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Structural and thermodynamic aspects of plasticization and antiplasticization in glassy encapsulation and biostabilization matrices☆

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ABSTRACT

The structural and thermodynamic properties of glassy carbohydrate matrices for the encapsulation and biostabilization of sensitive bioactive compounds, such as pharmaceutically active proteins and oxidation-sensitive compounds, are reviewed in the context of the plasticization and antiplasticization of glassy carbohydrates of intermediate and high molecular weight by low molecular weight diluents. Plasticization and antiplasticization may be monitored either by dynamic measures or by structural and thermodynamic features of the glassy matrices. Specifically, it is demonstrated that the decrease in size of the molecular free volume holes with increasing diluent content, as determined by positron annihilation lifetime spectroscopy (PALS), is related to the antiplasticization of glassy carbohydrate matrices, resulting in increased barrier properties of the glassy matrix. As far as could be ascertained from the available data, the regimes as identified by PALS map on those detected by neutron scattering and dielectric spectroscopy for glassy matrices consisting of trehalose and the diluent glycerol. The review is concluded by a survey of the published results on the stability of bioactive compounds encapsulated in carbohydrate glasses and an overview of outstanding questions.

Contents

1. Introduction

Amorphous materials are widely used in pharmaceutical applications, in several distinct roles. Polymer matrices, of a wholly or partly amorphous nature find application in delivery systems for the controlled release of drugs, in the coating of tablets and in soft capsules [1,2]. In the so-called solid dispersions, poorly soluble pharmaceutical compounds, with consequently a low bioavailability, are formulated in such a way that they are dissolved or dispersed in a molecular way in a matrix usually consisting of a polymer, and possibly of several additives, in order to enhance their bioavailability [3–6].

In the solid dispersion, the bioactive is quenched into a metastable, glassy state [6]. The amorphous state of the pharmaceutically-active compound in the solid dispersion is preserved following several mechanisms, the most important of which is that recrystallization of the pharmaceutical compound is impeded by vitreous state of the matrix. As large-scale molecular motions are needed to allow the translational and orientational mobility of any molecules apart from the smallest ones, recrystallization of the poorly soluble compound is only observed in the rubbery state above the glass transition temperature [6,7].

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The molecular dispersion of pharmaceutically active compounds in excipient matrices is also of key importance for cases where the bioactive compound is highly structurally labile or sensitive. This is the case for instance for proteins, which may easily denature or alter their tertiary structure and thereby lose their physiological activity [4,8–10]. The tertiary structure of such proteins can be stabilized in dehydrated states by molecularly entrapping them in glassy matrices consisting of low- and intermediate molecular weight compounds, often disaccharides and in particular trehalose [4,11–13].

Closely related to the biostabilization of complex biomolecules is the encapsulation of chemically-sensitive bioactive compounds. Many bioactive compounds, including drugs [14,15], vitamins [16], essential oils [17], polyunsaturated fatty acids [18] and proteins [19,20], are sensitive to oxidation [21] and often also to various physical and chemical changes induced by water [22]. Such sensitive bioactive compounds can effectively be protected by encapsulation in carbohydrate glasses [21,23]. Depending on their physico-chemical properties, the bioactive molecules can either be molecularly dissolved in the amorphous matrix, or be dispersed in the form of a separate phase in the amorphous matrix. In the latter case, a polymeric emulsifier is often used to stabilize small droplets of the hydrophobic bioactive compound in the generally aqueous solution of the matrix constituents prior to bringing the system into the glassy state [24]. For these hydrophobic bioactive compounds, which may be dissolved in an inert carrier oil, the encapsulation system is thus characterized by small, often liquid inclusions, usually in the size range around 1 μm, embedded in the glassy encapsulation matrix [25].

This review is focussed on the properties of amorphous matrices used for the encapsulation and biostabilization of labile or otherwise sensitive bioactive compounds. Such matrices should fulfill several conditions. In the first place, such a matrix should be physically stable during storage, i.e. it should not flow or collapse. For amorphous systems, this generally implies that the matrix should be in the glassy state under the conditions experienced during handling, transport and storage of the formulated system [23]. In the second place, the matrix constituents should not chemically react with or irreversibly bind to the encapsulated bioactive compounds. It is thought that a non-reducing carbohydrate, such as trehalose and sucrose, presents certain advantages in this respect over reducing carbohydrates, such as lactose, maltose and maltodextrin [26,27].

For the protection of sensitive compounds against external influences, it is imperative that the encapsulation matrix forms an effective barrier for both the encapsulated bioactive compound and for any outside chemical compound, which may react with the encapsulated bioactive. Because of the low solubility as well as the very slow diffusion, the glassy carbohydrate matrix constitutes a very good barrier against oxygen [23,28,29]. In case of biostabilization an essential further condition is that the encapsulation matrix forms a vitrified matrix embedding the encapsulated molecules [30,31]. This is an central element of several hypotheses on biostabilization, such as the glassy-state hypothesis and the water-replacement hypothesis [31,32].

According to the glassy-state hypothesis, the reduced mobility in the glassy state below T_g should be a sufficient condition to keep the encapsulated biomolecules in their functional states; this premise has however seen significant modification over the last years, as it turns out that not only the large-scale molecular relaxations and reorganizations associated with the α-relaxation should arrest, but that also the dynamic modes in the glassy state, specifically those associated with the β-relaxation, should be suppressed as much as possible [33]. It is observed that several measures of the dynamics in the glassy state, in particular the β-relaxation, directly relate to the stability during storage of encapsulated proteins [34]. It is thought that this is related to an enhanced physical stability of the encapsulated protein in glassy matrices with reduced dynamics, but also to reduced rates of permeation of low molecular weight molecules in the matrix, in particular water and oxygen [35]. This may lead to chemical degradation of the encapsulated bioactive [23].

The sub-T_g dynamics of matrices consisting of amorphous carbohydrates and biopolymers have consequently attracted significant attention, in particular in research connected to the pharmaceutical field. These dynamic modes and their relation to pharmaceutical stability have primarily been explored for trehalose [34,39]. Using techniques, such as neutron scattering [39] and dielectric spectroscopy (DES) [40–43], it was observed that several of the dynamic modes in the glassy matrices could be partly suppressed or slowed down by the addition of limited amounts of a low-molecular weight hydrogen-bond forming diluent, such as glycerol or sorbitol. This phenomenon was identified as the antiplasticization of the matrix by the diluent [39,44]. Empirically observed improvements [45] in the stability of encapsulated proteins were subsequently reinterpreted in terms of this antiplasticization phenomenon [39].

In parallel, several researchers have explored the structural and thermodynamic properties of amorphous polymers, biopolymers and amorphous carbohydrates in the rubbery state close to the glass transition and in the glassy state. Important properties, which were investigated, are the specific volume and the molecular hole volume as probed by positron annihilation lifetime spectroscopy (PALS). The studies were mainly focussed on starch [46] and starch-derived polymers and oligomers [47–50], but also included ethyl cellulose [51], gelatin [52,53], poly(vinyl) alcohol (PVA) [54], hydroxypropyl methylcellulose [55] and poly(ethylene) oxide (PEO) [56] as well as several disaccharides, including trehalose [57] and maltose [49,58]. Several of these studies were specifically aimed at investigating the impact of low molecular weight diluents, such as water [46–49,51,58], glycerol [52,53,59], sorbitol [53] and maltose [49,58] on the structure and thermodynamic properties of the glassy matrix.

From thermodynamic and structural studies on glassy polymer and carbohydrate matrices containing varying fractions of low-molecular weight hydrogen-bonding diluents, it has emerged that, depending on the molecular weight of the primary matrix constituent and the diluent, the matrices show plasticization as well as antiplasticization behavior [46,49,58,60]. In various studies, it was furthermore shown that the antiplasticization of the primary matrix constituent by the hydrogen-bonding diluent was related to a significant modification of the properties of the glassy matrices, including the barrier properties [28], the water vapor sorption [61] and the mechanical properties [60,62].

In this Review, I am primarily focussing on the structural and thermodynamic factors impacting or relating to the performance of amorphous matrices for the encapsulation and stabilization of sensitive bioactive compounds. The findings on the free volume properties and specific volume of carbohydrate and biopolymer matrices are assessed in relation to the plasticization and antiplasticization by water and other low molecular weight diluents. The various regimes, which may be distinguished as a function of the diluent content, are then critically evaluated against the current understanding of the relaxation behavior of glassy carbohydrate matrices. Following a survey of the available literature data on the performance of glassy systems for the encapsulation and stabilization of bioactive, I am summarizing the current understanding of the relation between the molecular organization in glassy polymer and carbohydrate matrices and their dynamics. The review is concluded by an outline of several axes for the further exploration of the mechanisms of protection and stabilization by glassy.

2. Structural signatures of plasticization and antiplasticization in glassy matrices

Even though it is obvious that in glassy matrices, structure and dynamics are intimately related, it is not immediately apparent which of the many structural and thermodynamic properties of amorphous encapsulation matrices are most directly related to the performance of the matrices in biostabilization and encapsulation. For instance, for a matrix consisting of a hydrophilic polymer, the molecular conformation of the polymer chain is highly relevant with respect to the molecular