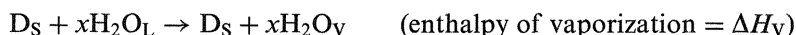
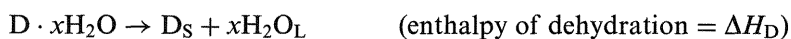


Lo (1976) showed that ampicillin trihydrate dehydrated to amorphous ampicillin, which had much poorer stability than the trihydrate. Upon storage the decomposition appears biphasic.

15. PSEUDO-POLYMORPHIC TRANSFORMATIONS

Dehydration, as mentioned above, may result in amorphous anhydrides, but it may also result in another crystalline phase (e.g., a lower hydrate or a crystalline anhydrate). These are, properly speaking, *pseudo-polymorphic transformations*. There are several steps in dehydration of a hydrate, and they can be summarized in the following manner, where S denotes solid, D denotes drug, V denotes vapor, and L denotes liquid (Han and Suryanarayanan, 1997).



i.e.,

$$\Delta H_T = \Delta H_V + \Delta H_S \quad (6.107)$$

so that different results can be obtained in DSC experiments depending on whether a crimped or open pan is used.

Bray et al. (1999) have shown such a diagram for [2(S)-[p-toluenesulfonyl amino]-3-[[5,6,7,8-tetrahydro-4-oxo-5-{5-[2-(piperidin-4-yl)ethyl]-4-H-pyrazolo[1,5-a][1,4]diazepin-2-yl]carbonyl]amino]-propionic acid.

Suihko et al. (1997) have employed DSC to show that dehydration of theophylline monohydrate is a two-step process.

16. POLYMORPHIC TRANSFORMATIONS

Polymorphic transformation rates have become of importance of late, and an example is a recent article by Agbada and York (1994) dealing with the dehydration kinetics of theophylline. The article by Ng (1975) is similarly instructive in the sense that it reviews all the equations that have been developed for polymorphic transformation kinetics.

In most cases the transformation kinetics are S-shaped curves, and before any model is imposed on the data, the following model should be considered. (This is comparable to the model proposed by Carstensen and Van Scoik, 1990). If the phenomenon that governs the transformation is essentially the nucleation lag time, then the curves may be considered as representing either a normal or a log-normal error curve, and the mean would be the mean (or geometric mean) nucleation time. What this states is that each particle, in a sense, acts as its own entity, that there is a nucleation time (with an error or a variance attached to it) and that the particle will endure the nucleation time and then decompose, individually, very rapidly.