

Advances in Characterization of Pharmaceutical Hydrates

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Hydrates are molecular complexes that have water molecules incorporated into their crystal lattice. The physicochemical, processing, mechanical and compaction behavior of pharmaceutical hydrates can be different from those of the corresponding anhydrous phases [1]. Food and Drug Administration's (FDA) requires that appropriate analytical procedures be used to detect the different solid forms of the drug substance. Byrn et al., have developed flow charts describing the most important regulatory and scientific issues with regard to characterization of pharmaceutical solids, including polymorphs, hydrates (solvates), desolvated solvates, and amorphous forms [1,5]. Among the different solid states of drugs, hydrate formation is one of the commonly encountered phenomena and may cause as many challenges as different polymorphs may cause. Many topics related to pharmaceutical hydrate have been extensively reviewed [4-16]. Here we focus on the recent developments in characterization of hydrates, the physical stability phase diagram, dehydration kinetics, and Process Analytical Technology (PAT).

New techniques for characterizing pharmaceutical hydrate

A comprehensive characterization of pharmaceutical hydrate should include a collective knowledge about structure identification, quantitation, thermodynamic properties, and phase diagrams [6,7,11,17]. The commonly used techniques including powder X-ray diffractometry and single crystal X-ray crystallography [18-20], thermal analysis [10,12], microscopy [21], vibrational spectroscopy, such as infrared spectroscopy (IR, FTIR, Raman and near IR) [22], solid-state NMR [23], and moisture sorption [24,25].

Recently, some new techniques and application have been used for the characterization of pharmaceutical hydrates. Humidity-controlling devices have been used with various techniques to obtain hydrate information under controlled environments. Powder X-ray diffractometry (Powder XRD) is widely used for the identification of pharmaceutical hydrates. If the purity of a sample is established, XRD is an excellent method to detect crystalline hydrate formation [2,18]. Humidity controlled XRD, DSC and TGA have been used to study the effect of water vapor pressure on the kinetics and mechanism of dehydration of carbamazepine dihydrate and nafragel hydrochloride [6,26]. Recently a humidity controlled XRD coupled with DSC (humidity controlled XRD-DSC) had been developed and used in characterizing pharmaceutical hydrates [27]. It provides both thermal and crystalline phase information simultaneously. Lane and Buckton also used a combined moisture sorption balance and FTIR to study the moisture sorption/desorption of pharmaceuticals, which has great potential for study hydrates [28].

Single crystal X-ray crystallography provides unambiguous information about the crystal structure of hydrates and is the best technique to obtain the stoichiometric number of water in the hydrates. For example, Te et al. investigated the single crystal to single crystal dehydration of thiamine hydrochloride monohydrate using XRD and solid state NMR [29]. It was found that the loss of water leads to a shrinkage of the unit cell volume and accompanied by an increase in molecular motion. Anhydrites and hydrates of olanzapine were also studied in detail by integrating crystallography, spectroscopy, and crystal modeling techniques for a better understanding of the crystallization outcomes [23].

Thermal analysis techniques, such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), solution calorimetry or microcalorimetry, permit both qualitative and quantitative studies of hydrates [10,30,31]. DSC was also used as a method to determine the water content in pharmaceutical hydrates. This was based on the assumption that the enthalpy of binding of n moles of water molecules in the hydrate is the same as that of n moles of water molecules in liquid water [32]. Pressure differential scanning calorimetry has been recently used to characterize pharmaceutical hydrates, such as carbamazepine dihydrate, ampicilline trihydrate and betaine monohydrate [24,33,34]. By enclosing a regular DSC cell in specially designed pressure housing, it is possible to perform differential scanning calorimetry under reduced or elevated pressures, which created a micro environment of saturated water vapor pressure around the sample and shifted the water evaporation to a higher temperature. So it is possible to separate the dehydration endotherm from the evaporation of water, which gives a very sensitive method to quantify the amount of hydrate phase in mixtures [24,34].

Development in physical stability phase diagram

Since pharmaceutical hydrates are co-crystals of water and drug molecules, the water activity in the environment plays as critical a role as the temperature of the environment for the physical stability of the hydrate systems. Different techniques have been applied to obtain the transition water vapor pressures of hydrates. One of the most commonly used methods is to equilibrate the solid sample under different relative humidity (RH) in desiccators maintained by saturated salt solutions [35]. Other methods to determine the equilibrium water vapor pressure of hydrate have also been reported in the literature [37-39]. These methods give similar results for the system of interest. Han and Suryanarayanan developed a simple kinetic method to rapidly determine the dissociation pressure of hydrates by a humidity controlled thermogravimetric analysis technique and using an equation, $k = k_0 \times (1 -$

$p/p_t)$. Where k is the dehydration rate constant at water vapor pressure p and k_0 is the dehydration rate constant at 0 water activities. When the data of k against p are plotted linearly, the dissociation water vapor pressure of the hydrate, p_t , can be determined when k extrapolate to 0 [36].

Recently, the humidity controlled microbalance systems have been widely used in the study of hydrate systems [24,25,40]. In addition to the controlling water vapor pressure in the surrounding environment, water and organic cosolvent approaches have been also employed to assess the phase diagrams of pharmaceutical hydrates. Bogardus investigated the hydrate and anhydrate phases of theophylline in dioxane-water mixtures. Above 5% water, the theophylline hydrate was stable; while below 5% of water, the anhydrate form was stable. Samples of caffeine equilibrated with 10-50% water, however, remained in the crystal form initially added [41]. Similar study of theophylline hydrate and anhydrate systems were studied using IPA-water and methanol-water systems with known water activities. It was concluded that (a) water activity is the major factor determining the nature of the solid phase of theophylline which crystallizes from methanol + water or IPA + water mixtures, (b) theophylline anhydrate and monohydrate, is in equilibrium at water activity of 0.25 at 25 °C [42].

Rethinking of dehydration kinetics

Solid-state reaction

The dehydration or hydration processes are solid-state reactions that are dramatically different from reactions occurring in a liquid or a gaseous state [43-48]. Some of the difficulties, due to the intrinsic heterogeneity of the solid phase system, will have significant impact on the kinetic studies. In fact, the concepts of "concentration" and "order of reaction" cannot be applied in the solid-state reactions. Because of the difficulty encountered in studying heterogeneous solid reaction systems, little experimental work has been conducted to elucidate actual reaction mechanisms [49,50]. Monkhouse and Van Campen reviewed the theoretical and experimental aspects of solid-state reactions [48]. Byrn et al. further addressed the issues related to the solid-state reactions of pharmaceuticals [1].

The kinetics of many solid-state reactions can be represented by the general equation, $f(\Delta) = kt$, where Δ is the fraction reacted in time, t , and the function, $f(\Delta)$, depends on the reaction mechanism and the geometry of the reacting particles. The most commonly used models for solid state reactions including: (1) diffusion controlled reactions (D1 to D4) (2) phase-boundary-controlled (R1 to R3), and (3) reactions which obey the Avrami-Erofe'ev equations (F1, A2 and A3). Hancock and Sharp reported a kinetic method to distinguish reaction mechanisms by using an equation, $\ln[-\ln(1-x)] = \ln B$

+ mlnt, based on the most common solid-state kinetic model equations (Table 1). In this equation, x is the fraction of product at time t, B is a constant the value of which depends in part on the nucleation frequency and linear rate of grain growth, and m is the Hancock-Sharp constant which can vary according to the reaction mechanism and the geometry of the system [51].

Table 1. Kinetic equations $g(x) = kt$ for common mechanisms of solid-state kinetics and values of Hancock-Sharp constant, m.

Symbol	$g(x)$	m value	Mechanism
R1	x	1.24	Zero-order(Polany-Wlgner equation)
R2	$2[1-(1-x)^{1/2}]$	1.11	Two-dimnsional phase-boundary
R3	$3[1-(1-x)^{1/3}]$	1.07	Three-dimensional phase-boundary
F1	$-\ln(1-x)$	1.00	First-order
A2	$[-\ln(1-x)]^{1/2}$	2.00	Two-dimensional growth of nuclei
A3	$[-\ln(1-x)]^{1/3}$	3.00	Three-dimensional growth of nuclei
D1	x^2	0.62	One-dimensional diffusion
D2	$-(1-x) \ln(1-x) + x$	0.57	Two-dimensional diffusion
D3	$[1-(1-x)^{1/3}]^2$	0.54	Three-dimensional diffusion
D4	$(1-2x/3)-(1-x)^{2/3}$	0.57	Three-dimensional diffusion
P1	$\ln[x/(1-x)]$	N/A	Prout-Tompkins equation

The majority of the solid-state reactions, including dehydration reactions, have been studied by fitting to one or more models listed above. Recently, a model free approach has been developed to studies the solid-state reactions [52-54]. Chou et al., applied the model free approach to the study of the dehydration of nedocromil sodium trihydrate and it was found that the model-free approach was better than the model-fitting approach for understanding the details of the solid-state dehydration reactions [55].

Smith-Topley effect

Smith and Topley first discovered that the rate of dehydration is a complicated function of the water vapor pressure in the sample environment. With increasing water vapor pressure, the rate constant at first decreases, passes through a minimum, and then increases to a maximum of similar to the rate in vacuum, and again falls more slowly [56-58]. The term of Smith-Topley effect is then used to describe this phenomenon of unusual variation in the dehydration rate with respect to the water vapor pressures. Although there is no universally accepted explanation for the Smith-Topley effect, several mechanistic models have been proposed [63-70]. We have studied the influence of the water vapor pressure on the kinetics and mechanism of dehydration of carbamazepine dihydrate using TGA, DSC and variable temperature XRD coupled with

a humidity-controlling device [66]. As the water vapor pressure increases, the Smith-Topley effect was observed for the system. We concluded that the change of dehydration rate constant is due to a change in the dehydration mechanisms, which also resulted different solid phases after dehydration. So it is unlikely to observe the Smith-Topley effect if there is no option of changing solid state for the dehydrated phase. For example, amoxicillin trihydrate can only form a poorly crystalline solid phase after dehydration, since no crystalline anhydrate exists, then the rate of dehydration will decrease linearly as the water vapor pressure increases, and the dehydration mechanism will not change either [36]. For the hydrate systems that observed the Smith-Topley effect, it is possible to produce a certain dehydrated solid phase by designing the dehydration conditions [67,71].

Introducing Process Analytical Technology (PAT)

Industry and regulatory agencies are seeking ways to improve manufacturing efficiency and quality by employing at-line or in-line sensors to monitor the manufacturing processes [7]. Process analytical technology (PAT) is a new initiative to enable real time process control during individual unit operations, so that to

decrease post production analysis and to improve the understanding of the manufacturing processes [72,73]. Wet granulation is one of the commonly performed unit operations for pharmaceutical manufacturing. During this operation, it is possible to have phase transitions between hydrate and anhydrate. Jorgensen et al. followed hydrate formation of two structurally related drugs, theophylline and caffeine, during wet granulation using fast and nondestructive spectroscopic methods. It was found both charge-coupled device (CCD) Raman spectroscopy and near-IR spectroscopy (NIR) can be applied to monitoring of hydrate formation of drugs during wet granulation. NIR revealed the state of water, and Raman spectroscopy gave information related to the drug molecules. NIR is more suitable for monitoring solid-water interactions [74]. In another study, Near-IR (IR) spectroscopy is used for the rapid, nondestructive identification and quantification of the hydrate form of drug compounds forming both single and multiple hydration states. Near-IR is shown to be useful in both bulk drug and in finished solid dosage forms. The technique is applied in a process environment for at-line analysis of active pharmaceutical ingredient hydration state during pharmaceutical processing [75]. Davis et al. applied a small-scale, top mixing granulator with novel X-ray powder diffraction equipment to study the wet granulation process. The unique polycapillary optic and X-ray source allowed the

transformation of the metastable to the stable phase to be followed during the granulation. Following a diffraction peak each for the metastable and stable forms demonstrated, the phase transformations during the wetting phase of granulation was followed successfully. It allows real-time control of the process by the adjustment of process parameters, such as granulation time, and clearly qualifies as a process analytical technology (PAT) [76]. This technique has great potential for study hydrate formation during wet granulations.

Summary

In this review, some of the new techniques for identifying and quantifying pharmaceutical hydrates have been described. It should be emphasized that no single technique can provide enough information for the understanding of hydrate systems. A comprehensive study of hydrate should include: structure information, such as powder XRD and crystal structure, solid state NMR; thermal properties, such as DSC, TGA data; vibrational spectroscopy profiles, such as Infrared Spectroscopy (IR), Fourier Transform Infrared spectroscopy (FTIR) and Raman Spectroscopy; and hygroscopicity, such as moisture absorption/desorption. In addition, the phase diagram of the hydrate system is essential information for determining the drug processing and storage conditions. As a result of the Smith-Topley effect for hydrates, the solid state after dehydration can be affected by changing the dehydration conditions and the mechanism of the dehydration can also be changed. As the process analytical technology (PAT) became more popular and necessary, some of the useful approaches for characterizing hydrate formation during wet granulations are also reviewed. So far, the most commonly used techniques include NIR, Raman, and XRD

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蘇州工業園區生物納米科技發展有限公司 Suzhou Industrial Park Bio & Nano Technology Development Company



蘇州這座歷史文化名城和著名的風景旅遊城市，近十年一躍成爲中國東部沿海最發達城市之一。美國《新聞周刊》、《遠東經濟評論》、《華爾街日報》分別載文將蘇州列爲全球九大新興技術城市之一，全球經濟高科技前哨城市和最熱點的製造基地。

蘇州工業園區位於古城東側，距離上海80公里。作爲中國和新加坡兩國政府間最大的經濟技術合作項目，其已成爲國內單項投資額最大的開發區。目前已有46家世界五百強企業在區內注冊了71家企業，其中包括輝瑞Pfizer、葛蘭素GSK、禮萊Eli Lilly、百特Baxter、碧迪BD、衛材Eisai、康寶萊Herbalife等跨國醫藥企業。在生物醫藥、電子信息、精密機械、新材料等領域形成了較爲完善的產業鏈。《紐約時報》說“選擇了蘇州工業園區就是選擇了成功。”

園區總規劃面積282平方公里，分爲中央商貿區、信息產業園、出口加工區、國際科技園、獨墅湖高等教育區、現代物流園等。其中獨墅湖高教區已有北京大學、復旦大學、中國人民大學、中國科技大學、西安交通大學、南京大學和蘇州大學以及英國利物浦大學和華威大學、新加坡國立大學、香港科技大學、美國代頓大學、愛爾蘭列姆萊克大學等高校簽約進駐。

蘇州工業園區的開發強調“以人爲本”理念，突出經濟發展、科技進步及人與自然的和諧統一。區內綠化率超過45%，通過了ISO14001環境管理示範區認證，形成了“一環三湖四園六廊八景十二苑”的綠色生態系統，爲居民提供了居住、商業、餐飲、商務、醫療、教育等齊全的生活配套。

蘇州工業園區今后的發展目標是用十年再造一個蘇州，把園區建設成爲具有國際競爭力的高科技園區和現代化、國際化、園林化的國際技術產業城市。目前在建項目包括國際科技園四期、中新科技城、生物科技園、創意產業園等……



蘇州工業園區生物納米科技發展有限公司於2005年10月成立，註冊資本5.5億元人民幣，是占地86.3公頃的生物科技園BIO BAY的開發主體。該園坐落在風景秀麗、書聲朗朗的獨墅湖畔高教區內。依托良好的文化氛圍和豐富的人才資源，本着“低門檻、少租金、優服務、全功能”的原則，積極鼓勵科技人才和企業創業、創新，大力吸引生物技術產業以創新爲目的的研發機構，爲其提供舒適而又科學的研發環境，成爲孕育擁有自主知識產權的科技創新項目和技術的良土。

爲積極吸引科技創新項目的入駐和科學家的引進，推動國家科技進步，蘇州工業園區以及生物科技園制定了一系列優惠和扶持政策，其中包括：對進駐的海內外科學家提供安家企業開辦的啓動資金、居留和落戶的便利、留學生融資擔保和創業基金、房租減免、稅收減免、貸款貼息、科技發展基金等。同時，中新蘇州工業園區創業投資公司與生物科技園聯動，爲進入區內的生物科技研發企業提供一億元針對種子期企業的天使基金和生物納米科技發展孵化器基金和發展平臺，以及法律、財務、專利、人事、信息等綜合服務平臺。

這裏有藍天和碧水，這裏有創業的熱土，我們虛席以待，期待你們一起來投身祖國發展，分享祖國的進步和繁榮。

請聯系我們，告訴我們您的想法和需求。

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