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Advanced Drug Delivery Reviews 48 (2001) 115–136

Advanced DRUG DELIVERY Reviews

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Chemical reactivity in solid-state pharmaceuticals: formulation implications

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Received 18 October 2000; accepted 21 December 2000

Abstract

Solid-state reactions that occur in drug substances and formulations include solid-state phase transformations, dehydration/desolvation, and chemical reactions. Chemical reactivity is the focus of this chapter. Of particular interest are cases where the drug-substance may be unstable or react with excipients in the formulation. Water absorption can enhance molecular mobility of solids and lead to solid-state reactivity. Mobility can be measured using various methods including glass transition (T_g) measurements, solid-state NMR, and X-ray crystallography. Solid-state reactions of drug substances can include oxidation, cyclization, hydrolysis, and deamidation. Oxidation studies of vitamin A, peptides (DL-Ala-DL-Met, *N*-formyl-Met-Leu-Phe methyl ester, and Met-enkaphalin acetate salt), and steroids (hydrocortisone and prednisolone derivatives) are discussed. Cyclization reactions of crystalline and amorphous angiotensin-converting enzyme (ACE) inhibitors (spirapril hydrochloride, quinapril hydrochloride, and moexipril) are presented which investigate mobility and chemical reactivity. Examples of drug-excipient interactions, such as transacylation, the Maillard browning reaction, and acid base reactions are discussed for a variety of compounds including aspirin, fluoxitine, and ibuprofen. Once solid-state reactions are understood in a pharmaceutical system, the necessary steps can be taken to prevent reactivity and improve the stability of drug substances and products.

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0169-409X/01/$ – see front matter
PII: S0169-409X(01)00102-8

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1. Introduction

Solid-state reactions can and do occur in drug substances and formulations. In formulations, solid-state reactions of the drug substance are of great interest. These can occur in cases where the drug substance is intrinsically chemically reactive or unstable. In such cases, the formulation can accelerate degradation in any or all of the following ways:

- Acceleration due to interaction with excipients
- Acceleration due to processing effects
- Acceleration induced by excipients (but not involving chemical reactions with the excipient)

Often, acceleration of reaction is due to the creation or presence of amorphous material. Thus, one of the best examples of these effects is the enhanced chemical reactivity of amorphous materials. In such cases processing or, possibly, simply interaction with the excipients can increase the amount of amorphous drug substance. This amorphous drug substance will then react due to its increased mobility and ability to interact with moisture.

Direct reaction of excipients with the drug substance can also occur, such as solid–solid acid base reactions. However, buffers or acids and bases are used to stabilize drug substances in formulations as well. In many cases these effects can be determined by mixing the drug substance with various excipients. In other cases processing is needed to induce the reaction.

The role of solid-state reactions in drug substances and formulations will be discussed here. Background information on solid-state reactions and mobility, as well as various examples of solid-state reactions in pharmaceutical applications will be presented.

2. Solid-state reactions

In order to understand more about the influence of formulations on solid state reactions it is worthwhile to review solid state reactions. Solid-state reactions in their broadest sense include solid-state phase transformations (polymorphic transformations), reactions in which solvent of crystallization is lost or gained, and a broad range of solid state chemical reactions. Most of the emphasis of this chapter will be on chemical reactivity.

It is necessary to establish criteria for solid state reactions in order to focus on true solid state reactions. This will avoid a liquid state reaction being identified as a solid state reaction. Morawetz suggested four criteria for determining whether a reaction is a true solid state reaction [1]. A fifth criterion can be added based on Paul and Curtin [2]. A reaction occurs in the solid when:

1. the liquid reaction does not occur or is much slower.
2. pronounced differences are found in the reactivity of closely related compounds.
3. different reaction products are formed in the liquid state.
4. the same reagent in different crystalline modifications has different reactivity or leads to different reaction products.
5. it occurs at a temperature below the eutectic point of a mixture of the starting material and products.

Once it has been established that the reaction is occurring in the solid-state, the reaction can be understood in terms of a four step process [2]:

1. *Loosening of Molecules at the Reaction Site*. It is reasonable to assume that molecular loosening achieves the mobility required to accomplish the next step.
2. *Molecular Change*. This step is similar to the corresponding solution reaction where the bonds of the reactant are broken and the bonds of the product are formed.
3. *Solid Solution Formation*. During the early stages of the reaction, a solid solution of the product in

the starting crystal is formed at the site of reaction. However, after the concentration of the product reaches a certain point, the product will separate.

4. *Separation of Product.* This step gives new crystals, either randomly oriented or with an orientation governed by the crystals of the starting material. This latter case is termed a topotactic reaction and will be discussed.

Solid-state reactions begin at one or more nucleation sites and spread through the crystal. For desolvations and some thermal reactions, the reaction begins at a nucleation site and spreads through the crystal in a front that advances through the crystal.

Nucleation sites (defects) for reaction are developed during crystallization or can sometimes be produced by mechanical deformations such as pricking with a pin or cutting the crystal. Exposing the starting crystal to product crystals may produce nucleation sites. In other cases, nucleation is random and neither mechanical deformation nor exposure to product crystals nucleates the reaction. Obviously, this variability in nucleation and the random number of nucleation sites that are present in crystals can greatly complicate the kinetics of solid state reactions.

For solid gas reactions, diffusion of gas into the crystal itself requires molecular loosening. Thus, for solid–gas reactions simultaneous or sequential molecular loosening and diffusion steps are involved.

The chemical reaction is generally considered to follow the same mechanism as the solution reaction. As the reaction proceeds a solid solution of the product in the reactant crystal will be formed. After the limit of product solubility in the starting crystal lattice is reached, the product will either crystallize or continue to accumulate in an amorphous form. This step would not influence the apparent rate of the reaction as measured by the amount of product formed or by the disappearance of the reactant. However, if the rate is measured using the diffraction intensities of crystalline product, the rates may differ from those measured chemically.

It is clear from the above discussion that the rates of solid state reactions depend on several factors, including nucleation and the molecular changes involved. It is important to realize that the crystal structure and crystal packing profoundly affect the molecular loosening and molecular change steps of a solid state reaction. The crystal packing determines the extent of molecular loosening required for the molecules to reorient sufficiently to undergo the required molecular changes. The crystal packing also determines the extent of molecular loosening required for gases to diffuse to the reaction site in solid–gas reactions. Thus, determining the relevant crystal structures and investigating the molecular mobility in these structures can bring about a great deal of insight into solid state reactions.

3. Mobility

Understanding the mobility of groups in solids can lead to insight into the mobility of molecules in solution, the forces responsible for conformational interconversions, and the factors responsible for solid state reactions. It is clear that solid state degradations of pharmaceuticals are often related to molecular mobility [3–5]. In addition, Ahlneck and Zografi [6] have suggested that water absorption enhances the molecular mobility of pharmaceutical solids, perhaps explaining the enhanced chemical reactivity of these materials in the presence of water. Recent studies by Zografi's laboratory and our laboratory confirm the relationship between molecular mobility and solid state reactivity as discussed in a later section.

Further study of the relationship between molecular mobility and solid state reactivity requires the development of new approaches to determining molecular mobility, especially in mixtures such as pharmaceutical dosage forms where single-crystal X-ray methods cannot be used.

Solid state NMR offers several attractive approaches to the study of the molecular mobility of solids. These include:

1. Determination of the activation energies from T_1 relaxation of individual carbon atoms using variable temperature solid-state NMR.
2. Study of processes which result in peak coalescence of solid-state NMR resonances using variable temperature solid-state NMR.
3. Use of interrupted decoupling to detect methylene and possible methine groups with unusual mobility.

4. Comparison of solid-state MAS spectra measured with and without cross polarization.

X-ray crystallography offers another approach to the measurement of mobility in the solid-state. Trueblood and Dunitz have used variable temperature X-ray crystallography to measure the force constants for vibration of methyl groups [7–10].

It is interesting to explore the possible relationship between studies of molecular mobility by solid-state NMR and X-ray crystallography. A priori there is no reason to expect that the force constants for methyl vibration (or any other motion) determined by X-ray crystallography and the activation energy for methyl rotation determined by solid state NMR would be correlated. Variable temperature solid state NMR is thought to measure activation energies for the rotation of methyl groups about their C_3 axes. (However, many of the barriers obtained for methyl rotation from solid state NMR are significantly lower than those expected based on molecular mechanics calculations of methyl rotation barriers.) In contrast, X-ray crystallography measures the vibrational motion of the individual atoms. One would expect that vibration (as measured by X-ray crystallography) and rotation of methyl groups (as determined by solid-state NMR) in solids may not always be correlated. On the other hand, if the crystal packing in the vicinity of two methyl groups in the same molecule is different, one might expect that the methyl group that is not as tightly packed might exhibit a lower force constant for vibration and also a lower activation energy for rotation. In our laboratory we have compared the relative barriers to methyl rotation of the multiple methyl groups in ibuprofen and phenacetin measured by solid state NMR to the force constants measured by variable temperature X-ray crystallography. These studies indicate that the methyl group with the greatest barrier to motion by solid state NMR also has the greatest force constant for vibration by X-ray crystallography.

Water is known to enhance the mobility of amorphous solids [6]. This is due to the plasticization that results when water is absorbed. In addition, water can be absorbed into amorphous regions in otherwise crystalline materials. Such solids that may contain a small or undetectable amount of amorphous material are expected to show enhanced reactivity. Once degradation begins in these small amorphous regions it can proceed throughout the crystal by forming eutectic melts of the products and reactants. Ahlneck and Zografi have pointed out that the effect of water is amplified in these cases because the small amounts of amorphous material can contain a relatively large amount of water; yet the total water content of the solid will be low [6]. Further studies of the mobility of solids in the presence and absence of water are needed in order to determine whether a predictive technique can be developed which will form the basis for selection of the most stable crystal form prior to stability studies.

4. Solid-state reactions of drug substances

The origin of solid-state reactions in a drug substance can be explained by various factors as discussed above. Solid-state reactions can include oxidation, cyclization, hydrolysis, and deamidation. Excipients present in formulated products may not be directly involved in the degradation mechanism, but may add parameters, such as water, which contribute to the solid-state reaction. Examples of degradation of drug substances alone and in formulations will be presented.

4.1. Oxidation reactions

4.1.1. Vitamin A

Solid-state oxidation reactions have been known for many years. Early studies suggested that these reactions were free radical processes. For example, Finkel'shtein and co-workers postulated the mechanism for the reaction of beta carotene (Fig. 1) because 2,6 di-*tert*-butyl-4-methyl phenol (BHT) and other antioxidants inhibit this reaction and the rate depends on oxygen pressure and temperature [11].

Crystalline esters of vitamin A (including the hemi succinate, the nicotinate, and the 3,4,5-trimethoxybenzoate) decompose by both polymerization and oxidation pathways [12,13]. Vitamin A exposed to air at room temperature for several years or heated at 100°C for 5 h gave at least five ketones on TLC plates treated with 2,4-dinitrophenylhydrazine [14]. We have found that vitamin A is a gummy yellow solid after 5 months of exposure to room light,

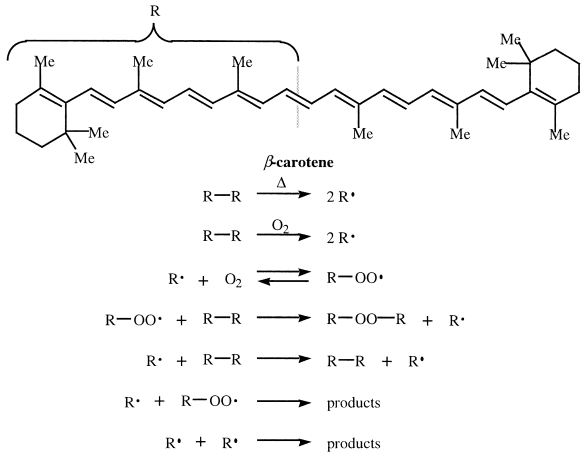

Fig. 1. Autooxidation scheme of β-carotene [11].

temperature, and air. Elemental analysis indicated that each molecule of vitamin A took up six oxygen atoms, and mass spectral studies indicated extensive degradation and the presence of many products.

Diluents with antioxidant properties stabilize vitamin A palmitate in vitamin preparations [15]. Aluminum salts of fatty acids such as stearic acid stabilize vitamin A, as does combination with gelatin and dextrin, which probably contain reducing sugars [16].

An interesting correlation of the melting points of the vitamin A (retinoic acid) esters with their zero order rate of solid state decomposition has been observed [13]. As the melting point increased, the rate of decomposition decreased. The rates of decomposition of these esters in solution were virtually identical. These results were interpreted in terms of crystal lattice energy. It was argued that the higher melting esters had more crystal-lattice energy and thus were more stable to the solid–gas oxidation reaction. Thus, the higher the melting point the more efficient the packing and, conceivably, the less permeable the crystal is to reacting gas. A better measure of lattice energies in a series of compounds is based on the heat of sublimation [17].

4.1.2. Peptides

There is substantial interest in understanding more about the solid-state oxidation of methionine in peptides and proteins. One impediment to studying this oxidation reaction is that the process is complicated because it produces a variety of products. Xu [18] has carried out a preliminary study of methionine oxidations by monitoring the disappearance of the peptide as well as monitoring the formation of the sulfoxide and sulfone products, as shown in Fig. 2.

Three model peptides (Fig. 3) were investigated: DL-Ala-DL-Met (a zwitterionic dipeptide), *N*-formyl-Met-Leu-Phe methyl ester (a neutral tripeptide), and Met-enkaphalin acetate salt (a weakly acidic pentapeptide). These peptides were chosen for investigation because both crystalline and amorphous material could be produced. To complete the study in a reasonable time, the oxidation of these peptides was accelerated by exposure of the peptides to UV radiation (254 nm) using a 15 W tube. Fig. 4 shows the results for the study of the degradation of crystalline and amorphous DL-Ala-DL-Met. Similar

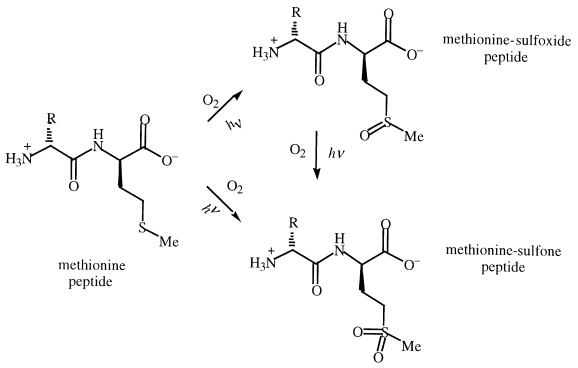

Fig. 2. Methionine oxidation reactions [18].

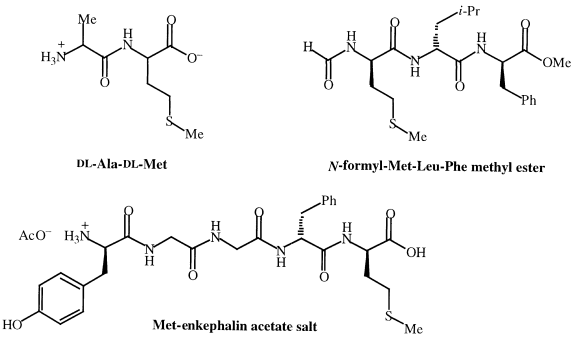

Fig. 3. Model peptides DL-Ala-DL-Met (a zwitterionic dipeptide), *N*-formyl-Met-Leu-Phe methyl ester (a neutral tripeptide), and Met-enkaphalin acetate salt (a weakly acidic pentapeptide).

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