EDITORS | RICHARD A. STOREY | INGVAR YMÉN

# Solid State Characterization of Pharmaceuticals

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Editors

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WILEY

A John Wiley & Sons, Ltd., Publication

This edition first published 2011
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*Registered office*
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

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*Library of Congress Cataloging-in-Publication Data*

Solid state characterization of pharmaceuticals / edited by Richard A. Storey, Ingvar Ymén.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4051-3494-1 (cloth) – ISBN 978-0-470-65935-9 (ePDF)
1. Solid dosage forms. 2. Drugs–Design. 3. Pharmaceutical chemistry. I. Storey, Richard A. II. Ymén, Ingvar.
[DNLM: 1. Chemistry, Pharmaceutical. 2. Drug Design. 3. Pharmaceutical Preparations–chemistry. QV 744]
RS201.S57S63 2011
615′.19–dc22

2010053725

A catalogue record for this book is available from the British Library.

Print ISBN: 9781405134941
ePDF ISBN: 9780470659359
oBook ISBN: 9780470656792
ePub ISBN: 9781119970170
eMobi ISBN: 9781119970187

Set in 9/11pt Times-Roman by Laserwords Private Limited, Chennai, India
Printed in Great Britain by Antony Rowe Ltd, Chippenham, Wiltshire

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**Dr Ingvar Ymén** is Principal Scientist at AstraZeneca R&D, Medicines Development, Physical Science, 151 85 Södertälje Sweden (ingvar.ymen@astrazeneca.com). He obtained his PhD in Inorganic Chemistry and Crystallography on metal-organic compounds in 1983 at the University of Lund. He then moved to Norsk Hydro Fertilizers and Explosives, where he held scientific as well as managerial positions from 1984 to 1992. There he did scientific work on heterogeneous equilibrium, including polymorphism, crystallization and reaction controlling of ammonium nitrate-containing compounds. By determining and exploring binary, ternary and quarternary phase diagrams, together with mass and energy balances, he also designed and implemented stable, continuous, large-scale, granulation and prilling processes for fertilizers and explosives. In 1992, he moved to Astra to work as a solid state scientist and became manager of the Solid State Analysis Team in Södertälje in 1995, a position he held until 2003, when he returned to a purely scientific position as principal scientist. He has remained in this role and is today involved in research on heterogeneous equilibrium, especially towards crystallization, polymorphism and salt screening. As of today he has been working in the field of heterogeneous equilibrium for more then 30 years.

# Preface

Drug products are, in an overwhelming number of cases, produced as solid materials – for example, as tablets or granules in capsules. Even when formulated as liquids, the active pharmaceutical ingredient (API) is still usually produced as a solid prior to the final dissolution. During the development of a pharmaceutical formulation, knowledge of the physical properties of pharmaceutical materials – the APIs, the raw materials and the process intermediates for the API production, as well as the excipients and other chemicals for formulation – can help mitigate risks and offer opportunities for improved delivery. Knowledge of material properties is essential in a large number of activities when substances are brought in and out of the solid state, either as singular entities or as mixtures. Investigations into the effects of processes on materials present are termed 'solid-state work' and can have an effect during crystallization, dissolution, milling, drying, mixing, granulation, tableting, and so forth. Materials used in and obtained from these processes need to be characterized in a number of different ways, depending on what type of information is desired and on the properties of the material. For a solid-state scientist it is quite important to know which method of characterization to use for a particular material, how to design and run the instruments and how to use and evaluate the data from each technique. Unfortunately there is, to our knowledge, nowhere where a full academic education in pharmaceutical solid-state science is given; hence there is a continuous need for literature in this field.

One solid-state activity of special importance is the selection of the most suitable solid form of the API. This is a key solid-state process for successful scale-up and launch. Usually, a crystalline solid is desired because it provides an ideal solid for development due to its reproducible properties, such as solubility, and because it provides an excellent purification method during manufacture.

The form selection involves initial trials to crystallize the free form of the API, followed by salt-, co-crystal- and polymorph screening. Finally, the different solid phases obtained must be put on a thermodynamic stability scale so that the risks of future processing can be assessed without undesired surprises. It is critical that the correct solid form is selected for development as changes late in development and even in launch can affect the bioavailability of the API and hence its performance on dosing.

Solid form selection requires input from a wide number of disciplines including crystallization, stability assessment, biopharmaceutics, materials science and formulation, using a wide range of techniques, including high-throughput screening and computer predictions, for a successful nomination. Eventually, after the final selection has been made, patents covering some or perhaps all of the solid forms obtained during the selection work must be written.

Due to the importance of the different types of 'solid-state work' noted above, specifically the form selection, this book has been compiled to provide the reader with a single reference point. It incorporates an introduction to the crystalline state, a wide range of techniques for the

assessment of solid forms and chapters on their prediction, as well as the applicability of solid forms for patenting.

We hope that this book will provide the reader with a full toolbox for solid-state characterization and that the reader will have as much pleasure reading it as we have had producing it.

*Richard A. Storey*
*Ingvar Ymén*

# 1

# Introduction to the Solid State – Physical Properties and Processes

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## 1.1 Introduction

Pharmaceutical substances consist of organic molecules alone, or in combination with metal cations (metal salts), organic cations, organic or inorganic anions, neutral organic molecules (co-crystals) or solvent molecules (solvates). Even though some are salts, these have little resemblance with inorganic salts, the typical properties of which include high melting points, high hardness and strong ionic bonding. In fact, pharmaceutical substances, as salts or not, generally have similar properties, which are dominated by the presence of the organic molecules and their typical, weak intermolecular interactions. Crystals formed by organic substances are usually referred to as molecular crystals (Kitaigorodsky 1973) and it is the properties of this type of molecules that will be referred to when talking about the properties of pharmaceutical substances. In the following the physical states of a pure pharmaceutical substance will be discussed with reference to Figure 1.1 where the approximate areas of existence as a function of temperature are shown.

### 1.1.1 The Gas/Vapour and Liquid States

A gas consists of molecules, moving independently of each other, but occasionally colliding with each other or with the vessel in which it is contained. The collisions make up the gas pressure and the more collisions the higher is the pressure. A gas containing small, point-like molecules with negligible molecular interactions is called ideal. For such a gas:

$$pV = nRT$$

*Solid State Characterization of Pharmaceuticals*, First Edition. Edited by Richard A. Storey and Ingvar Ymén.
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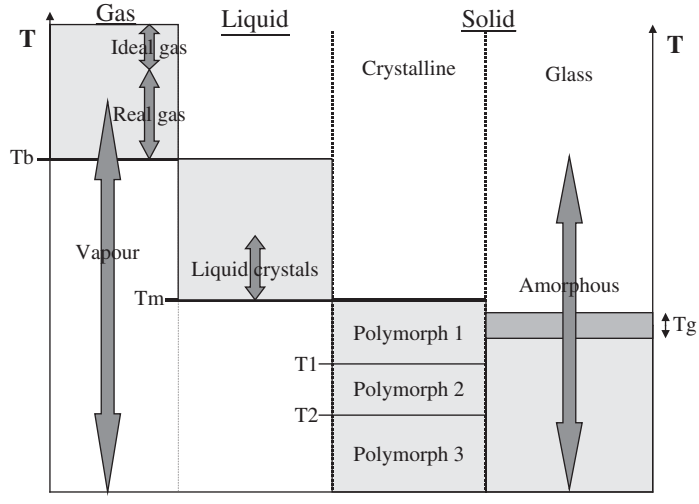


***Figure 1.1*** *Different possible physical states of a pharmaceutical substance as a function of temperature; it is assumed that the pressure is constant at 1 atmosphere*

where p = pressure, V = volume, n = the number of moles, T = temperature and R = the gas constant. Most gases are nonideal because their molecules are not pointlike and they interact to some extent. Gases at high temperatures are closest to ideal and the deviation from ideality increases closer to the point of condensation. In a mixture of ideal gases each gas will exert a pressure, which is proportional to the amount of that gas. The total pressure is the sum of the individual pressures so that for n different ideal gas molecules:

$$p_{tot} = p_1 + p_2 + \cdots + p_n.$$

In a gas each molecule may interact with itself in an intramolecular way, thus forming various conformations. If the temperature of the gas is close to the condensation point, a certain conformation may be dominating but as the temperature of the gas increases the molecular vibrations and rotations increase. This leads to an increased number of conformations becoming available. Molecular structures of reasonably complex gaseous molecules are usually determined by means of gas-phase electron diffraction (Rankin and Robinson 1995) or microwave spectroscopy (Consalvo and Stahl 1998).

There can only be one gas phase, regardless of the number of different molecular species in it. Such a gas phase will be completely isotropic (have the same physical properties in all directions), have a very low density, low viscosity and a high compressibility.

Lowering the temperature, the gas molecules will gradually lose translational and vibrational/rotational energy. At a certain temperature, the condensation/boiling point, the molecules will, when colliding, start forming aggregates and a liquid will form. The temperature at which this occurs, depends on the size of the molecule and on the number and strength of the bonds formed. Small molecules, forming only weak intermolecular interactions, will have low boiling points whereas larger molecules, forming stronger, or a larger number of, intermolecular bonds have higher boiling points. It should be noted that the condensation process depends on seeds on which the drops of liquid can form. In the absence of seeds the vapour may be supercooled.

Upon condensation the entropy decreases and a latent enthalpy of condensation is given off, thus lowering the total energy of the liquid. The molecules in the liquid will, however, still have

energy enough to perform translational motion, but not enough to escape molecular interactions. Consequently molecular movement will no longer be independent. There will also be a tendency towards fewer molecular conformations and towards the formation of larger molecular entities, such as dimers. For this reason the molecules themselves are no longer completely randomly oriented. This short-range order in liquids can be analysed with small angle X-ray diffraction, SAXS (Klug and Alexander, 1974) and the presence of dimers and larger aggregates can be determined by spectroscopic methods (Spitaleri et al. 2004)). Still, the lack of long-range order makes all physical properties of liquids isotropic. These properties are, however, distinctly different from those of the gas.

A liquid at ambient conditions will establish equilibrium with its own gas phase, referred to as the liquids vapour (this word is sometimes also used to describe gases close to the condensation point). The pressure, which is a function of temperature, is called the vapour pressure. The maximum amount of vapour in equilibrium with liquid water at a certain temperature is called the saturation vapour pressure, $p_{sat}$. This pressure increases with increasing temperature and for water it becomes 101 kPa at 100 °C, the boiling point of water. Dividing the actual water vapour pressure, $p_{H_2O}$ at a certain temperature with the saturation vapour pressure at the same temperature yields the relative humidity or the %RH:

$$\%RH = 100^{*}(pH_2O/p_{sat}).$$

To avoid confusion one must always relate the %RH to temperature. The measurement of water vapour pressure in ambient air, $p_{H_2O}$ is usually done as a dew point measurement (Moss 1934). An important difference between liquid and gas is that different liquids, when brought together, need not mix. Thus multiple liquid phases may be observed together, for instance in emulsions.

### 1.1.2 The Crystalline State

As a liquid is cooled the molecular movements decrease. Depending on the rate of cooling and on the properties of the liquid, either crystallization or glass formation will occur. For small, simple molecules at low cooling rates crystallization will normally occur at or below the freezing/melting point. There the molecules start forming intermolecular bonds, which are strong enough to stop translational, but not vibrational/rotational, motion. The freezing/melting point, like the boiling point, will be higher for larger molecules and for molecules with more and stronger interactions.

Upon crystallization the entropy decreases and a latent enthalpy of crystallization is released, which may be recorded as an exothermic event with, for instance, a DSC. Since crystallization is always more or less supercooled, an accurate determination of the theoretical onset temperature of crystallization (the freezing point) must instead be performed as a melting point analysis. The degree of super-cooling of the freezing point depends on molecular complexity and on presence of seeds.

The main similarity between the liquid and crystalline states is that, because the intermolecular distances are similar, the number of molecules per unit volume is roughly the same. This gives crystalline material numerical values of some physical properties, which are in a similar range to those of the liquid, for instance density and compressibility.

The big difference between liquids and crystals is the lack of translational motion and the presence of long-range order in crystals. In a crystal each molecule, with some exceptions (Dunitz and Gavezzotti 2005), has the same conformation and is fixed in one of a few possible, symmetry-related, positions. In this position, the molecule is bonded to its neighbours via weak intermolecular bonds (for example, hydrogen bonds or van der Waals bonds). In this way a crystal structure, which defines many of the physical properties, is formed.

The crystal structure may be described as a three-dimensional brick structure, built up of identical units cells, each of which is uniquely defined by its three unit cell axes a, b and c and the three

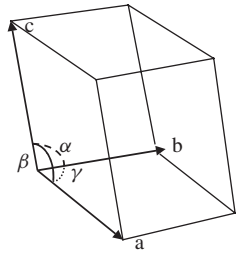


***Figure 1.2*** *The unit cell with unit cell axes and angles indicated*

***Table 1.1*** *The seven crystal systems*

| Crystal system | a | b | c | $\alpha$ | $\beta$ | $\gamma$ |
|---|---|---|---|---|---|---|
| Triclinic | a | b | c | $\neq 90^*$ | $\neq 90^*$ | $\neq 90^*$ |
| Monoclinic | a | b | c | 90 | $\neq 90$ | 90 |
| Orthorhombic | a | b | c | 90 | 90 | 90 |
| Tetragonal | a | b | a | 90 | 90 | 90 |
| Trigonal | a | a | a | $\neq 90^*$ | $\neq 90^*$ | $\neq 90^*$ |
| Hexagonal | a | b | a | 90 | 120 | 90 |
| Cubic | a | a | a | 90 | 90 | 90 |

*In the trigonal system all three angles are the same but in the triclinic they are all different.

angles $\alpha$, $\beta$, and $\gamma$, between these axes (Figure 1.2). The combination of these axes and angles gives rise to seven possible crystal systems (Table 1.1). Any crystal structure can be described with a unit cell from one of the crystal systems.

The unit cell usually contains more than one molecule, and these molecules, if having the same conformation, are related to each other via symmetry operations, described by the space group (Giacovazzo 1992). The smallest part of the unit cell in which there is no symmetry is called the asymmetric unit (often only one molecule). The number of asymmetric units in the unit cell is denominated as Z and it is basically the number of different molecular conformations present in the crystals structure. There is a relation between Z, the unit cell volume V, the molecular weight $M_w$, Avogadro's number $N_A$ and the density d:

$$d = ZM_w/VN_A$$

With this, densities are accurately calculated or, with an accurate density from, for example, pycnometry (Tamari and Aquilar-Chávez 2004) and a unit cell from X- ray data, the molecular weight can be checked.

In a crystal structure the molecules are packed efficiently and once the crystal structure is determined the packing efficiency can be calculated as the amount of filled space in the unit cell divided by the total unit cell volume. The value obtained is called the packing coefficient, which for organic molecules usually is in the range 0.65–0.73 (Kitaigorodsky 1973). Packing coefficients below 0.6 are rarely encountered.

Historically crystallography relied a lot on microscopy but today more than 99% is performed using X-rays together with either single crystals (SXRD) or a microcrystalline powder (XRPD). Table 1.2 lists a number of investigations, which can be performed by means of crystallography.

Both the crystal habit and the fracture of crystals are closely related to the crystal structure. Directions in the crystal structure where intermolecular bonding is weak will give rise to long unit cell axes and directions of stronger bonding give shorter axes. The crystal growth rate will

***Table 1.2*** *Typical crystallographic information obtained from single crystal X-ray diffraction (SXRD), X-ray powder diffraction (XRPD) and polarized light microscopy (PLM). Figures indicate which method is most suitable*

| Information searched | SXRD | XRPD | PLM |
|---|---|---|---|
| Is the sample crystalline or amorphous? | 3* | 1 | 2 |
| What is the degree of crystallinity of the sample? | | 1 | |
| Fingerprint identity of a single phase | 3* | 1 | 3 |
| Is the sample a single phase? | 3* | 1 | 1 |
| Quantify the amounts of several phases in a mixture | | 1 | |
| Determination of crystal structure | 1 | 2 | |
| Unit cell data | 1** | 1** | |
| Optical data | | | 1 |

*SXRD uses one or a few single-crystals and will thus not give relevant information for larger microcrystalline samples.
**It is usually easier to determine the unit cell using SXRD but XRPD gives a higher accuracy of the unit cell parameters. Therefore XRPD is often used to refine unit cell data obtained using SXRD.

be higher in the direction of stronger bonds, so a needle-shaped crystal will usually have the strongest bonds (a short unit cell axis) in the needle direction. Similarly, a very thin plate shaped crystal will have a long unit cell axis (weakest bonding direction) perpendicular to the plane of the plate. Likewise, when forces are applied on crystals they are likely to fracture along directions of weakest bonding, classical examples of which are talcum and graphite.

Control of crystal habit and of crystal size is of great importance, because these may have a large impact on material processing such as filtration, transport (flow properties), tableting, granulation and so forth. The most common ways to affect the crystal growth and habit are by choice of solvent and of supersaturation level for the crystallization. Moreover, because small amounts of foreign molecules may also have a large (usually negative) impact on both size and habit of crystals, it is common practice to purify materials as much as possible prior to crystallization. However, if done in a controlled way, the addition of small amounts of carefully selected substances may be beneficial both for habit modification and crystal size (Meenan et al. 2002).

The optical properties of crystals are also strongly related to the crystal structure and is more discussed by Bunn (1948).

### 1.1.3 The Glassy State

As noted above, depending on the rate of cooling and on the properties of the liquid, either crystallization or glass formation will occur. If a liquid containing comparably large and complex molecules, is cooled at a high rate the onset of crystallization might be severely overshot, resulting in the formation of a super-cooled liquid. Such a liquid will have a high viscosity, which upon continuous cooling eventually will become so high, that translational molecular movement will almost stop, at least compared to the time-scale of normal experiments. At this point the viscosity will be roughly $10^{13}$ poise (Ediger et al. 1996) and a glass has formed.

A glass is often referred to as an amorphous material, which is somewhat ambiguous if one wants to distinguish it from a normal or a supercooled liquid. All three types of materials are in fact amorphous, meaning that they all lack the long-range order found in crystals. A comparison of the three by means of XRPD analysis shows that they all lack sharp peaks. Although lacking long-range order, amorphous materials usually have some short-range ordering such as the formation of hydrogen-bonded dimers, trimers and so forth in solutions of carboxylic acids.

Materials that are partially crystalline are sometimes observed. In XRPD-diffractograms this is indicated by an increased background level in some regions an/or as peak broadening (Klug and Alexander 1974). Partial crystallinity may be described by a one-phase model or a two-phase

model (Westdahl 1996), where the one-phase model assumes disorder in the crystalline material and the two-phase model assumes that the sample is a mixture of two phases, one completely crystalline and one completely amorphous. Which method is preferred depends on what type of material one is working with. For pharmaceutical substances the latter model is normally used. The degree of crystallinity may then be analysed with various techniques (Saleki-Gerhardt et al. 1994; Buckton and Darcy 1999).

Along the cooling process, from the melting point until the point of glass formation, all physical properties of the super-cooled liquid show the same gradual change upon cooling, as they do for the melt above the melting point. At the point of glass formation, the molecules have come so close together that this gradual change can no longer continue. Instead, upon continued cooling a different path is now followed so a new type of material has indeed appeared. The most common physical properties used to describe glass formation are the specific heat $C_p$ or the specific volume $V_{sp}$, both of which show distinct changes when the glass forms (Figures 1.3 and 1.4).

The point of glass formation is called the glass transition temperature, $T_g$. Despite its name, it does not signify a true phase transition. Its value is not a constant but varies with the rate of cooling, so that the lower the rate, the lower the glass transition temperature and the lower the $C_p$ and the $V_{sp}$. This is a consequence of the fact that at a slower rate the molecules have more time to pack more efficiently.

The glass transition is usually analysed using DSC and most conveniently using the modulated type. With a hot stage microscope, in heating mode, $T_g$ can also be seen as the morphological change from a chip-like solid to a rounded liquid drop.

The glass transition temperature can also be affected by impurities and will in many cases drop significantly by the uptake of water. This is the basis for the determination of the amount of

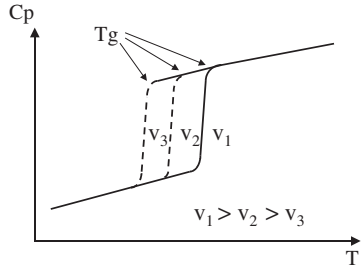


***Figure 1.3*** *Variation of $C_p$ as a function of temperature for a liquid that becomes a glass; the effect of different cooling-rates v1, v2 and v3, is also indicated*

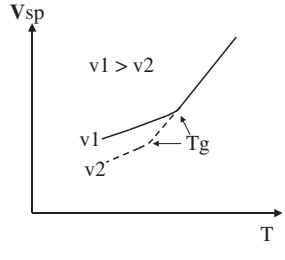


***Figure 1.4*** *Variation of $V_{sp}$ as a function of temperature for a liquid that becomes a glass; the effect of different cooling-rates v1 and v2, is also indicated*

glass in a sample, using isothermal calorimeters (Ahlneck et al. 1994). The material is allowed to take up water so that $T_g$ gradually drops. Crystallization occurs when it reaches the temperature of the calorimeter. The heat of crystallization is proportional to the amount of glass present in the sample. Since grinding of pharmaceutical substances often destroys parts of the crystal structure, amorphous material may be formed upon milling or grinding. The isothermal calorimeter measurements described above works very well for the quantification of the amount of amorphous material thus formed (Buckton et al. 1994).

The best analyses for the identification of a glass are polarized light microscopy (indicates optically isotropic behaviour), XRPD (no peaks) and DSC (shows $T_g$).

Other methods, such as isothermal calorimetry, moisture sorption and spectroscopic methods, will not offer identification on their own but they are good complimentary methods.

## 1.2 Neutral Pharmaceutical Molecules

Figure 1.5 shows a typical hypothetical, neutral pharmaceutical molecule in which different parts or groups are circled. What parts are present and how these are combined will determine the molecular properties and at the macroscopic level also the physical properties of the substance. Some fundamental molecular properties of importance from the solid-state perspective will be discussed below.

In a pharmaceutical molecule the groups with the lowest or highest pKa values can be exploited when preparing salts. The molecule in Figure 1.5 has a typically acidic group, a carboxylic acid and a typically alkaline group, a secondary amine. These groups will be responsible for the main protolytic properties of the molecule – that is, they will have the highest and the lowest $pK_A$ values. In fact, a substance like this, having both an acidic and an alkaline group, may establish an internal acid – base equilibrium and thus behave as a zwitterions in the pH range between the two $pK_A$-values.

The $pK_A$ value of an isolated functional group is usually easy to predict from the approximate ranges given in an organic chemistry textbook. However, when neighbouring groups interact, by means of resonance, inductive effects and so forth, things become more difficult. Database computer programs may be used to assist but, to be on the safe side, experimental $pK_A$-determinations should be made by acid-base titrations or NMR analysis (Kubal et al. 1994). It should be noted that $pK_A$-values, which are usually measured in water solutions, can also be determined in nonaqueous solvents, wherein they will take different values (Barcza and Buvári-Barcza 2003).

Some pharmaceutical molecules are very soluble in water but not in oil whereas others behave in more-or-less the opposite way. This type of behaviour is expressed by means of the partition coefficient between oil and water, $K_p$, which measures the molecules' approximate affinity for

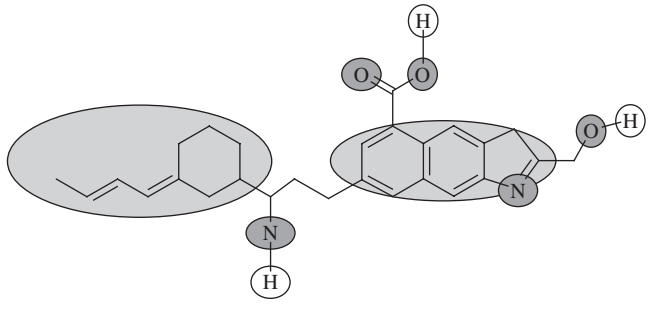


***Figure 1.5*** *A hypothetical pharmaceutical molecule with various functionalities marked*

water and for oil. A molecule with a high affinity for water is referred to as hydrophilic and one with a high affinity for oil as hydrophobic. On a molecular level the main difference between water and oil is the dipole moments of the molecules, that of water being quite high and that of a typical molecule in oil being low. This is the main reason for the high dielectricity constant of water compared to oil. Since most oils almost entirely consist of hydrocarbons it should be clear that hydrocarbon groups in a molecule are hydrophobic. A typical such part is circled in the leftmost side of Figure 1.5.

The parts of the molecule, which have local, high dipole moments, that is, groups in which there are local large charge separations, will be hydrophilic. Such areas are marked with dark circles in Figure 1.5. The fact that the molecule has one hydrophobic and one hydrophilic end means that it is very likely to have surface-active properties. At the interface between a hydrophilic and a hydrophobic medium, it will thus orient itself with its hydrophobic end towards the hydrophobic medium and the hydrophilic end towards the hydrophilic.

The number, size and position of the various hydrophilic and hydrophobic areas of a molecule will be responsible for 'the molecular part' of the solubility of a crystalline substance in a certain solvent (Yalkowsky and Banerjee 1992). This part mainly accounts for how well the molecules fit in and interact with the solvent molecules and is related to the partition coefficient. The other part, which determines the solubility of a substance is 'the crystal structure part', defined by how well the molecules interact in a crystal structure. This part has a strong relation to the melting point. Computer programs aiming to predict solubility solely from the knowledge about molecular structure have so far, for this reason, had limited success.

The density of pharmaceutical substances depends on the molecular density (molecular weight/molecular volume) and on how well the molecules pack in the solid (see packing coefficient in 1.4). The molecular density is usually the same for substances containing only C, H, N and O, the crystal density of which usually are between 1.2–1.4 kg/l. With the presence of heavier elements such as Si, S, P and halogens the molecular and crystal density typically increase.

The lowest energy conformation of a hypothetical molecule in a state without any interactions with other molecules can be calculated by means of quantum mechanics 'in vacuum' (Leach 2001). This conformation will be a consequence of the molecule's ambition to lower its total energy by minimizing steric effects and optimizing intramolecular bonding. Steric effects may be overcome if the molecule has enough flexibility, that is, low energy rotational bonds. From the bonding perspective the molecule strives to maximize the number and strength of the bonds formed. The formation of strong intramolecular hydrogen bonds may complicate the molecular analysis. These form between hydrogen bond donors (groups containing circled hydrogen atoms in Figure 1.5) and hydrogen bond acceptors (circled O- and N-atoms in the figure). If the molecule is large, folding so as to maximize van der Waals contacts might also become very important, as will interactions involving $\pi$-systems. The central aromatic system in Figure 1.5 will be quite inflexible and essentially planar. Quite possibly, in vacuum the terminal unsaturated hydrocarbon chain would fold over the central aromatic ring system so as to optimize $\pi - \pi$ interactions.

Today, quantum chemical modelling may also involve solvent, explicitly or implicitly, allowing more adequate data to be compared to experimental results in solution. However, in many cases theoretical models may fail to properly represent real liquid or solid pharmaceutical systems.

The absorption of visible and ultraviolet light in neutral pharmaceutical molecules is due to the presence of 'chromophores'. These are unsaturated parts of molecules containing multiple bonds. In Figure 1.5 there are many parts that act as chromophores, the unsaturated carbohydrate chain, the central aromatic ring system and the carboxylic acid. Coloured solid pharmaceutical substances usually contain large chromophore systems, in which there are many possible resonance structures.