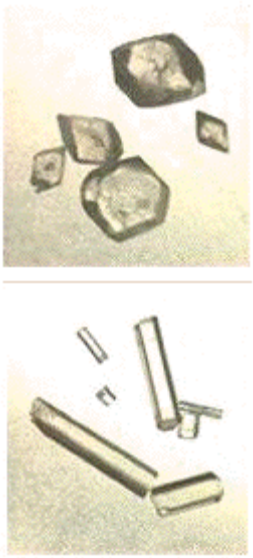
Polymorphism of a Compound

Polymorphs of a compound are different crystal forms in which the lattice arrangement of molecules are dissimilar. These distinct solids usually have different melting points, solubilities, densities and optical properties. Many polymorphic compounds have flexible molecules that may assume different conformations, and X-ray examination of these solids shows that their crystal lattices impose certain conformational constraints. When melted or in solution, different polymorphic crystals of this kind produce the same rapidly equilibrating mixture of molecular species. Polymorphism is similar to, but distinct from, hydrated or solvated crystalline forms. It has been estimated that over 50% of known organic compounds may be capable of polymorphism.

The ribofuranose tetraacetate, shown at the upper left below, was the source of an early puzzle involving polymorphism. The compound was first prepared in England in 1946, and had a melting point of 58 ºC. Several years later the same material, having the same melting point, was prepared independently in Germany and the United States. The American chemists then found that the melting points of their early preparations had risen to 85 ºC. Eventually, it became apparent that any laboratory into which the higher melting form had been introduced was no longer able to make the lower melting form. Microscopic seeds of the stable polymorph in the environment inevitably directed crystallization to that end. X-ray diffraction data showed the lower melting polymorph to be monoclinic, space group P2. The higher melting form was orthorhombic, space group $P2_12_12_1$. Polymorphism has proven to be a critical factor in pharmaceuticals, solid state pigments and polymer manufacture. Some examples are described below.



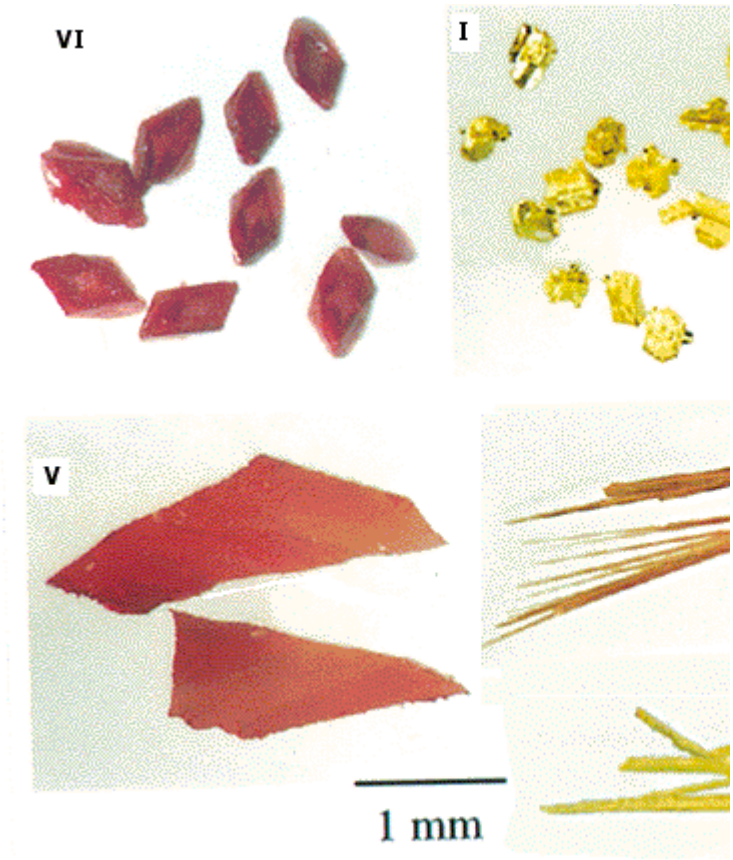
Two Polymorphs of Acetaminophen

Acetaminophen is a common analgesic (e.g. Tylenol). It is usually obtained as monoclinic prisms (upper picture) on crystallization from water. A less stable orthorhombic polymorph, having better physical properties for pressing into tablets, is shown beneath the first.

Quinacridone is an important pigment used in paints and inks. It has a rigid flat molecular structure, and in dilute solution has a light yellow color. Three polymorphs have been identified. Intermolecular hydrogen bonds are an important feature in all off these. The crystal colors range from bright red to violet.

The anti-ulcer drug ranitidine (Zantac) was first patented by Glaxo-Wellcome in 1978. Seven years later a second polymorph of ranitidine was patented by the same company. This extended the licensing coverage until 2002, and efforts to market a generic form were thwarted, because it was not possible to prepare the first polymorph uncontaminated by the second.

The relatively simple aryl thiophene, designated EL1, was prepared and studied by chemists at the Eli Lilly Company. It displayed six polymorphic crystal forms, pictures of which are shown on the left.



Polymorphic Crystals of EL1
(5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbo

Polymorphs of EL1

Example	Color/Shape	Crystal Form
I	yellow prisms	monoclinic $P2_1/n$[14]
II	reddish plates	monoclinic $P2_1/n$[14]
III	orange needles	monoclinic $P2_1/c$[14]
IV	yellow needles	triclinic P1[2]
V	orange plates	orthorhombic Pbca[61]
VI	red prisms	triclinic P1[2]

A common example of changes in polymorphism is shown by chocolate that has suffered heating and/or long storage. Over time, or when it resets after softening, it may have white patches on it, no longer melts in your mouth, and doesn't taste as good as it should. This is because chocolate has more than six polymorphs, and only one is ideal as a confection. It is created under carefully-controlled factory conditions. Improper storage or transport conditions cause chocolate to transform into other polymorphs. Chocolate is in essence cocoa mass and sugar particles suspended in a cocoa butter matrix. Cocoa butter is a mixture of triglycerides in which stearoyl, oleoyl and palmitoyl groups predominate. It is the polymorphs of this matrix that influence the quality of chocolate. Low melting polymorphs feel too sticky or thick in the mouth. Form V, the best tasting polymorph of cocoa butter, has a melting point of 34 to 36 ºC, slightly less than the

interior of the human body, which is one reason it melts in the mouth. Unfortunately, the higher melting form VI is more stable and is produced over time.

Polymorphs of Chocolate		
Polymorph	**Melting Point**	**Comments**
I	17.4 ºC	Produced by rapid cooling of a melt.
II	23.4 ºC	Produced by cooling the melt at 2 ºC/min.
III	26 ºC	Produced by transformation of form II at 5-10 ºC.
IV	27 ºC	Produced by transformation of form III by storing at 16-21 ºC.
V	34 ºC	Produced by tempering (cooling then reheating slightly while mixing).
VI	36-37 ºC	Produced from V after spending 4 months at room temperature.

Source : http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/physprop.htm#exp3