Capsule size alters the timing of metabolic alkalosis following sodium bicarbonate supplementation

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Conflict of interest statement

Author contribution statement

IM, SAS and LRM designed the study. IM, DJT, NKL, and NPH collected the data. IM, NPH and SAS analysed the data. All authors contributed to the interpretation of data and of the writing of the manuscript. All authors have read and approved the final version of the manuscript and agree with the final order of presentation of the authors.

Keywords

buffering, Gastrointestinal disturbance, performance, Acid base balance, palatability

Abstract

Word count: 350

INTRODUCTION: Sodium bicarbonate (NaHCO3) is a well-established nutritional ergogenic aid that is typically ingested as a beverage or consumed in gelatin capsules. Whilst capsules may delay NaHCO3 release and reduce gastrointestinal (GI) side-effects compared with a beverage, it is currently unclear whether capsule size may influence acid-base responses and GI symptoms following supplementation. AIM: To determine the effects of NaHCO3 supplementation administered in different sized capsules on acid-base responses, GI symptoms and palatability. METHODS: Ten healthy males (mean ± SD: age 20 ± 2 y; height 1.80 ± 0.09 m; weight 78.0 ± 11.9 kg) underwent three testing sessions whereby 0.3 g·kg-1 body mass NaHCO3 was consumed in either small (size 3), medium (size 0) or large (size 000) capsules. Capillary blood samples were procured pre-ingestion and every 10 min post-ingestion for 180 min. Blood samples were analysed using a Radiometer (Radiometer ABL800, Denmark) to determine blood bicarbonate concentration ([HCO3–]) and potential hydrogen (pH). Gastrointestinal (GI) symptoms were measured using a questionnaire at the same timepoints, whereas palatability was recorded pre-consumption. RESULTS: Capsule size had a significant effect on lag time (the time [HCO3-] changed Tlag) and the timing of peak blood [HCO3–](Tmax). Bicarbonate Tlag was significantly higher in the large (28 ± 4 min) compared with the small (13 ± 2 min) sized capsules (P = 0.009). Similarly, Tmax was significantly lower in the small capsule (13 ± 2 min) compared with both the medium (22 ± 6 min; P = 0.005) and large (28 ± 4 min; P = 0.001) sized capsules. The GI symptom scores were similar for small (3 ± 3 AU,), medium (5 ± 3 AU) and large (3 ± 3 AU) sized capsules, with no significant difference between symptom scores (F = 1.3, P = 0.310). Similarly, capsule size had no effect on palatability (F = 0.8, P = 0.409), with similar scores between different capsule sizes. CONCLUSION: Small capsule sizes led to quicker Tlag and Tmax of blood [HCO3–] compared to medium and large capsules, suggesting that individuals could supplement NaHCO3 in smaller capsules if they aim to increase buffering capacity more quickly.

Contribution to the field

Whilst the use of both liquids and capsules to deliver sodium bicarbonate to research participants and athletes, seeking an ergogenic benefit are common, no one has investigated the size of the capsule. We undertook this work to determine which best improved the acid base response. Furthermore we also investigated the palatability of the capsules and the effects on any gastrointestinal disturbances.

Funding statement

Ethics statements

Studies involving animal subjects
Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects
Generated Statement: The studies involving human participants were reviewed and approved by Department of Sport and Physical Activity Research Ethics Committee, Edge Hill University . The patients/participants provided their written informed consent to participate in this study.

Inclusion of identifiable human data
Generated Statement: No potentially identifiable human images or data is presented in this study.

Data availability statement

Generated Statement: The datasets presented in this article are not readily available because We will not provide this data to others. Requests to access the datasets should be directed to lars.mcnaughton@edgehill.ac.uk.

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Abstract

INTRODUCTION: Sodium bicarbonate ($NaHCO_3$) is a well-established nutritional ergogenic aid that is typically ingested as a beverage or consumed in gelatine capsules. Whilst capsules may delay the release of $NaHCO_3$ and reduce gastrointestinal (GI) side-effects compared with a beverage, it is currently unclear whether capsule size may influence acid-base responses and GI symptoms following supplementation. **AIM:** To determine the effects of $NaHCO_3$ supplementation administered in different sized capsules on acid-base responses, GI symptoms and palatability. **METHODS:** Ten healthy males (mean ± SD: age 20 ± 2 y; height 1.80 ± 0.09 m; weight 78.0 ± 11.9 kg) underwent three testing sessions whereby 0.3 g·kg^{-1} body mass $NaHCO_3$ was consumed in either small (size 3), medium (size 0) or large (size 000) capsules. Capillary blood samples were procured pre-ingestion and every 10 min post-ingestion for 180 min. Blood samples were analysed using a Radiometer (Radiometer ABL800, Denmark) to determine blood bicarbonate concentration ($[HCO_3^-]$) and potential hydrogen (pH). Gastrointestinal (GI) symptoms were measured using a questionnaire at the same timepoints, whereas palatability was recorded pre-consumption. **RESULTS:** Capsule size had a significant effect on lag time (the time $[HCO_3^-]$ changed T_{lag}) and the timing of peak blood $[HCO_3^-]$(T_{max}). Bicarbonate T_{lag} was significantly higher in the large (28 ± 4 min) compared with the small (13 ± 2 min) sized capsules ($P = 0.009$). Similarly, T_{max} was significantly lower in the small capsule (94 ± 24 min) compared with both the medium (141 ± 27 min; $P < 0.001$) and large (121 ± 29 min; $P < 0.001$) sized capsules. The GI symptom scores were similar for small (3 ± 3 AU,), medium (5 ± 3 AU) and large (3 ± 3 AU) sized capsules, with no significant difference between symptom scores (F = 1.3, $P = 0.310$). Similarly, capsule size had no effect on palatability (F = 0.8, $P = 0.409$), with similar scores between different capsule sizes. **CONCLUSION:** Small capsule sizes led to quicker T_{lag} and T_{max} of blood $[HCO_3^-]$ concentration compared to medium and large capsules, suggesting that individuals could supplement $NaHCO_3$ in smaller capsules if they aim to increase extracellular buffering capacity more quickly.

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Introduction

Sodium bicarbonate ($NaHCO_3$) is an extensively researched nutritional ergogenic aid, shown to be particularly effective in improving short-duration (~1-10 min) high intensity exercise performance (Matson and Tran, 1993, Carr, Hopkins and Gore, 2011, Gough et al., 2018). Supplementation with $NaHCO_3$ serves to enhance endogenous bicarbonate buffering capacity, by inducing temporary elevations in extracellular bicarbonate concentrations and resultantly, enhancing efflux of hydrogen cations (H^+) from skeletal muscle. Consequently, an improved H^+ efflux attenuates muscular fatigue and has been shown to positively impact multiple performance measures such as total work done (McNaughton, 1992a), power output (Kilding, Overton and Gleave, 2012) and time to exhaustion (Higgins, James and Price, 2013) and recovery between exercise bouts (Gough et al 2019).

The ergogenic potential of $NaHCO_3$ is widely acknowledged (Close et al 2016), but some individuals suffer adverse gastrointestinal symptoms (Burke and Pyne, 2007, Hilton et al., 2019) (GIS) that may be deleterious to performance (Deb et al 2018; Saunders et al 2014). Recently, some authors have attempted to find strategies to alleviate the severity of GIS by using delayed release (2019) and enterically coated capsules (Hilton et al., 2020a). This strategy builds on the concept of reducing GIS by delaying the release of HCO_3 into the stomach thereby limiting carbon dioxide production that occurs when $NaHCO_3$ is ingested (Ibekwe et al., 2008, Oliveira, Saunders and Artioli, 2018). At present these coatings make this ergogenic strategy expensive. Indeed, the most frequently used ingestion strategy is gelatine capsule delivery of $NaHCO_3$. This is both a cheap alternative, improves the palatability compared to the traditional solution, and is widely used by athletes and researchers.

Encapsulation may result in reductions in the HCO_3 lost in the stomach and bring about comparable acid-base changes using smaller doses than required from aqueous delivery (Oliveira et al., 2018). There is however some suggestion that encapsulation may impair or slow bicarbonate availability, through decreased gut transit time (Barbosa, Conway and Merchant, 2017) changing the optimal pre-exercise ingestion time. Additionally, while the

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gastro-resistant properties of different capsule forms and their subsequent effects on bicarbonate bioavailability have begun to be elucidated (Hilton et al., 2019, 2020a, 2020b), the effects of the physical properties of capsules such as their overall size, (and therefore surface area) on bicarbonate bioavailability remains unclear.

In the pharmaceutical industry, the bioavailability of a substance is carefully considered as part of delivery vehicle testing, and is affected by size, surface area and surface area/volume of the capsule. Furthermore, there is a direct relationship between the surface area of a substance and its dissolution rate, specifically, an increase in total surface area of a delivery vehicle in contact with the gastrointestinal fluids causes an increase in the dissolution rate (Ashford 2017). Indeed, the dissolution of substances from capsules is a complex function of four key factors: (1) the rates of the dissolution of the capsule shell, (2) the rate of penetration of the gastrointestinal fluids into the gastrointestinal mass, (3) the rate at which the mass disaggregates in the gastrointestinal fluids and (4) the rate of dissolution of the dispersed substance particles (Ashford, 2017). Such factors are rarely considered in the delivery of ergogenic aids, despite these processes being highly variable and subject to potentially large inter-individual variation (Sparks et al., 2017). Given the considerable evidence of the ergogenic effects of $NaHCO_3$ and the widespread use of capsules as an ingestion strategy, understanding how capsule size (and therefore surface area) impacts bioavailability is of high importance for optimising pre-exercise ingestion timing (Boegman et al., 2020). Therefore, the aim of this study was to determine the effects of $NaHCO_3$ supplementation administered in different sized capsules on blood acid-base responses, GIS and palatability.

Method

Participants

Ten recreationally active males with the following (Mean ± SD) characteristics volunteered for this study: age, 20 ± 2 y; height, 1.8 ± 0.2 m; body mass, 78.0 ± 11.9 kg. All participants undertook regular (≥ 3 days·wk^{-1}) exercise for at least 30 min per session. Following medical screening, all participants were deemed healthy, free from GI disorders, and were not taking

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any nutritional supplements or prescription medication. The protocol was explained in full and questions were answered before the participants gave written, informed consent to participate in the study. The study was approved by the Departmental Research Ethics Committee.

Study design

Participants visited the laboratory on three separate occasions after an overnight fast and at the same time of day (Reilly et al., 1990). Visits were separated by between 24-72 hours to allow acid base balance variables to return to normal (Siegler et al., 2009; Bishop et al. 2004). Participants maintained their habitual diet before experimental testing (Spencer, Bishop and Lawrence, 2004; McNaughton et al. 2011) and refrained from alcohol ingestion and strenuous exercise at least 24 hours before each visit. During the initial visit, height (Seca, Germany) and body mass (Holtain, UK) were recorded before participants consumed 300 mg·kg^{-1} body mass $NaHCO_3$ in gelatine capsules (Bulk Powders™, Colchester, UK). This dose was chosen based on previous findings of improved exercise performance and is a dose widely recognised to be ergogenic within the literature (McNaughton, 1992; McNaughton & Cedaro, 1991; McNaughton et al. 1991; Gough et al. 2018). Capsule sizes were administered using a repeated measures crossover design, following the use of a Latin square to determine trial order allocation for participants (Kuehl, 2000). The three trials used either standard small (size 3), medium (size 0) and large (size 000) capsules. Each capsule contained 0.4, 0.8 and 1.6 g $NaHCO_3$ and the mean number of capsules consumed was 59 ± 9, 29 ± 4 and 15 ± 2 capsules which equated to a total capsule surface area for the bolus of 23.3 ± 3.5, 20.7 ± 3.1, and 16.4 ± 2.5 cm^2 for the small, medium and large capsule sizes respectively. Capsules were consumed with 400 ml of water which was at room temperature (18 °C). Capsule palatability was recorded immediately post-ingestion. Participants remained seated for 180 min while blood acid-base responses and GI symptoms were monitored throughout.

Acid-base responses

During experimental protocol, exposure response was established through mapping the time course of blood [HCO_3^-] and potential hydrogen (pH). Fingertip capillary blood procurement

was chosen as it is a method widely used in the exogenous buffering intervention literature (McNaughton 1992; Bishop et al., 2004; Carr et al., 2011; Boegman et al., 2020; Hilton et al., 2020b), and is a recognised method for blood gas analysis. Capillary blood was drawn pre-ingestion and then post-ingestion every 10 minutes for 3 hours, an established protocol for examining acid-base changes following exogenous buffer ingestion (Gough et al., 2018; Hilton et al., 2019; Hilton et al., 2020a). Samples were collected in 100 μL heparin-coated glass capillary tubes (Radiometer Medical Ltd, Denmark) using an aseptic technique and were analysed immediately using a blood gas analyser (Radiometer ABL800 BASIC, Denmark). These data were then used to determine the peak in $[HCO_3^-]$ change (C_{max}), the absolute change in $[HCO_3^-]$ (ΔC_{max}), the time to reach C_{max} (T_{max}), the area under the concentration-time curve (AUC), and the time lag (T_{lag}). The T_{lag} was defined as an increase in $[HCO_3^-]$ beyond normal daily variability (Hilton et al., 2020a).

Gastrointestinal symptoms and palatability

At the same time points, GI symptoms were measured using a 9-item questionnaire which included stomach cramping, flatulence, nausea, belching, stomach-ache, diarrhoea, vomiting, bowel urgency and stomach bloating (Carr et al., 2011). Each symptom was measured on an 11-point scale, whereby '0 = no symptom' and '10 = severe symptom'. Palatability was recorded immediately post-ingestion using a 9-point hedonic scale, where '1 = extremely dislike' and '9 = extremely like' (Jones, Peryam and Thurstone, 1955).

Statistical Analysis

All data were assessed for normality the Shapiro–Wilk test and by visual inspection of the normality plots (Grafen and Hails, 2002). Blood acid-base responses (HCO_3^- and pH) and GI symptoms were analysed using two-way (condition × time) analysis of variance (ANOVA) with repeated-measures. A general linear model ANOVA was used to analyse absolute acid-base values (peak blood $[HCO_3^-]$, time-to-peak blood $[HCO_3^-]$, peak blood pH, time-to- peak blood pH, and area under the curve (AUC)), GI symptoms and perceived palatability. Two-tailed

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statistical significance was set at $p < 0.05$. Effect sizes were reported as partial eta-squared (ηp^2) and are described as trivial (< 0.20), small ($\eta p^2 = 0.20-0.49$) moderate ($\eta p^2 = 0.50-0.79$) and large (≥ 0.80), respectively (Cohen, 1988).

Results

Blood bicarbonate responses

There were significant increases in blood [HCO_3^-] ($F = 93.2$, $p < 0.001$, $\eta p^2 = 0.91$) in all $NaHCO_3$ conditions compared with pre-consumption values (Figure 1b). Capsule size had no significant effect on [HCO_3^-] ($F = 2.3$, $p = 0.151$, $\eta p^2 = 0.21$) post-consumption, although a significant condition × time interaction was observed ($F = 3.3$, $p = 0.014$, $\eta p^2 = 0.27$), suggesting that the large capsules changed [HCO_3^-] more slowly in the initial part of the post ingestion period, and the medium sized capsule sustained [HCO_3^-] for longer (Figure 1b).

[INSERT FIGURE 1 NEAR HERE]

Capsule size also had a significant effect on T_{lag} ($F = 3.8$, $p = 0.043$, $\eta p^2 = 0.30$), with significantly longer times in the large (28 ± 4 min) compared with the small (13 ± 2 min) sized capsules ($p = 0.009$). Similarly, capsule size had a significant effect on T_{max} ($F = 157.6$, $p = 0.000$, $\eta p^2 = 0.94$), with significantly shorter times in the small capsule compared with both the medium ($p = 0.000$) and large ($p = 0.000$) sized capsules (Table 1). No significant differences were observed for C_{max} ($F = 0.6$, $p = 0.574$, $\eta p^2 = 0.06$), ΔC_{max} ($F = 0.3$ $p = 0.731$, $\eta p^2 = 0.03$) or AUC ($F = 2.1$, $p = 0.148$, $\eta p^2 = 0.19$) between conditions (Table 1). There appeared to be a large inter-individual variability in response to the capsule ingestion (Figure 2).

[INSERT TABLE 1 NEAR HERE]

[INSERT FIGURE 2 NEAR HERE]

Blood pH responses

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Blood pH increased in all NaHCO$_3$ conditions (F = 41.5, p < 0.001, ηp^2 = 0.82) compared with pre-consumption values (Figure 1a). Capsule size had a significant effect on blood pH (F = 3.9, p = 0.040, ηp^2 = 0.30) overall, although no significant condition × time interaction was shown for blood pH (F = 0.9, p = 0.628, ηp^2 = 0.09; Figure 1a). There were no significant differences in either peak blood pH (F = 1.5, p = 0.249, ηp^2 = 0.14) and time-to-peak blood pH (F = 1.9, p = 0.181, ηp^2 = 0.17) between conditions.

Gastrointestinal symptoms and palatability

Gastrointestinal symptom scores were similar for small (3 ± 3 AU,), medium (5 ± 3 AU) and large (3 ± 3 AU) sized capsules, with no significant difference between symptom scores (F = 1.3, p = 0.310, ηp^2 = 0.12). Similarly, capsule size had no effect on palatability (F = 0.8, p = 0.461, ηp^2 = 0.08), with similar scores between different capsule sizes (Figure 3). Palatability scores ranged from 1–9 AU, 1–9 AU and 1–7 AU for small, medium and large capsules, respectively.

[INSERT FIGURE 3 NEAR HERE]

Discussion

This study showed that different capsule sizes led to differences in T$_{lag}$ and T$_{max}$ of blood [HCO$_3^-$], without affecting the absolute increases in circulating HCO$_3^-$ or AUC of the increases over 180 min. Since T$_{lag}$ (versus large capsules) and T$_{max}$ was shorter (versus medium and large capsules) for small capsules, and palatability was similar albeit also without affecting GI symptoms, this suggests that smaller capsules may be a better form of ingestion for individuals wishing to increase their extracellular buffering capacity more quickly. Those using capsules to administer NaHCO$_3$ should also be cognisant of the trade off in palatability and participant comfort due to the inverse relationship between capsule size and the number of capsules needed to deliver a potentially ergogenic dose (Hayakawa et al., 2016). Despite the mean differences in HCO$_3^-$ kinetics when smaller capsules are consumed, we observed

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considerable individual variability in responses, similar to those previously reported (Sparks et al 2015, Jones et al., 2016, Oliveira et al., 2020).

Alternative forms of $NaHCO_3$ ingestion will lead to different pharmacokinetic profiles, with the most common forms in solution or gelatine capsules, with apparently different HCO_3^- kinetics (Oliveira et al., 2020). Enterically-coated and delayed-release forms also lead to different HCO_3^- kinetics compared to gelatine capsules (Hilton et al., 2019, 2020a, 2020b). These novel data now show that different sizes of gelatine capsules lead to different blood HCO_3^- kinetics, with quicker increases and time to reach peak values with smaller capsules. Previously the dissolution rates for individual size 0 and 3 gelatine capsules have been observed to be similar at around 100 s (Chiwele et al., 2000). However, in the present study, the large differences between the number of capsules ingested between capsule size conditions results in considerable differences in the total surface area of the ingested substance. Consequently, the greater total surface area of the smaller capsules, is likely to liberate their contents quicker. There were no differences between the medium and large-sized capsules shown here. For those intending to ensure the start of exercise coincides with C_{max}, these data suggest that individuals could adapt the capsule size in which they ingest $NaHCO_3$ depending on when they can supplement. The present study also standardised the temperature of the fluid ingested with the capsules, but consuming hotter fluids is likely to reduce T_{max}, and colder fluids are likely to increase T_{max}. (Chiwele et al., 2000). At present, no studies have considered the temperature of the fluid on the pharmokinetics of extracellular buffers such a $NaHCO_3$, but athletes and sports nutrition practitioners should be aware that this is likely to alter the expected time duration at which $NaHCO_3$ should be ingested prior to exercise. It would be of interest to determine whether enteric-coated versions of these capsules also lead to different, and more favourable, HCO_3^- kinetics following ingestion.

Side-effect associated with $NaHCO_3$ ingestion include nausea, vomiting, GI discomfort, diarrhoea and headache (McNaughton, 1992a, 1992b). There has been some suggestion that minimising neutralisation of stomach acids due to the increased $NaHCO_3$ load might lead to reduced GI discomfort and increased circulating HCO_3^- (Oliveira et al., 2018). This explains

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why enterically-coated and delayed-release forms of $NaHCO_3$ reduce the incidence and severity of GI disturbances compared to gelatine capsules (Hilton et al., 2019, 2020a, 2020b). Despite the different HCO_3^- profiles here, there were no differences in the side-effect symptom scores between the different capsule sizes suggesting individuals need not concern themselves with side-effects when choosing which size of gelatine capsule to use for $NaHCO_3$ supplementation. Nonetheless, further work should elucidate whether enteric-coated versions of these different capsule sizes can reduce their side-effects since discomfort associated with $NaHCO_3$ can be ergolytic to exercise performance (Saunders et al., 2014).

A limitation of this study is that we only analysed the time course of blood HCO_3^- and pH kinetics following $NaHCO_3$ supplementation in different capsules sizes. It could have been interesting to determine whether different exercise performance responses were shown between the capsules. Nonetheless, it could be hypothesised that similar performance improvements would be shown seen if exercise was performed at TTP since there were no differences between capsules sizes for peak HCO_3^- change, absolute HCO_3^- at peak, and the HCO_3^- AUC. It is possible that performance differences might be found should standardised ingestion times be employed prior to exercise, since T_{max} was different between capsules sizes. Therefore, it is important to ensure that individual responses to the specific type of capsules that are being used, are determined in order to optimise the pre-exercise timing of their ingestion.

In conclusion, small capsule sizes led to quicker T_{lag} and T_{max} of blood $[HCO_3^-]$ compared to medium and large capsules, without affecting absolute increases in circulating HCO_3^- or AUC. Palatability and GI symptoms were similar between all capsule sizes. Individuals could supplement $NaHCO_3$ in smaller capsules if they aim to increase extracellular buffering capacity more quickly.

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Author Contributions

IM, SAS and LRM designed the study. IM, DJT, NKL, and NPH collected the data. IM, NPH and SAS analysed the data. All authors contributed to the interpretation of data and of the writing of the manuscript. All authors have read and approved the final version of the manuscript and agree with the final order of presentation of the authors.

Table 1. Mean (SD) bicarbonate kinetic variables following the consumption of 0.3 g·kg^{-1} body mass NaHCO$_3$ in small, medium and large sized capsules.

Variable	Small	Medium	Large
T$_{lag}$ (min)	13 ± 2	22 ± 6	28 ± 4[a]
C$_{max}$ (mmol·L^{-1})	31.7 ± 1.7	32.1 ± 1.5	31.8 ± 1.4
ΔC$_{max}$ (mmol·L^{-1})	7.1 ± 1.1	6.7 ± 1.4	6.8 ± 0.8
T$_{max}$ (min)	94 ± 24[b]	141 ± 27[b]	121 ± 29[b]
AUC (mmol·min·L^{-1})	5316 ± 256	5373 ± 264	5239 ± 263

Notes: T$_{lag}$, lag time; C$_{max}$, peak bicarbonate concentration; ΔC$_{max}$, change in peak bicarbonate concentration; T$_{max}$, time-to-peak bicarbonate concentration; AUC, area under the curve. ([a]) Denotes a significant difference between the large and small capsules ($p < 0.05$); ([b]) Denotes a significant difference between all capsules ($p < 0.001$).

In review

Figure Captions

Figure 1. Mean (±SD) temporal blood pH (a) and bicarbonate concentration [HCO_3^-] responses, following the consumption of 0.3 g·kg^{-1} body mass $NaHCO_3$ in small, medium and large-sized capsules. (*) denotes a condition*time interaction between small and medium capsules where p <0.05. (∇) denotes a condition*time interaction between small and large capsules where p <0.05. (■) denotes a condition*time interaction between medium and large capsules where p <0.05.

Figure 2. Mean (±SD) and individual peak changes in blood bicarbonate concentration [HCO_3^-] (ΔCmax) following the consumption of 0.3 g·kg^{-1} body mass $NaHCO_3$ in small, medium and large-sized capsules. Small markers represent individual responses, and large markers represent mean data for each capsule condition. X and Y whiskers represent the SD of the sample in each condition for time-to-peak [HCO_3^-] (Tmax) and ΔCmax respectively.

Figure 3. Mean (±SD) palatability scores following the consumption of 0.3 g·kg^{-1} body mass $NaHCO_3$ in small, medium and large sized capsules.
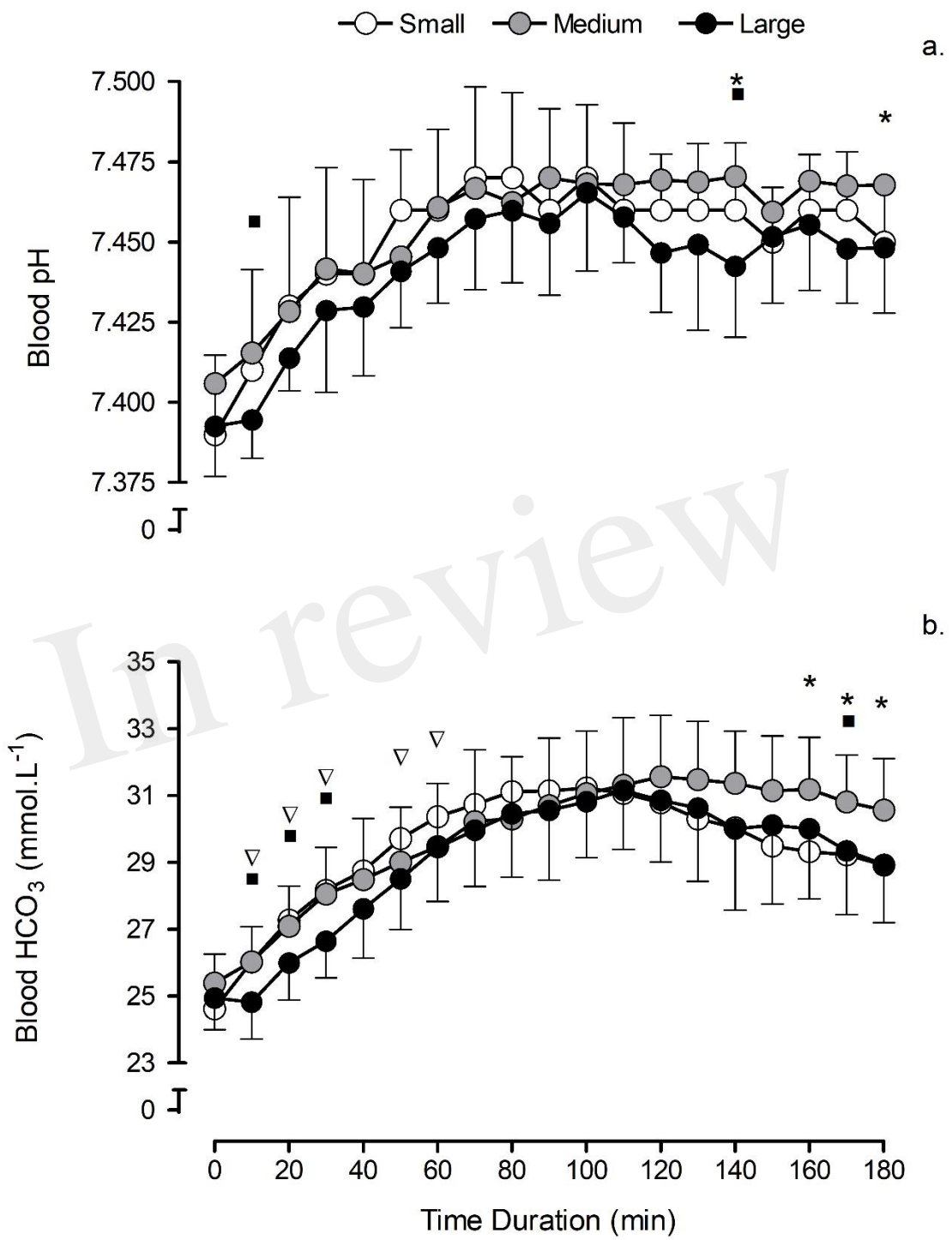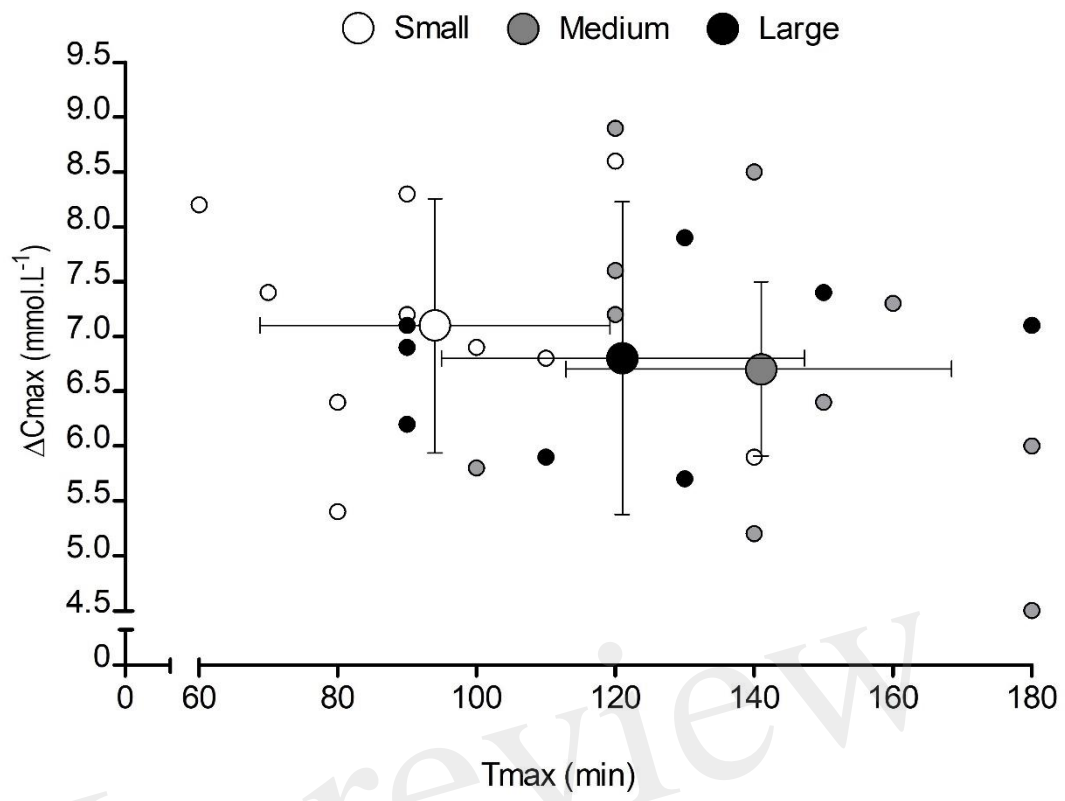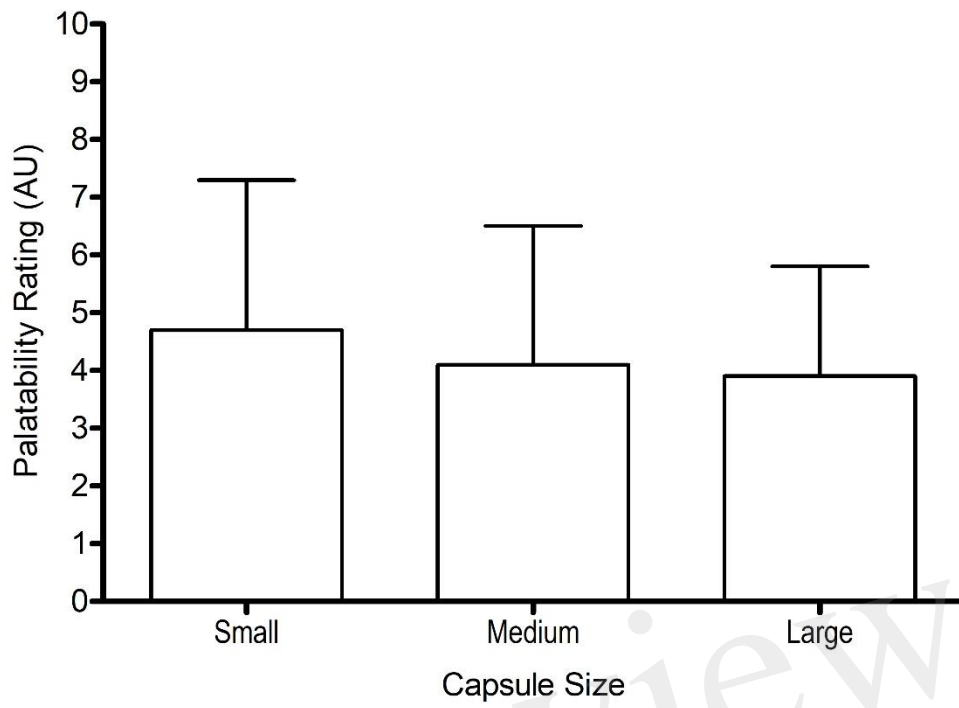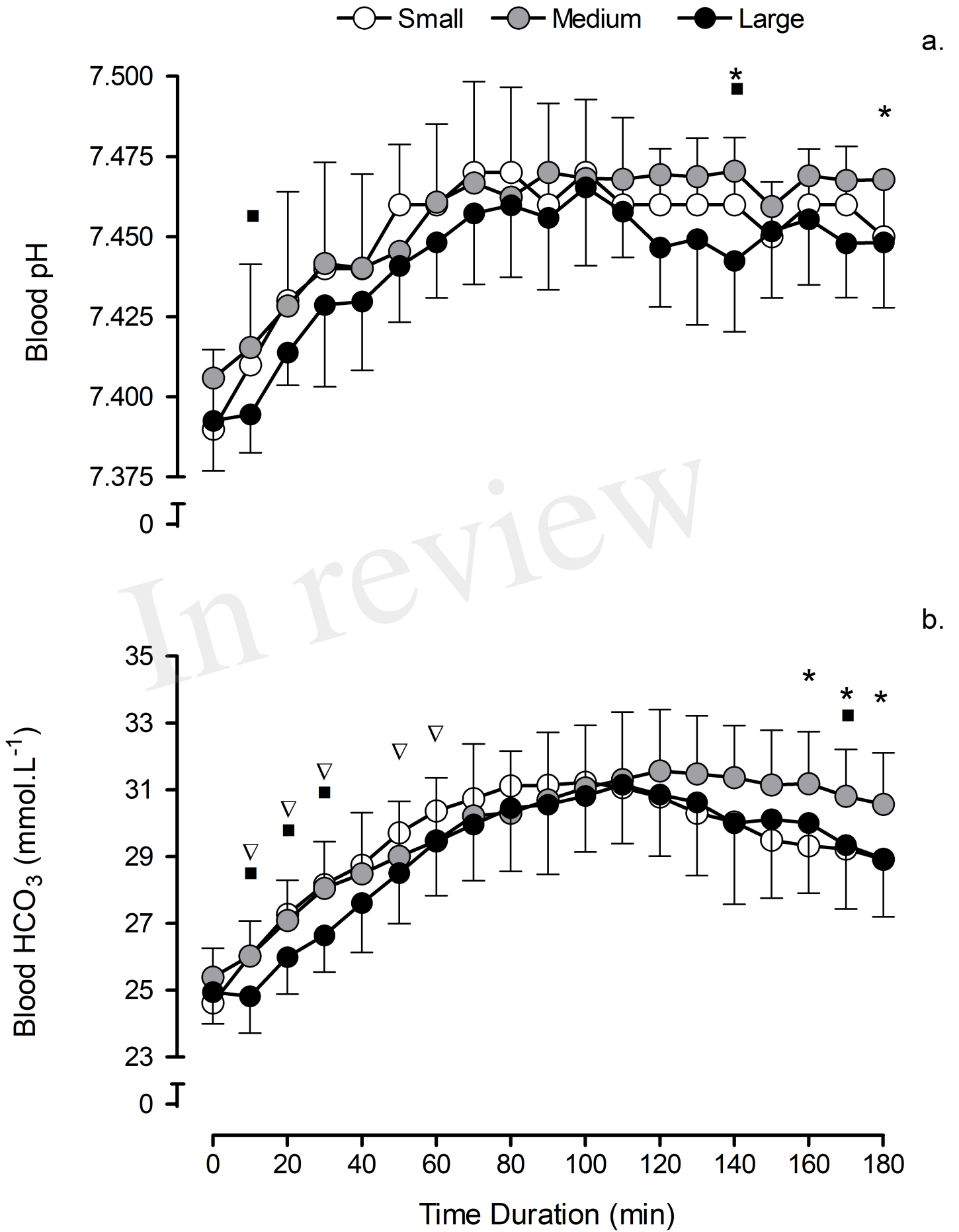
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Figure 1

Figure 2.

Figure 3.

Figure 1.JPEG

Figure 2.JPEG

Figure 3.JPEG