlinear optical activity. Hall studied the two polymorphic structures of PAN and it shows NLO behaviour and another is inactive.\(^{16}\) The active form was prepared from rapid cooling or evaporation which suggests that it is the kinetically stable form. The inactive one was formed by slow cooling or evaporation to give the thermodynamically stable form. Serbutoviez (1994) discovered that the polarity of solvent can also affect nonlinear optical activity. The NLO- active polymorph is preferred in non-polar solvents and inactive one is favoured in polar solvents. He demonstrated the effect by using pyrrolidine to 2:1 ethanol/water solvent mixture to prepare optical active crystal. The crystal is a polymorphic
monohydrate with two forms. The active one was obtained from pyrrolidine and the inactive one was obtained without pyrrolidine.

3.7. Chromoisomerism, photochromism and thermochromism

Nassau (1983) stated “Changes in the colour of a substance resulting from perturbations which result in change in structure or environment — so-called ‘chromogenic effects’”. Chromoisomerism and photochromism are the phenomena related to colour change. First, chromoisomerism in “a pure substance could lead to concomitantly crystallising crystals of different colour”. This was demonstrated by Toma (1994) when he studied 9-phenylacridinium hydrogen sulfate which has red and green polymorphs. The molecular structures and hydrogen-bonding patterns of the two forms are both identical and the only difference is their packing in the solid state. This results in different electronic structures so that they have different colours. Photochromism is the colour change caused by light. This phenomenon can be applied in optical devices. According to Burns (1988), he formed 3-ethyl-1, 5-diphenylformazan with two polymorphic forms. One form is orange and light stable whilst another form, prepared in the dark, has a red colour.

Thermochromism is colour change due to temperature changes. Dias (2003) found that a trinuclear copper(I) complex showed a temperature-induced phase transformation. This compound is orange at room temperature and becomes red on cooling to 77 K. This study showed that temperature change caused structure transformation. These phenomena proved that polymorphism affects the colour of molecule materials.

4. Methods for exploring polymorphism

4.1. Infrared and Raman spectroscopy

IR and Raman spectroscopy are very useful technologies to understand structure-property relationships. They are particularly useful for investigating intramolecular and intermolecular hydrogen bonding. Nash (1985) examined two forms of dithioglycolic acid by Raman spectroscopy. Form I is thermodynamically stable and shows a strong peak at 536 cm\(^{-1}\). Form II is kinetically stable and shows a peak at 510 cm\(^{-1}\). Such studies show that infrared and raman spectroscopy are useful tools to examine polymorphism.

4.2. Hot-stage microscopy

Hot-stage microscopy (HSM) examines melting points to study polymorphism. It is a rapid method to search for polymorphs. During, heating materials have solid-solid transition and the phase changes are detected by polarised light. Burger (2000) discovered the phase changes in D-mannitol, which are observed that three forms melt at 166.5, 166, and 150-158\(^{\circ}\)C respectively. Bakar (2009) studied the behaviour of sulfathiazole (compound VII).
Sulfathiazole (compound VII)

He observed two phase transitions during heating as shows in Fig. 4.2. Sulfathiazole has two polymorphic forms. Form II exists at 100 °C and it transfers to more stable Form I at 142.6 °C.

![Fig. 4.2 Melting behaviour of sulfathiazole by HSM](image)

**4.3. Powder x-ray diffraction**

Powder x-ray diffraction provides direct evidences for differences in crystal structure and is particularly powerful for the characterisation of polymorphs. It uses the Bragg relation \( n\lambda = 2d \sin \theta \) to determine crystal structure. Powder diffraction shows that materials with different polymorphs have different dimensions and fingerprints. Grotenhuis (1999) studied milk fat in butter or cream by X-ray powder diffraction and found that it has three polymorphs see Fig 4.1. The three different polymorphic forms appear at different temperatures: \( \gamma \)-form appears at – 50 °C, \( \alpha \)-form at – 5 °C and \( \beta' \)-form at room temperature.
Fig. 4.1 Characteristic X-ray powder diffraction (XRD) patterns of the three polymorphic forms found in milk fat.

4.4. Differential scanning calorimetry
Differential scanning calorimetry is a thermal method for quantitative analysis and provides information about the relative stabilities of polymorphs. It measures energy changes by heat flow into sample during a transition. Schwarz and Buhr (1998) studied polymorphs of sulfapyridine by DSC. The results are shown in Fig. 4.4. Region A undergoes a second-order glass transition with no energy change. Sharp curve B shows an unstable supercooled liquid. Region C is the transformation from liquid to a metastable form at 145 °C.
Fig. 4.4 Characterise polymorphism of sulfapyridine by DSC

5. Conclusion
Polymorphism in molecular crystals means that these materials can have more than one solid form. This different crystal packing can affect many properties such as solubility, bioavailability, conductivity, magnetic behaviour, optical activity, thermal sensitivity, pressure sensitivity and colour. The effect on these properties makes polymorphism an important phenomenon in pharmaceuticals, dyes and explosives. In the pharmaceuticals field, polymorphism affects solubility and bioavailability which are important factors for drug delivery. For dyes and pigments, polymorphism affects the colour because of the different crystal structures. Polymorphism can make energetic materials sensitive to initiation and pressure.

Scientists make a considerable effort and spend huge money in drug development. Characterise polymorphs plays key role in this research since polymorphism can affect drug’s properties. Even the same drug will change the properties because of existing different polymorphs. Polymorphism occurs by different processing conditions such as pressure and temperature. This makes analytical techniques becoming critically important for monitoring drug development. Moreover, modern drugs contain active pharmaceutical ingredients which make analysis more complicated and difficult. Therefore, drug development needs more rapid and accurate techniques to investigate polymorphic forms and the properties of drugs. Thus it has great potential to find advanced and effective analysis of polymorphism in pharmaceutical field.
Reference