Inactivation model and risk-analysis design for apple juice processing by high-pressure CO₂

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Abstract Sigmoidal microbial survival curves are observed in high-pressure carbon dioxide (HPCD) pasteurization treatments. The objectives of this study were to use the Gompertz primary model to describe the inactivation in apple juice of the pathogen *Escherichia coli* CGMCC1.90 and to apply probabilistic engineering to select HPCD treatments meeting at least 5 log₁₀ reductions ($SV \geq 5$) at 95% confidence. This required secondary models for the temperature (T , °C) and pressure (P , MPa) dependence of the Gompertz model parameters. The expressions $b(T, P) = 14.21 + 0.011P - 0.67T + 0.0085T^2$ and $c(T, P) = -0.10 + 0.0023P + 0.0037T$ selected using goodness-of-fit measures and assessments based on Akaike and Bayesian information criteria were consistent with proposed mechanistic models for HPCD bactericidal effects. Monte Carlo simulations accounting for the variability and uncertainty of the parameter b and c estimates were used to predict SV

values for a given time, temperature and CO₂ pressure combination and desired confidence boundary. A similar approach used to estimate process times meeting $SV \geq 5$ at 95% confidence for a given temperature and CO₂ pressure combination, showed that HPCD processes met this requirement only for relatively long processing times, i.e., 35–124 min in the experimental range of 32–42 °C and 10–30 MPa. Therefore, further HPCD research is required to reduce processing time.

Keywords High-pressure carbon dioxide (HPCD) · Gompertz model · Bacterial pathogen · *Escherichia coli* CGMCC1.90 · Apple juice

Introduction

Thermal processing has been used for more than 200 years to reduce microbial safety risks, extend shelf-life, and improve the palatability of foods. In spite of continuous thermal processing improvements, developing non-thermal technologies has become necessary because of the increasing consumer demand for safe foods with close-to-fresh quality, high retention of nutrients, and high bioavailability of phytochemicals associated with desired health improvement (Cruz et al. 2011; Serment-Moreno et al. 2015a). Processing by high pressure carbon dioxide (HPCD), also called dense phase carbon dioxide (DPCD), has been proposed as a non-thermal pasteurization alternative (Spilimbergo 2002). Supercritical CO₂ at or above its critical point (31.1 °C, 7.38 MPa) can diffuse through solids like gases and has liquid-like solvent properties (Garcia-Gonzalez et al. 2007). HPCD has been reported to inactivate Gram-positive and Gram-negative bacteria, bacterial spores, and fungi as filament or spores (Zhang

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et al. 2006; Garcia-Gonzalez et al. 2007). Ferrentino et al. (2013) reported that an HPCD treatment (50 °C, 12 MPa for 15 min) was sufficient to reach non-detectable *Listeria monocytogenes* counts in dry cured ham with an initial microbial count of 10^7 CFU/g. Several studies have shown the inactivation of *Escherichia coli* and the natural microflora in apple and grapefruit juice treated by HPCD (Erkmen 2001; Liao et al. 2007, 2008; Peleg 2002). Liao et al. (2007) tested HPCD treatments in the 32–42 °C and 10–30 MPa range for the inactivation in apple juice of *E. coli* CGMCC1.90 (China General Microbiological Culture Collection Center, Beijing, China), a Risk Group 2 pathogen strain (Zhou 2015).

The HPCD inactivation efficiency depends on temperature and CO₂ pressure (Hong and Pyun 1999; Lin et al. 1992, 1993). Previous work suggests that several mechanisms may be involved, including enzyme inhibition by CO₂, cell disruption, cell membrane modification, and extraction of cellular components (Damar and Balaban 2006; Garcia-Gonzalez et al. 2007). Thermal inactivation is unlikely to occur at the temperature levels typically used for HPCD treatments (~ 30–50 °C). However, CO₂ diffusivity and the fluidity of bacterial membranes increase around 30–50 °C, enhancing the penetration of CO₂ into bacterial cells (Hong and Pyun 1999). The intracellular and external pH of microbial cells can also change with HPCD, although the pH of CO₂ does not decrease significantly in the supercritical range (Meyssami et al. 1992).

As specified in 21 CFR Section 101.17(g), the U.S. Food and Drug Administration (FDA) now requires the application of Hazard Analysis Critical Control Point (HACCP) procedures when producing retail-packaged fruit and vegetable juices and beverages. Furthermore, they must be processed to achieve five decimal reductions ($SV = 5$) of the pathogens of concern or to bear a safety warning statement (Center for Food Safety and Applied Nutrition (CFSAN) 2002; Food and Drug Administration 2009). The selected process should reach this safety goal with a high probability, e.g., 95% of production batches will reach $SV = 5$ when following exactly the same pasteurization procedures (Gayán et al. 2012, 2014; Salgado et al. 2011).

Primary models predicting microbial inactivation as a function of time are essential tools when analyzing inactivation data and designing industrial processes. The application of these primary models can be extended by secondary models describing the pressure and temperature dependence of the primary model parameters (Serment-Moreno et al. 2014, 2015b). Non-linear HPCD inactivation kinetics of *E. coli* has been frequently reported but secondary models describing the process pressure and temperature effects remain in debate (Ferrentino et al. 2008, 2009; Liao et al. 2007). A modified Weibull model

with two pressure dependent parameters was suggested by Peleg (2002) to describe the survival of *E. coli* suspended in Ringer solution when subjected to CO₂ under pressure. Ferrentino et al. (2008) fitted the modified Weibull model to the survival of the natural apple juice microflora when HPCD-treated at 7–16 MPa and 35–60 °C. The authors concluded that the Weibull shape parameter was only temperature dependent, while the Weibull scale parameter was both temperature and pressure dependent. Erkmen (2001) used a Gompertz model to describe the survival of *E. coli* in nutrient broth in the 2.5–10.1 MPa and 25–45 °C range (i.e., including conditions outside the supercritical range), suggesting that the Gompertz model parameters were only temperature dependent but no secondary models were developed.

The objectives of this study were the development of a Gompertz primary model describing the inactivation in apple juice of the pathogen *E. coli* CGMCC1.90 and of secondary models for the temperature (T , °C) and pressure (P , MPa) dependence of its parameters. The modified Gompertz model and Monte Carlo simulations were then used in a probabilistic engineering approach to design HPCD treatments ensuring $SV = 5$ with a 95% confidence.

Materials and methods

HPCD processed apple juice

Microbial reduction SV values defined as $\text{Log}(N_0/N_t)$ with N_0 and N_t denoting initial microbial counts and those after t min corresponds to HPCD inactivation data directly provided by Liao et al. (2007). Briefly, the authors inoculated *E. coli* strain CGMCC1.90 into 100 ml nutrient broth (Beijing Aoboxing Biological Technology Co. Ltd., Beijing, China). After 12 h at 37 °C to reach the early stationary growth phase, cells were harvested to inoculate 500 ml sterile apple juice (pH 3.9, °Bx 11.5) yielding N_0 values ranging $1.03\text{--}6.75 \times 10^7$ CFU/ml. Juice samples were treated for 5–75 min at 32–42 °C and 10–30 MPa in a HPCD system designed by China Agricultural University (Beijing, China), and the Huaan Supercritical Fluid Extraction Co. Ltd. (Jiangsu, China). Viable *E. coli* counts on nutrient agar were determined after incubation for 24 h at 37 °C.

Pathogen inactivation model

The Gompertz model (Eq. 1) was used to describe microbial log reductions (SV) as a function of HPCD processing time (t) (Serment-Moreno et al. 2017), where the asymptote difference (A) was fixed as the log difference between N_0 ($1.03\text{--}6.75 \times 10^7$ CFU/ml) and the TPC quantification limit (N_{qt} , CFU/ml = 25).

$$SV = \log \frac{N_0}{N_t} = A \cdot \exp[-\exp(b - c \cdot t)] \quad (1)$$

$$A = \log \frac{N_0}{N_{qt}} \quad (2)$$

Statistical analysis

The statistical analysis was performed using R statistical software (R-Studio Version 1.0.44, R Development Core Team 2010). The Gompertz model parameters were obtained by minimizing the residual sum of squares (RSS) using the nonlinear least square function (*nls*). Multiple linear regression was used to obtain secondary models describing the Gompertz parameters b and c as a function of temperature (T) and pressure (P). A set of candidate models describing their pressure (P), temperature (T), and interaction dependence ($T \cdot P$) were proposed (Eqs. 3–4). The secondary model selection using the linear regression function (*lm*) was based on model performance evaluations including mean squared error (MSE), coefficient of determination R^2 , and p values obtained from t tests on regression coefficients. The Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were also considered for model selection. Models with a better goodness of fit yield smaller MSE values and R^2 values approaching 1. While the goodness of fit indicates how well a model fits experimental observations, the fit can be improved by increasing the model complexity, even though the resulting model may describe random error or noise instead of the true underlying relationship. The AIC provides a balance between the goodness of fit of the model and its complexity, penalizing it for the number of variables in the model. Similar to AIC, BIC is also a standard model comparison tool with the main difference being a stronger penalization on the complexity of the model (Serment-Moreno et al. 2015b). Therefore, the preferred model should show significant regression coefficients ($p < 0.05$), low AIC, BIC and MSE values, and $R^2 > 0.90$.

$$b = b_0 + b_1 \cdot P + b_2 \cdot P^2 + b_3 \cdot T + b_4 \cdot T^2 + b_5 \cdot P \cdot T \quad (3)$$

$$c = c_0 + c_1 \cdot P + c_2 \cdot P^2 + c_3 \cdot T + c_4 \cdot T^2 + c_5 \cdot P \cdot T \quad (4)$$

Monte Carlo model simulations

Monte Carlo simulations were used to describe the response to the variability of the secondary model parameters $b(T, P)$ and $c(T, P)$ of a complex mathematical model such as Gompertz containing exponential function terms (Vose 2008). Within the range of the experimental data $b(T, P)$ and $c(T, P)$ were assumed to follow normal distributions with the parameter estimate and standard error

obtained for each T and P combination as the mean and standard deviation, respectively. Each iteration of the secondary model parameters generated with the Monte Carlo simulation was subsequently used as input in the primary Gompertz model (Eq. 1) to estimate microbial inactivation SV values within the range of experimental data. The 95% quantile was determined to define the confidence boundary of SV estimates for a given process time and temperature/pressure combination using the *quantile* function. In addition, the Gompertz model rewritten in the form of Eq. (5) and the *quantile* function were used to estimate the process time required to achieve $SV = 5$ with 95% confidence for T and P levels within the range of the experimental data.

$$t = \left(\frac{1}{c}\right) * \left(b - \ln\left(\ln\left(\frac{A}{SV_{target}}\right)\right)\right) \quad (5)$$

Increasing the Monte Carlo simulation sample size (n) reduces the uncertainty of the model providing better estimates of the population variability (Chotyakul et al. 2011; Vose 2008). A desirable n value was determined using the coefficient of variation (CV) of the population of estimated values for the Gompertz model parameters b and c . Briefly, the CV for each parameter and simulated sample size ($n = 50, 100, 500$, and 1000) was calculated 100 times. The simulation size n was considered large enough when CV values for each P/T combination were similar. In addition, the mean area under the HPCD SV curve ($t = 0$ –75 min) for each experimental P/T combination was also calculated. The simulation sample size n was considered large enough when area values became stable.

Results and discussion

Primary pathogen inactivation model

The Gompertz primary model fitted survival curves for *E. coli* CGMCC1.90 in apple juice (Fig. 1) yielding R^2 in the 0.90–0.95 range (Table 1). Also, Gompertz MSE values were lower than those observed for the Weibull model (data not shown) reflecting its limitations when it is used to describe sigmoidal survival curves. Visual inspection supported by high R^2 and lower MSE values than the Weibull alternative provided positive evidence that the Gompertz regression model (Eq. 1) described the observed data well.

It should be noted that $t = 0$ in the Gompertz primary model corresponds to the process come-up time, i.e., when the HPCD system reaches the desired pressure–temperature combination. The asymptote difference ($A = 5.37$), describing the log difference between the initial pathogen load N_0 and its TPC quantification limit ($N_{qt} = 25$ CFU/ml), indicates that the initial load was sufficient to reach

Fig. 1 Observed microbial load reductions (circles with error bars) expressed as SV values at 10, 20, and 30 MPa (left to right) and 32, 37, and 42 °C (top to bottom) were obtained directly from Liao et al. (2007). Solid and dash lines are the estimated mean and 95% certainty

boundary of SV Gompertz model estimates. Horizontal and vertical dotted lines denote the $SV = 5$ target value and estimated process time to achieve it at 95% confidence, respectively

$SV = 5$, the required pathogen inactivation level to demonstrate apple juice safety. The estimation of an inactivation lag time (λ) using Eq. (6) as suggested by Zwietering et al. (1990) and providing a physical meaning to the parameters b and c , yielded higher values than CUT. At 37 °C, CUT values to reach the supercritical pressure (7.2 MPa) and the operating pressures of 10, 20 and 30 MPa were 0.5, 2.5, 3.5 and 4 min, respectively (Table 2). Under the same operating conditions, SV values for $t = 5$ min after CUT were respectively only 0.3, 0.5 and 0.6 with λ of 2.0, 2.7 and 3.1 min (Table 2). These values suggest that inactivation during CUT was negligible.

$$\lambda = \frac{(b - 1)}{c} \quad (6)$$

Under isothermal conditions, lag time decreased when CO_2 pressure increased (Table 2) suggesting that increasing the CO_2 pressure enhanced the diffusion of supercritical gas into the cell (Stahl et al. 2012). However, lag time values were less sensitive to pressure (Table 2), supporting the inactivation mechanisms that suggest temperature levels around 30–50 °C enhances CO_2 penetration by increasing both the CO_2 diffusivity (Stahl et al. 2012) and the cell membrane fluidity (Garcia-Gonzalez et al. 2007; Jones and Greenfield 1982; Spilimbergo et al. 2002).

Table 1 Gompertz primary model parameters describing the survival of *Escherichia coli* CGMCC1.90 in apple juice treated by HPCD

HPCD conditions		b	c	R ²
P (MPa)	T (°C)			
10	32	1.56	0.05	0.91
20	32	1.64	0.07	0.95
30	32	1.73	0.08	0.95
10	37	1.15	0.06	0.93
20	37	1.06	0.07	0.90
30	37	1.46	0.12	0.93
10	42	1.17	0.08	0.93
20	42	1.21	0.10	0.93
30	24	1.33	0.13	0.91

The Gompertz model asymptote difference (A) was fixed as the log difference between the initial pathogen load and its TPC quantification limit yielding the constant value $A = 5.37$

Table 2 Estimated lag time (λ) and reported come-up time (CUT)^a for the inactivation of *Escherichia coli* CGMCC1.90 in apple juice as a function of the pressure and temperature of the HPCD treatment

P (MPa)	λ (min)		CUT (min)	
	T (°C)			
	32	37	42	37
7.2 ^b				0.5
10	12.7	2.0	1.6	2.5
20	9.8	2.7	2.3	3.5
30	8.5	3.1	2.7	4.0

^aObtained from data reported by Huang et al. (2009) for the same HPCD unit

^bSupercritical pressure at 37 °C (Stahl et al. 2012)

Pressurization increased the partial CO₂ differential, further increasing the diffusion of supercritical gas into the cell but it did not increase the fluidity of the membrane (Jones and Greenfield 1982; Spilimbergo et al. 2002), in accordance with previous findings that bacteria cell walls remain largely unchanged after HPCD process in Gram-positive and Gram-negative bacteria (Dillow et al. 1999).

The parameter c increased with pressure, whereas the trend observed for the parameter b depended on temperature (Table 1). At 37 °C, the parameter c followed a convex behavior against pressure, while at 32 and 42 °C, the concavity inverted and b values followed a similar trend as parameter c . Under isobaric conditions, c increased with temperature while b showed a convex behavior. This data behavior suggested that the parameter c depends on both temperature and pressure, whereas parameter b is only sensitive to temperature. This latter behavior is consistent with the difference in the pressure and temperature effects

on the inactivation mechanism previously described (Garcia-Gonzalez et al. 2007; Jones and Greenfield 1982; Spilimbergo et al. 2002). This also explains the large shortening of the lag time when temperature increases under isobaric condition, while it is less sensitive to CO₂ pressure under isothermal conditions (Table 2).

Secondary pathogen inactivation models

Empirical models describing the combined temperature and pressure effect on the primary microbial inactivation kinetics model were developed (Eqs. 7–8). Multiple linear regression was sufficient to determine the relationship between the Gompertz model parameters b and c and the process temperature and CO₂ pressure yielding similar statistical evaluations for several candidate models. Based on minimum AIC and BIC values (data not shown), significant model coefficients ($p < 0.05$), and inspection of residual plots, the secondary model selected to fit the Gompertz parameter b consisted of an intercept, a first-order pressure and a second-order temperature term (Eq. 7), while the parameter c could be described as the sum of a first-order pressure and a first-order temperature function (Eq. 8). The Gompertz secondary models for the parameters b (Eq. 7) and c (Eq. 8) yielded R² of 0.90 and 0.89, respectively. Significant coefficients ($p < 0.05$) confirmed the dependence of the response on the explanatory variables. Neither model parameter showed a significant $T \cdot P$ interaction ($p < 0.05$). The form of the secondary models confirmed the previous suggestion that the parameter c is T and P dependent, and that while significantly influenced by P , the parameter b is more T sensitive. Erkmen (2001) concluded that the Gompertz model parameters were only temperature dependent for *E. coli* inactivation in nutrient broth (2.5–10.1 MPa; 25–45 °C range), whereas Liao et al. (2008) reported that they were temperature pressure dependent in agreement with the findings of this study.

$$b(T, P) = 14.21 + 0.011 \cdot P - 0.67 \cdot T + 0.0085 \cdot T^2 \quad (7)$$

$$c(T, P) = -0.10 + 0.0023 \cdot P + 0.0037 \cdot T \quad (8)$$

Using parameter estimates obtained with Eqs. (7–8), predicted SV values using Eq. (1) for the inactivation of *E. coli* in apple juice treated under the HPCD conditions included in this study are shown in Fig. 1. Curves generated using the primary (data not shown) and secondary Gompertz model were similar confirming that the latter described well the effect of HPCD T and P conditions on the survival of *E. coli*. Furthermore, experimental values were generally in close agreement with predicted values providing further evidence that the secondary Gompertz model generated good approximations.

Monte Carlo model simulations to estimate inactivation levels (SV)

A Monte Carlo method was used to evaluate the effect of the variability and uncertainty effects of the Gompertz model parameters on the estimated reduction of *E. coli* counts by HPCD treatments of apple juice. The Monte Carlo simulation size ($n > 500$) was determined to be large enough by examining the sample size effect on the CV for the parameters b and c , and the variability of the mean area under the SV curve (data not shown). In this study, 1000 values of parameter b and c were simulated within the experimental temperature (32–42 °C) and pressure range (10–30 MPa).

A similar simulation process using the rearranged Gompertz equation (Eq. 5) was used to predict the process time required to achieve $SV = 5$ with a 95% confidence (Table 3). For HPCD treatments in the 32–37 °C and 10–30 MPa range, the predicted process time to fulfill this food safety requirement varied from 35 to 124 min (Table 3). These values are long when compared to the thermal pasteurization times recommended by the National Food Processors Association (NFPA, 3 s at 71.1 °C) to achieve $SV = 5$ for *E. coli* O157:H7, *Salmonella*, and *L. monocytogenes* when processing single strength apple, orange, and white grape juice (see Section C.5.2, U.S. Food and Drug Administration 2015). The data reported by Erkmén (2001) for the inactivation of *E. coli* in nutrient broth shows that ~ 30 min would be required to reach $SV = 5$ for an HPCD treatment at 10.1 MPa and 45 °C. Using Eq. (5), the estimated time for the same HPCD conditions would be 44 min. However, it should be noted that the strain and media are different and that the predicted value is an extrapolation beyond the T used to obtain the Eq. (5) model parameters (42 °C) and thus not reliable. In addition, this author did not provide information on the variability and confidence in their findings further limiting comparisons with this study. While Ferrentino et al. (2008) reported the inactivation of the natural microflora in apple juice by HPCD treatments in the 35–60 °C and 7–16 MPa

range, the difference in the microorganisms tested prevented further comparisons with this study.

Conclusion

In this study, secondary models for the effect of temperature and CO₂ pressure were obtained for the modified Gompertz primary model. This is the first time that secondary pressure–temperature Gompertz models were developed to describe the microbial survival of *E. coli* in apple juice when treated by HPCD. The model combined with Monte Carlo simulations allowed the estimation of the time required to achieve $SV = 5$ with a 95% confidence. However, in the 10–30 MPa and 32–42 °C range studied, the treatment time required is long when compared to conventional thermal pasteurization showing the need for research on strategies enhancing the HPCD microbicidal effect, particularly in commercially important commodities such as apple juice. Although, the data used in this study is limited to a single strain *E. coli* in apple juice, the methodology developed could be applied to other microorganisms and media treated with HPCD.

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Table 3 Estimated time (min) to achieve the required number of decimal reduction ($SV \geq 5$) with a 95% confidence for the inactivation of *Escherichia coli* CGMCC1.90 in apple juice as a function of the pressure and temperature of the HPCD treatment

Pressure (MPa)	Temperature		
	32 °C	37 °C	42 °C
10	124	74	55
20	70	49	40
30	54	41	35

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