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Factors Affecting Thermally Induced Furan Formation

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Furan, a potential carcinogen, can be induced by heat from sugars, ascorbic acid, and fatty acids. The objective of this research was to investigate the effect of pH, phosphate, temperature, and heating time on furan formation. Heat-induced furan formation from free sugars, ascorbic acid, and linoleic acid was profoundly affected by pH and the presence of phosphate. In general, the presence of phosphate increased furan formation in solutions of sugars and ascorbic acid. In a linoleic acid emulsion, phosphate increased the formation of furan at pH 6 but not at pH 3. When an ascorbic acid solution was heated, higher amounts of furan were produced at pH 3 than at pH 6 regardless of phosphate's presence. However, in linoleic acid emulsion, more furan was produced at pH 6 than at pH 3. The highest amount of furan was formed from the linoleic acid emulsion at pH 6. In fresh apple cider, a product with free sugars as the major components (besides water) and little fatty acids, ascorbic acid, or phosphate, small or very low amounts of furan was formed by heating at 90−120 °C for up to 10 min. The results indicated that free sugars may not lead to significant amounts of furan formation under conditions for pasteurization and sterilization. Importantly, this is the first report demonstrating that phosphate (in addition to pH) plays a significant role in thermally induced furan formation.

KEYWORDS: Furan; heat; pH; phosphate; temperature; sugars; ascorbic acid

INTRODUCTION

Furan, a cyclic dienic ether with a boiling point of 31 °C, is "reasonably anticipated to be a human carcinogen" according to the U.S. Department of Health and Human Services (*1*), while the International Agency for Research on Cancer classifies it as "possibly carcinogenic to humans" (*2*). Furan is found in a wide range of thermally processed foods with furan levels as high as 170−5,000 ng/g in some foods (*3, 4*). Heating solutions of carbohydrates, ascorbic acid, and fatty acids produces furan (*4*−*7*). Thermally processed fruit juice contained furan levels ranging from below 2.0 ng/g to 31 ng/g (*3, 4*) since fruit juices contain high amounts of free sugars and ascorbic acid. Both U.S. FDA and European Food Safety Authority are seeking data on furan (*8, 9*), particularly related to its occurrence and formation in food, factors and mechanisms that contribute to its formation, and its toxicity. The long-term effects of furan to the health of children is unknown, but the presence of furan in baby foods is a concern because of their high sensitivity to carcinogens in addition to the larger amounts (relative to body weight) of certain foods (such as apple juice) that are consumed. Many factors can affect the formation of furan. For example, ferric ions increased the formation of furan in linoleic acid by 79%, while addition of reducing agents such as sulfites reduced its formation from ascorbic acid (*10*).

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Phosphates are widely used as chelators and emulsion stabilizers in many processed food products, such as soups and processed meat products. Phosphates also function as a synergist with primary antioxidants (*11*). Our earlier study (*6*) suggested that pH had an influence on furan formation due to irradiation and thermal processing. A more recent study (*12*) confirmed the importance of pH in thermally induced furan formation in model systems containing free sugars and/or ascorbic acid. It is unknown whether phosphate will have any effect on the formation of furan as a result of thermal treatment at different pH values. The present study is the first demonstration of the important role played by phosphate in furan formation.

Pyrolysis of carbohydrates and ascorbic acid at very high temperatures (300 °C) resulted in the formation of furan (*4, 13*). However, the conditions used in these studies do not represent the conditions used in the processing of foods such as juices and soups. A recent study (*14*) showed that significant amounts of furan was formed from fruit and vegetable juices after treatment at 123 °C for 22 min. The effect of heating time and temperature on furan formation has not been systemically investigated under the conditions of pasteurization and sterilization. Therefore, the objective of the present study was to investigate the effect of heating time and heating temperature on furan formation in apple cider and the effect of pH and phosphate on its formation in solutions of furan precursors. Fresh apple cider, which contains mostly free sugars besides water

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and has little phosphate, ascorbic acid, or fatty acids (*15*), was chosen because of its simplicity and is ideal to study the formation of furan from sugars.

MATERIALS AND METHODS

Chemicals and Materials. Furan (99%), furan-d_4 (99%), D-fructose, D-glucose, linoleic acid, and L-ascorbic acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). Commercial nonpasteurized (fresh) apple cider was obtained from an apple cider producer (Zeigler Beverage Co., Lansdale, PA, USA). The cider was either used within three days of processing or stored at −20 °C for later use. The cider had a soluble solids content (Brix) of 11.1 and a pH of 3.47.

Thermal Treatments. The samples (1 mL) of apple cider or solutions were injected, using a syringe, into 1.2 mL ampule vials (Wheaton, Millville, NJ, USA). The vials were flame sealed and then placed in an ice water bath. The cooled samples were then submerged into a heated 350CST silicone oil (Chemistrystore.com Inc. Cayce, SC) bath (Polystat, Cole-Parmer Instrument Co., Vernon Hills, IL) with pre-established temperatures. During the first minute of treatment, the vials were shaken to allow uniform heating. After heating, the vials were removed from the oil bath and placed into an ice water bath. The temperature changes of the samples in the vials during heating were not monitored because it was impossible to flame-seal the vials with a temperature sensor. To estimate the temperature changes during heating, a type-T thermocouple (wire size 40 AWG, Model TT-T-40-SLE, Omega Engineering Inc., Stamford, CT) was inserted through a high temperature silicone stopper (Nalge Nunc International, Rochester, NY) and a screw cap into a 3-mL vial (Alltech, Deerfield, IL) containing 1 mL of apple cider. The temperature of the apple cider sample in the vial during heating and cooling was monitored through a data acquisition board (5508-TC, ADAC Inc., Woburn, MA) and a data acquisition tool (Daisy Laboratory Version 5.0). The temperature data were collected every second. At temperatures >100 °C, the internal pressure built up inside of the 3-mL vials and caused small leakages.

Effect of Heating Time and Temperature on Furan Formation in Apple Cider. Apple cider (1 mL) in the 1.2 ampule vials was heated to 90, 100, 110, and 120 °C for 0, 2, 4, 6, 8, and 10 min. After heating and cooling, the vials were opened, and samples were spiked with the internal standard (furan-d_4) and analyzed for furan.

Effect of pH and Phosphate on the Formation of Furan from Solutions of Sugars, Linoleic Acid, and Ascorbic Acid. Solutions of 5% fructose, sucrose, glucose, and 1% ascorbic acid were prepared either in 100 mM NaCl or Na-phosphate solutions with pH of 6 and 3, representing pH values of sugar solutions and many fruit juices, respectively. NaCl served as a control for Na-phosphate as NaCl did not affect furan formation (data not shown). An emulsion of 0.1% linoleic acid was also prepared in ~100 mM Cl^- or phosphate solutions with pH of 6 and 3 by homogenizing the mixture using a homogenizer (Virtishear, Virtis, Gardiner, NY, USA) at a speed setting of 70 for 1 min. Different concentrations of the compounds were used either to simulate fruit juices or because of low solubility (linoleic acid). The pH of the solutions was adjusted using 1 M HCl or phosphoric acid. The solutions (or emulsion) were then placed into the 1.2 mL ampule vials, sealed, and heated for 10 min at 120 °C using the oil bath. After being cooled in ice water for 5 min, the vials were opened and spiked with furan-d_4. Furan was then analyzed.

Measurements of Furan. Furan was analyzed as described earlier (*6, 7*) with minor modifications. After being treated, the samples were spiked with furan-d_4 to a concentration of 5 ng/g and spiked before being transferred to 10 mL glass vials that contained stir bars. The glass vials, sealed with septa and caps, were incubated at 35 °C in a water bath for 25 min on a Corning heat/stir plate (Supelco, Bellefonte, PA, USA) before a solid phase microextraction (SPME) fiber (85 μm Carboxen-PDMS) was inserted into the headspace of a vial. After 20 min of extraction time, the SPME fiber was inserted into the GC injection port maintained at 240 °C and held for 5 min to desorb furan. Compounds were separated by a Hewlett-Packard 5890/5971 GC-MSD (Agilent Technologies, Palo Alto, CA, USA) equipped with a 3.5 m × 0.32 mm (i.d.) GasPro capillary column connected to a 30 m × 0.32 mm (i.d.), 0.1 μm DB-5 column (J & W Scientific, Folsom, CA) using a Universal Presstight Connecter (Restek Chromatography Products, Bellefonte, PA, USA). The temperature of the GC oven was set to 50 °C for 2 min, increased to 130 at 10 °C/min, then to 250 at 15 °C/min, and held for 2 min at the final temperature. Helium was the carrier gas and was supplied at a flow rate of 39 cm/s. The transfer line was held at 250 °C during the entire run. Furan and furan-d_4 were identified by comparing the spectra and the retention time of the sample compounds with those of standards. The m/z 39 and 68 ions and the ratio of 39/68 were used for the confirmation of furan, and m/z 68 was used as the quantifier. The m/z 41 and 72 ions and the ratio of 41/72 were used for the confirmation of furan-d_4, and m/z 72 was used as the quantifier. Furan was quantified using a standard curve established in the individual matrix (apple cider or other solutions).

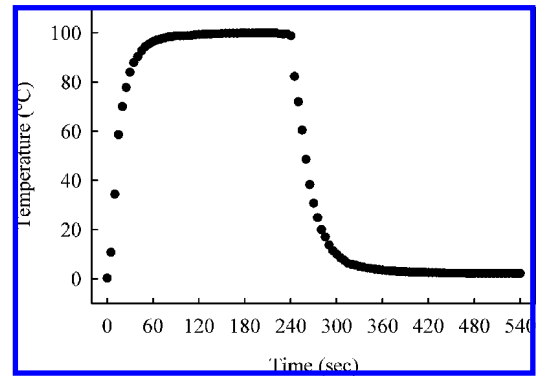

Figure 1. Changes in temperature of apple cider during heating and cooling.

Statistical Analysis. The experimental design was a completely randomized design with four replicates. Data were subjected to statistical analysis using SAS Version 8.2 (SAS Institute, Cary, NC, USA). The differences between treatments were analyzed by the least significant difference (LSD) test using the general linear model. Only significant differences ($P < 0.05$) are discussed unless stated otherwise.

RESULTS AND DISCUSSION

Temperature Profile during Heating and Cooling. The temperature of apple cider increased rapidly after being submerged in the oil bath (**Figure 1**). The time for reaching 99% of targeted temperature was about 1.5 min. During cooling, the sample cooled down to 3 °C within 2 min. Several types of container systems were tested for the heating treatments. Different types of glass vials with either screw or crimp caps were tested first. They all leaked during heating as indicated by gas bubbling from the vials. Also tested was a thermal death time (TDT) disk made of an aluminum cylinder chamber (17 mm id × 4 mm length) (*16*). We found that the TDT disk worked at temperatures of 100 °C or lower, but leaks occurred at higher temperatures (110 and 120 °C). It was decided that flame-sealed small ampule vials would be used as heating containers. In many earlier studies when large vials containing the samples were heated using heating blocks or water baths (*6, 7, 17*), it was impossible to study the effect of heating time because it took more than five minutes to reach the desired temperature. In our system, we used smaller vials (1.2 mL), flame sealing, and submerged heating. The desired temperature of 1 mL apple cider samples in 3 mL vials was reached within ~1.5 min as indicated by temperature readings. It was therefore assumed that the temperature in the 1.2 mL vials also reached the target temperatures in ~1.5 min. This come-up time was shorter than the heating times of 2, 4, 8, and 10 min.

Effect of Heating Time and Temperature on Furan Formation in Apple Cider. Heating apple cider at 90 °C for up to 10 min produced little furan (**Figure 2**). However, heating apple cider at 100 °C for 4 min induced a detectable level of

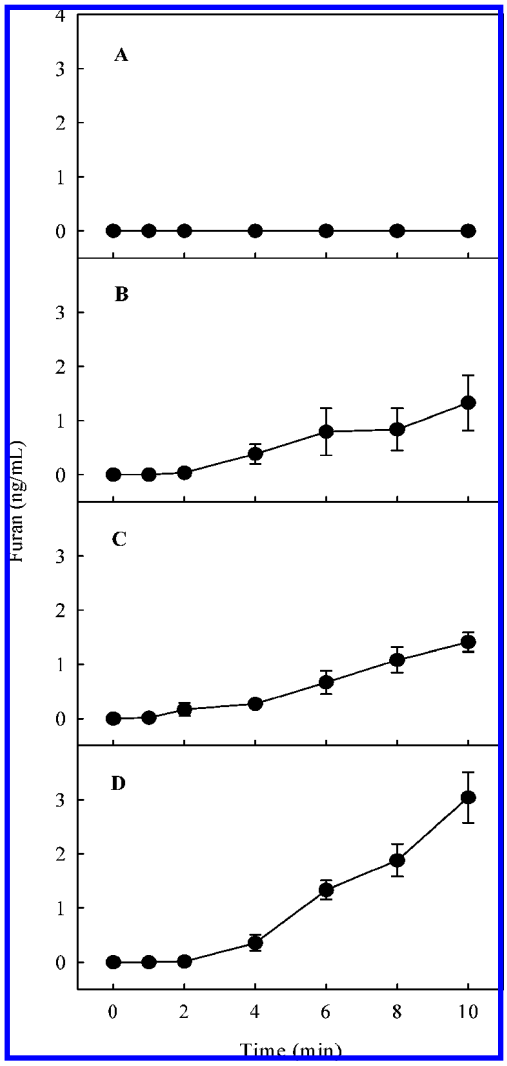

Figure 2. Formation of furan in apple cider as a function of heating time at 90 °C (**A**), 100 °C (**B**), 110 °C (**C**), and 120 °C (**D**).

furan. As heating time increased from 4 to 10 min, furan formation increased linearly. Similarly, there was a linear increase in furan formation as heating time at 110 °C increased from 4 to 10 min. However, the amount (1.4 ng/mL) of furan formed after 10 min of heating at 110 °C was not significantly higher than that (1.3 mg/mL) heated at 100 °C. Compared to heating at 100 °C, much higher levels of furan were formed at 120 °C. However, only about 3 ng/g of furan was formed even after heating at 120 °C for 10 min. FDA analysis has found that furan is present in thermally processed apple juice purchased from supermarkets with furan levels ranging from nondetectable to ~8.2 ng/mL (*3*). Our results showed that small amounts of furan accumulated in the vials during the first 2 min of heating regardless of final temperatures (100−120 °C) because it took about 1.5 min to reach targeted temperatures. Our results further suggested that a small amount furan in apple cider was formed at 90 °C and about 3 ng/mL furan was formed at 120 °C for 10 min. Therefore, it is possible that the presence of furan in the commercially processed apple juice that contained more than 3 ng/mL of furan is due to prolonged heating at high temperatures. In addition, U.S. FDA's survey (*3*) found that the higher amount of furan is mainly present in juices intended for consumption by babies. Those juices are often fortified with vitamin C (ascorbic acid) prior to thermal processing, which would increase furan formation as ascorbic acid is one of furan's precursors. Furthermore, food intended for consumption by babies may have been heated at high temperatures to ensure that the product is microbiologically safe, which again increases furan formation. For inactivating foodborne pathogens in apple cider, heating at 90 °C for a few seconds is sufficient to achieve a 5-log reduction of the bacterial population and little furan would be formed during such processes.

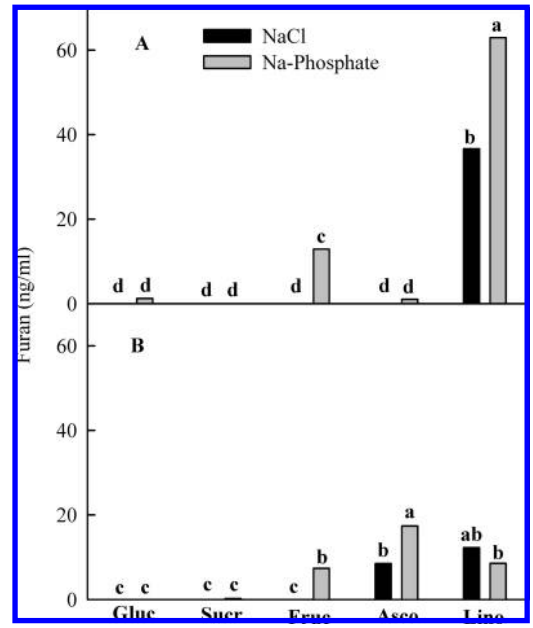

Figure 3. Effects of pH and phosphate on furan formation in solutions of sugars, ascorbic acid, and linoleic acid. One milliliter solutions of 5% fructose (Fruc), 5% glucose (Gluc), 5% sucrose (Sucr), 1% ascorbic acid (Asco), and 0.1% linoleic acid (Lino) prepared in 100 mM NaCl or Na-phosphate of pH 6 (**A**) and 3 (**B**) were heated to 120 °C for 10 min. Bars with the same letter are not significantly different (LSD, $P < 0.05$). Comparison was made within the same pH.

Effect of pH and Phosphate on the Formation of Furan from Solutions of Sugars, Linoleic Acid, and Ascorbic Acid. At pH 6 and in 100 mM NaCl solution, 36.7 ng/mL furan was formed from linoleic acid after 10 min of heating at 120 °C (**Figure 3**). No detectable furan was formed from solutions of any sugar or ascorbic acid. At pH 6 and in the presence of 100 mM phosphate, furan was formed from all solutions except sucrose solution. These observations suggest that the presence of phosphate increased furan formation from solutions of glucose, fructose, linoleic acid, and ascorbic acid at pH 6. Heating the solutions at pH 3 in the presence of NaCl did not produce furan from any sugar but induced 8.5 and 12.3 ng/mL furan from ascorbic acid and linoleic acid, respectively. In the presence of phosphate, the amount of furan produced from linoleic acid at pH 3.0 was 8.6 ng/mL, a much lower level than that (62.9 ng/mL) at pH 6. At pH 3.0, the presence of phosphate promoted furan formation from solutions of fructose and ascorbic acid. These results suggest the importance of pH in furan formation. Whether the pH increased or decreased furan formation depended on the nature of the substrate. Similar to our earlier study (*6*), the results in the present study indicated that heating primarily induced the formation of furan from fructose solution among the three sugars tested. Higher amounts (~100 ng/g) of furan have been found in products that contained both meat and vegetables such as vegetable beef soups (*3, 18*). Meats and meat products contain as high as 4% linoleic acid (*15*) and have a neutral pH. Our results suggest that more furan is formed from linoleic acid at neutral pH than at low pH during heating.

Compared to solutions prepared in NaCl, the presence of phosphate significantly increased furan formation in linoleic acid solutions at pH 6, but not at pH 3, indicating that the stimulating effect of phosphate on furan formation also depends on pH.

Our results showed that fatty acids upon thermal treatment produced a much higher amount of furan than sugars and that heating ascorbic acid solutions often generated more furan than heating sugars. Furthermore, treating apple cider, which contains mainly sugars with small amounts of ascorbic acid and fatty acids (*15*), at 120 °C for 10 min only produced a low amount (3 ng/mL) of furan. Heating (123 °C for 22 min) pumpkin puree, which contains much lower sugars and much higher fatty acids and ascorbic acid (*15*), produced 49 ng/g of furan (*14*). Therefore, it appears that furan from sugars represented a minor route, which is in agreement with the earlier study (*14*) showing that only about 20% of furan was generated from sugars. Ascorbic acid is also only a minor precursor of furan (*12*) in pumpkin puree juices. Therefore, fatty acids (or a combination of fatty acids with other compounds) may be responsible for the formation of high amounts of furan in foods.

The reason we used pH 6 for all of the solutions was that the pH of sugar solutions without any pH adjustment was around 6. Our preliminary results showed that heating induced a similar amount of furan in sugar solutions either in water or in 100 mM NaCl solutions, suggesting that NaCl had no effect on furan formation. Changing the phosphate concentration from 100 mM to 50 mM had no significant effect on furan formation in sugar solution (data not shown). In addition, changing the pH from 6 to 3 had little effect on the partitioning of furan from solutions to headspace (data not shown (*19*)). Furthermore, increasing ascorbic acid from 1% to 5% did not increase furan formation (data not shown), indicating that the concentrations of phosphate and ascorbic acid were not the limiting factors under the experimental conditions. Earlier studies (*12, 14*) showed that there is not always a direct correlation between concentration of precursors and furan formation. For example, when glucose concentrations were increased from 2 g/100 g to 4 g/100 g, furan formation due to pressure cooking increased from 64.4 ng/g to 98.8 ng/g, but further increase of glucose to 6 g/100 g reduced furan formation from 98.8 ng/g to 61.5 ng/g. Addition of 56 mg/kg ascorbic acid to orange juice, which already contained 48 mg/kg ascorbic acid, reduced thermally induced furan formation by 16%.

Our results suggest that phosphate increased furan formation in solutions of fructose and ascorbic acid, and this is the first demonstration of phosphate effect on furan formation. Phosphates are common ingredients in many food products, such as soups. It is unclear why phosphate affected furan formation. Phosphates are known to enhance the emulsification of fat (*20*). Therefore, the increased furan formation in linoleic acid in the presence of phosphates may be partially due to the increase in solubility of the fatty acid. An earlier study has found that the addition of ferric ions promoted furan formation from linoleic and linolenic acids (*17*). The authors suggested that furan formation occurred through a radical chain reaction that proceeds via a hydroxyperoxide route (lipid peroxidation).

Studies on furan formation from precursors tended to be sometimes contradictory (*4*). One of the reasons may be due to an unrealized phosphate effect. In some studies, solutions of furan precursors were prepared in phosphate buffer (*12, 14*) without the knowledge that phosphate would affect furan formation. The formation of furan would be significantly different if prepared in the absence of phosphate. Therefore, some of the conclusions in previous studies that involved the use of phosphate may be questionable and may have to be re-examined. In future studies, the concentration and presence of phosphate would have to be carefully controlled and specified. Another reason for the contradictory results in furan formation may be due to the difference in pH and the presence of phosphate that may be used in buffers. Therefore, it is important to specify pH and phosphate concentration in the solutions when publishing results relating to furan formation.

There are studies showing interactions of phosphate with sugar in chemical reactions. For example, it has been found that sugar solutions became bactericidal after being heated in the presence of phosphate (*21, 22*). Recent studies (*12, 14*) have shown that when sugars and ascorbic acid were heated in the presence of phosphate (without realizing the phosphate effect), many compounds besides furan were produced including acetic acid, formic acid, acetaldehyde, and glycolaldehyde. It has also been demonstrated that furan is produced from the recombination of reactive C2/C3 fragments such as acetaldehyde and glycolaldehyde (*12, 14*). Phosphates may increase furan formation from sugars through the formation of those reactive intermediate compounds and the subsequent recombination of the compounds, which leads to the formation of furan.

It has been shown that the formation of furan is associated with the thermal treatment of Maillard reaction precursors (*10, 23*). Phosphate buffer catalyzes Maillard reactions, and the browning of solutions increased with increasing phosphate concentration (*24, 25*). It was suggested that phosphate can simultaneously donate and accept a proton and act as a bifunctional catalyst for the nucleophilic reaction of the amine with the carbonyl (*26, 27*). However, Maillard reactions occur in the presence of amino acids or proteins and reducing sugars, and accelerates with increasing temperature. In the present studies, there was no amino acid or protein present, suggesting that furan can be formed independent of Maillard reactions. The mechanism for the phosphate-promoted furan formation needs further study.

In summary, our results suggested that significant amounts of furan were produced in apple cider only at higher temperatures (100 °C or above) and prolonged treatment time (more than 4 min). The pH and presence of phosphate played a significant role in furan formation in solutions of individual food components. This is the first article about the effect of phosphate on furan formation. The exact mechanism of phosphate and pH effect needs further study.

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