



# Amorphization of thiamine chloride hydrochloride: A study of the crystallization inhibitor properties of different polymers in thiamine chloride hydrochloride amorphous solid dispersions



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## ABSTRACT

Amorphous solid dispersions of thiamine chloride hydrochloride (THCl) were created using a variety of polymers with different physicochemical properties in order to investigate how effective the various polymers were as THCl crystallization inhibitors. THCl:polymer dispersions were prepared by lyophilizing solutions of THCl and amorphous polymers (guar gum, pectin, κ-carrageenan, gelatin, and polyvinylpyrrolidone (PVP)). These dispersions were stored at select temperature (25 and 40 °C) and relative humidity (0, 23, 32, 54, 75, and 85% RH) conditions and monitored at different time points using powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). Moisture sorption isotherms of all samples were also obtained. Initially amorphous THCl was produced in the presence of ≥ 40% w/w pectin, κ-carrageenan, gelatin, and guar gum or ≥ 60% w/w PVP. Trends in polymer THCl crystallization inhibition (pectin ≥ κ-carrageenan > gelatin > guar gum ≫ PVP) were primarily based on the ability of the polymer to interact with THCl via hydrogen bonding and/or ionic interactions. The onset of THCl crystallization from the amorphous dispersions was also related to storage conditions. THCl remained amorphous at low RH conditions (0 and 23% RH) in all 1:1 dispersions except THCl:PVP. THCl crystallized in some dispersions below the glass transition temperature ( $T_g$ ) but remained amorphous in others at  $T \sim T_g$ . At high RHs (75 and 85% RH), THCl crystallized within one day in all samples. Given the ease of THCl amorphization in the presence of a variety of polymers, even at higher vitamin concentrations than would be found in foods, it is likely that THCl is amorphous in many low moisture foods.

## 1. Introduction

Thiamine (vitamin B<sub>1</sub>) is an essential water soluble vitamin that has many physiological roles and benefits for human metabolism, and thiamine fortification programs in developed countries have reduced overall rates of thiamine deficiencies (Rolland & Truswell, 1998). Unfortunately, the degradation of vitamins during food production and storage is inevitable, and thiamine is sensitive to heat, alkali, oxygen, sulfites, and radiation, with a reported cooking loss of up to 80% (Bitsch & Bitsch, 2011; Gregory, 2008; Spitzer, 2007). Higher relative humidities (RHs) and temperatures increase thiamine degradation rates in both synthetic and natural forms (Bendix, Heberlein, Ptak, & Clifcorn, 1951; Mauri, Alzamora, & Tomio, 1992). The synthetic

salt forms of thiamine, chloride hydrochloride and mononitrate, are commonly used for fortification purposes (Coppock, Carpenter, & Knight, 1956), and both are distributed as deliquescent crystalline solids (Hiatt, Taylor, & Mauer, 2010). Interestingly, thiamine chloride hydrochloride is commonly referred to as thiamine hydrochloride.

Solid state properties play an important role in dictating the stability of a compound, and the tendency of a material to undergo a phase transition is a critical factor in stability. Important crystalline ingredient phase transformations impacting stability include: polymorphic transitions, conversions of the salt to the free form (Guerrieri & Taylor, 2009), dehydration of a crystal hydrate which can lead to a new crystal form or a disordered material (Li, Han, Zhang,

**Abbreviations:** DSC, differential scanning calorimetry; EMC, equilibrium moisture content; Exp, experimental; FD THCl, Freeze-dried thiamine chloride hydrochloride; FTIR, Fourier transform infrared spectroscopy; GEL, gelatin; GG, guar gum; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; KG, κ-carrageenan; PEC, pectin; PM, physical mixture; Pre, predicted; PVP, poly (vinylpyrrolidone); PXRD, powder X-ray diffraction; RH, relative humidity; RH<sub>0</sub>, deliquescence point; SD, solid dispersion;  $T_g$ , glass transition temperature; THCl, thiamine chloride hydrochloride; wwb, wet weight basis

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Grant, & Suryanarayanan, 2000), and crystal-to-solution transformations which may be the result of deliquescence or dissolution in moisture brought in by co-formulated ingredients (Hiatt, Ferruzzi, Taylor, & Mauer, 2008; Hiatt et al., 2010; Ortiz, Ferruzzi, Taylor, & Mauer, 2008; Ortiz, Kestur, Taylor, & Mauer, 2009). Although the commercially available thiamine chloride hydrochloride (THCl) is commonly reported to be a monohydrate, it is in fact a non-stoichiometric hydrate whereby the water present in the crystal is loosely bound with easy ingress and egress as a function of RH (Te, Griesser, Morris, Byrn, & Stowell, 2003). The fluctuation in the amount of water present in THCl is problematic, since the water content of the crystal is not well established leading, for example, to analytical issues with determining the exact mass of thiamine in a sample. Furthermore, it is well established that THCl is chemically labile in complex blends, in particular those containing alkali components (Waibel, Bird, & Baumann, 1954). The chemical instability has been attributed in part to the tendency of THCl to dissolve in moisture brought in by other components (Waibel et al., 1954) or to deliquesce above 88% RH at ambient temperature (Hiatt et al., 2010).

Although the synthetic salt forms of thiamine are crystalline, it is possible (and likely) that amorphous thiamine structures are formed by interactions with polymeric ingredients in some foods and/or upon exposure to food processing conditions such as grinding, milling, freeze drying, or spray drying (Hancock & Zografi, 1997). There is an increasing interest in amorphization in many scientific fields due in part to the enhanced solubility, dissolution rate, and oral absorption of amorphous forms compared to their crystalline counterparts; however, these advantages are balanced by the challenges associated with higher degradation rates of amorphous forms as well as their tendency to recrystallize (Baghel, Cathcart, & O'Reilly, 2016). Amorphous compounds are thermodynamically and chemically less stable than their crystalline counterparts and can exhibit significant molecular motion over timescales relevant to food shelf-life, both above and below the glass transition temperature ( $T_g$ ) albeit at different rates (Slade & Levine, 1988). The  $T_g$  is where an amorphous substance changes from a glass with much greater viscosity (low molecular mobility, below  $T_g$ ) to a super-cooled liquid with relatively low viscosity (high molecular mobility, above  $T_g$ ) (Zografi, 1988). Maintaining the amorphous compound in the glassy rigid state, below the  $T_g$ , slows but does not prevent recrystallization (Vyazovkin & Dranca, 2007; Yoshioka, Hancock, & Zografi, 1994). Many polymers including pectin, guar gum, gelatin,  $\kappa$ -carrageenan, and PVP have crystallization inhibition properties, thus increasing the stability of the amorphous target ingredient to crystallization when the polymer and ingredient are combined at the 'right' ratio for a given preparation technique (Ford, 1986; Serajuddin, 1999). Molecular mobility is reduced in the presence of a polymer, due to interactions between the polymer and the target molecule which lead to a coupling of molecular motions, and this can inhibit the target molecule from rearranging into a more ordered crystalline structure (Shamblin & Zografi, 1998). Although the amorphous form of a material is inherently less stable than the crystalline form, the presence of other ingredients in a food can have a protective effect and can make the amorphous form more stable than expected (Li et al., 2013).

Understanding which formulations or processes induce the formation of amorphous THCl and in which conditions the amorphous THCl will recrystallize will lead to strategies for improving the stability of added thiamine in processed food products. The objectives of this study were to: 1) create amorphous solid dispersions of THCl using several polymers commonly used in food and pharmaceutical products that have different functional groups and properties; 2) characterize the moisture sorption,  $T_g$ , and intermolecular interaction properties of the solid dispersions; 3) monitor the physical stability of the dispersions over time in different environments and document when THCl crystallization occurred (and to some extent what crystal polymorph was formed); and 4) correlate the THCl crystallization inhibitor properties of the polymers to the moisture sorption,  $T_g$ , and intermolecular interaction data.

## 2. Materials and methods

### 2.1. Materials

Thiamine chloride hydrochloride (THCl), guar gum (GG, average molecular weight (MW) 220,000),  $\kappa$ -carrageenan (KG, MW 400–560 kDa), poly (vinylpyrrolidone) (PVP, MW 40,000), and pectin (PEC, from citrus peel with a ~61% degree of esterification, MW 32,000–86,000) were purchased from Sigma-Aldrich Inc. (St. Louis, MO). Gelatin (GEL, MW 20,000–200,000) was purchased from Ward's Science (Rochester, NY). These amorphous polymers represent a variety of ingredients commonly used in the food and pharmaceutical industries that have a diversity of hydrogen bonding or ionic interaction potential with THCl, hygroscopicity, and  $T_g$ . Drierite™ (calcium sulfate), used to create 0% RH storage conditions, was obtained from W.A. Hammond Drierite Company, LTD (Xenia, OH). The saturated salt solutions used to create specific RH conditions in desiccators (reported here at 25 °C) were magnesium chloride ( $MgCl_2$ , 32% RH), magnesium nitrate ( $Mg(NO_3)_2$ , 54% RH), sodium chloride (NaCl, 75% RH), and potassium chloride (KCl, 85% RH) purchased from Sigma-Aldrich Inc. (St. Louis, MO). Potassium acetate ( $CH_3CO_2K$ , 23% RH at 25 °C) was obtained from Acros Organics (NJ).

### 2.2. Formation of solid dispersions via lyophilization

To prepare the solid dispersions, first 0.25 g of each polymer was dissolved in 35 mL deionized water in a 45 mL amber centrifuge tube. The polymer solutions were then heated using a digital heat block (VWR International LLC., Bristol, CT) at 60 °C for 30 min in order to increase the solubilization. The solutions were cooled to ambient temperature, and THCl (0.25 g on dry weight basis) was added. Samples were mixed with a Roto-Shake Genie® SI-1100 (Scientific Industries, Inc., Bohemia, NY) for approximately 10 h until uniform one-phase solutions were obtained. In addition to these 1:1 THCl:polymer dispersions, additional dispersions were made by varying the THCl:polymer ratio from 0% to 100% w/w polymer in 10% polymer increments, keeping the total solids content constant. Solutions containing only polymer and only THCl were made by dissolving 0.5 g of the compound in 35 mL of deionized water. The solution pHs were determined using an Orion Star A211 pH meter (Thermo Fisher Scientific Inc., Waltham, MA). The solutions were frozen at –20 °C for at least 40 h before lyophilization. Freeze drying was conducted using a VirTis Genesis 25 ES (VirTis, Gardiner, NY) for at least 96 h. The samples withdrawn from the freeze dryer were immediately transferred into 20 mL amber glass containers and placed into desiccators. Physical blends of the crystalline THCl and amorphous polymers were also prepared and analyzed for comparative purposes.

### 2.3. Storage treatments

Solid dispersions were stored in RH controlled desiccators (0, 23, 32, 54, 75, and 85% RHs) at two different temperatures (25 °C and 40 °C) maintained by water jacketed incubators (Forma Scientific, Inc., Marietta, OH). Conditions were chosen to be representative of the water activities of a wide range of low and intermediate moisture food products and the temperatures to which they might be exposed. Samples were removed from storage at selected time points and further analyzed. Changes in sample mass were periodically tracked until samples reached equilibrium ( $\pm 0.001$  mg in consecutive weightings), and these data were used to document moisture content prior to DSC analysis. All samples were prepared such that duplicates could be removed from storage at different time points for each of the analyses described in the following sections.

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