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Vitrification from solution in restricted space: Formation and stabilization of amorphous nifedipine in a nanoporous silica xerogel carrier

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Abstract

Purpose: The goal was to find thermodynamic criteria that must be satisfied in order to prevent formation of crystalline state of drugs within a confined space (e.g., nanopores of inorganic solid). Similarly, criteria that lead to stabilization of amorphous drug within such pores were investigated.
Methods: In the theoretical part, the classical thermodynamics of nucleation is applied to the conditions of a restricted space. The theoretical findings are verified using porous silica as a carrier and nifedipine as a model drug. The amorphicity of the latter is checked using XRD and thermal analysis (DTA, DSC) in combination with BET measurements.
Results: It is shown that there exists a critical pore radius of a host below which the entrapped substance will solidify in an amorphous form. There also exists a critical pore radius below which the entrapped amorphous solid will not be able to crystallize. Specifically, incorporation of NIF into a silica xerogel with an average pore diameter of about 2.5 nm produces and stabilizes its amorphous form.
Conclusion: Entrapment of drugs into solid nanoporous carriers could be regarded as a potentially useful and simple method for production and/or stabilization of non-crystalline forms of a wide range of drugs.

Keywords: Thermodynamics; Nucleation; Amorphous drugs; Structural stabilization; Porous carriers

1. Introduction

Incorporation of solid substances into appropriate porous matrices has been a subject of numerous investigations (Böhlmann et al., 1999; Lucas et al., 2001; Czuryszkiewicz et al., 2002; Quaranta et al., 2003; Maria Chong and Zhao, 2004; Vallet-Regi et al., 2004; Chytil et al., 2005; Zhao et al., 2005; Prasad and Quijano, 2006). In the case of drug incorporation, for example, the common goal has been control of drug release. It is reasonable to expect that the average rate of drug release will be decreased if a drug is entrapped into a web of pores within a solid inorganic host material. With emerging nanosciences and nanotechnologies, entrapment into "nanosized pores" (conventionally termed meso- or micropores, if size <50 nm or <2 nm, respectively) has become particularly popular. The thorough research in this area has resulted in many interesting findings shedding light on the nature of matter confined in nano-domains of host material (Shin and Chang, 2001; Chong and Zhao, 2004; Kim et al., 2004; Bögershausen et al., 2007; Sotiropoulou and Vamvakaki, 2005; Kim et al., 2006; Wang and Song, 2006). However, in all these studies the authors apparently neglected a very important phenomenon that is expected to occur when matter is confined into a small space – the possible change of its structure. Namely, it is known from the classical nucleation-and-growth theory (Defay, 1966; Adamson and Gast, 1997; Sugimoto, 2001; Christian, 2002) that typical nuclei formed in the course of crystallization process consist of many (tens to hundreds) constituent particles (atoms, molecules). If so, several fundamental questions *par excellence* arise: What happens if there is not enough space for nuclei to form? Does matter confined into nanosized pores inherently solidify in the amor-

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phous rather than in the crystalline state and, if yes, what are the critical pore dimensions when the transition from one to the other state occurs? And finally: What is the stability of the amorphous state within the confined space (e.g., within pores, channels) of host matrix? We try to answer these fundamental questions both theoretically and experimentally, using an example of pharmaceutical interest, that is, entrapment of nifedipine into silica nanosized pores. The treatment itself, however, is general enough that the findings can be generalized to most solid materials confined within restricted domains of host materials.

In the theoretical part, we refer to the classical theory of nucleation based on random fluctuations in a metastable assembly. This theory was mainly developed by Volmer, Becker and Döring (Volmer, 1939), although other workers have also made significant contributions. It was first formulated for the simplest nucleation process, the condensation of a pure vapour to form a liquid. Later on, it was modified to describe systems such as nucleation in solution, in a supercooled melt, in the solid state (Christian, 2002). The formation of a stable nucleus in contact with a surface (heterogenous nucleation) was introduced by Volmer (Volmer, 1929). Turnbull expanded the treatment to the nucleation process in cylindrical and conical cavities (Turnbull, 1950a). Massive research has been done in the field of nucleation in the vitreous state (Rowlands and James, 1979a,b; Shneidman and Weinberg, 1996; Wakayama et al., 1999; Andronis and Zografi, 2000). A theory for the nucleation in solid solutions has also been developed (Slezov et al., 1997). Recently, the influence of elastic strain on the thermodynamics and kinetics of nucleation in the vitreous state was studied by Gutzow and Schmelzer (Schmelzer et al., 1995; Möller et al., 1998; Schmelzer et al., 2004; Fokin et al., 2005).

Based on these and similar works, we formulate general thermodynamic criteria that must be satisfied for occurrence of crystalline matter from saturated solution confined within a restricted space. We further formulate similar general criteria for formation of confined amorphous solid matter. The occurrence of amorphous phase upon cooling of the melt in pores below a certain pore size has been reported in the case *o*-terphenyl, benzyl alcohol (Jackson and McKenna, 1996) and nitrobenzene (Sliwinska-Bartkowiak et al., 2001) confined into nanoporous glass materials.

In the experimental part, the validity of the theoretically developed criteria for crystallization from supersaturated solution and from amorphous state, respectively, is checked. As a model system, we selected nifedipine (NIF) entrapped in a porous silica xerogel. NIF, a potent systemic calcium channel blocker, was chosen because of its high crystallinity, poor solubility in water and a high tendency of its amorphous form to crystallize. It is used in the treatment of angina pectoris and hypertension. Silica xerogels are well-known carrier systems exhibiting significant porosity on the nanometre scale. Zusman et al. (1990) reported the use of doped silica glasses for pH sensors in analytical chemistry. Chen and Dong (2003) and Shankaran et al. (2003) produced sol–gel composite based glucose biosensors. Conventional drug molecules have also been incorporated into silica xerogels, mostly to achieve controlled release. Kortesuo and Ahola (2001, 2002) studied the effect of synthesis parameters on the release rate of dexmedetomidine from silica gel microparticles and monoliths. Ahola and Kortesuo (2000) produced silica xerogel carrier material for controlled release of teoremifene citrate. Tian and Blacher (1999) studied the effect of acid and water content on the incorporation of aliphatic polyesters into silica gels.

2. Theoretical

2.1. Crystallization from supersaturated solution in restricted space

It is well-known that the process of crystallization consists of two steps: formation of nuclei (that is, clusters of atoms, molecules, etc.) and their subsequent growth (Defay, 1966; Adamson and Gast, 1997; Sugimoto, 2001; Christian, 2002). The formation of critical nuclei may be viewed as random fluctuations of density, in which about 50–250 molecules come together to form a nucleus of the size observed experimentally (Defay, 1966). Based on this fundamental knowledge, we hypothesize that entrapment of a dissolved drug into a solid matrix that contains constrained spaces (e.g., pores) smaller than the critical nucleation radius, will prevent the process of drug crystallization upon removal of solvent. The resulting solid drug is then expected to occur in the amorphous rather than in crystalline form.

We assume that all pores in a given solid matrix (for example, porous silica carrier) are of the same shape and size with no preferential sites on the surface. Let the pores contain a saturated solution of a drug. There are two possible sites for nucleation to start: either on the existing solid surfaces (walls of silica pores) or in the volume of saturated solution. The former scenario (heterogeneous nucleation) will take place if the contact angle between the embryo of the new solid phase and the surface of the existing phase, θ (Fig. 1) is within the range $0 \leq \theta \leq \pi$ (Christian, 2002). Then the following equation will hold:

$$\gamma^{AS} = \gamma^{BS} - \gamma^{AB} \cos\theta \quad (1)$$

where γ^{XY} is the interfacial free energy between phases X and Y. If, however, θ is outside the aforementioned limits, the phase with the lower interfacial energy spreads over the whole solid surface and Eq. (1) does not hold anymore. In this case, nucleation in the bulk solution (homogeneous nucleation) is expected to occur—*pure confinement effect*. To determine which of the

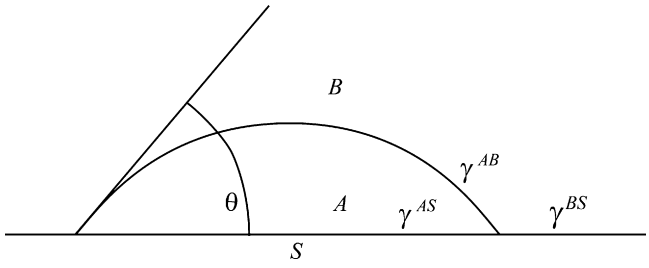

Fig. 1. Hypothetical embryo formed on a solid surface. In the present context, B could represent the NIF solution, S the silica surface, and A a crystalline nucleus of NIF.