INTERNATIONAL JOURNAL OF SPORT NUTRITION and EXERCISE METABOLISM

Enteric-coated sodium bicarbonate attenuates gastrointestinal disturbances and alters acid-base responses

Journal:	*International Journal of Sport Nutrition & Exercise Metabolism*
Manuscript ID	IJSNEM.2019-0151.R2
Manuscript Type:	Original Research
Keywords:	Buffering agent, Acid-base balance, Delayed-release

ABSTRACT

Enteric-formulated capsules can mitigate gastrointestinal (GI) side-effects following sodium bicarbonate ($NaHCO_3$) ingestion however, it remains unclear how encapsulation alters post-ingestion symptoms and acid-base balance. The current study aims to identify the optimal ingestion form to mitigate GI distress following $NaHCO_3$ ingestion. Fourteen trained males ingested 300 $mg \cdot kg^{-1}$ body mass (BM) $NaHCO_3$ in gelatine (GEL), delayed-release (DEL) and enteric-coated (ENT) capsules or placebo (PLA) in a randomised crossover design. Blood bicarbonate anion concentration [HCO_3^-], potential hydrogen (pH) and GI symptoms were measured pre- and post-ingestion for 3 h. Fewer GI symptoms were reported with ENT $NaHCO_3$ than with GEL (P = 0.012) but not DEL (P = 0.106) in the post-ingestion phase. Symptom severity decreased with DEL (4.6 ± 2.8 AU) compared to GEL (7.0 ± 2.6 AU; P = 0.001) and were lower with ENT (2.8 ± 1.9 AU) than with both GEL (P < 0.0005) and DEL (P = 0.044) $NaHCO_3$. Blood [HCO_3^-] increased in all $NaHCO_3$ conditions compared to PLA (P < 0.0005), although this was lower with ENT than GEL (P = 0.001) and DEL (P < 0.0005) $NaHCO_3$. Changes in peak blood pH were reduced with ENT than with GEL (P = 0.047) and DEL (P = 0.047) $NaHCO_3$ with no other differences between conditions. Ingestion of ENT $NaHCO_3$ attenuates GI disturbances up to 3h post-ingestion. Therefore, ENT ingestion forms may be favourable for those who report GI disturbances with $NaHCO_3$ supplementation, or for those who have previously been deterred from its use altogether.

Key words: buffering agent, acid-base balance, delayed-release

INTRODUCTION

Gastrointestinal (GI) disturbances are widely reported following sodium bicarbonate ($NaHCO_3$) supplementation (Burke & Pyne, 2007; Cameron et al., 2010; Kahle et al., 2013) and although the aetiology of GI disturbances involves multiple mechanisms, the neutralisation of gastric acid is considered a prominent factor (Turnberg, 1970). Rapid increases in gastric carbon dioxide tension occur from an effervescent reaction between gastric acid and $NaHCO_3$, which can induce bloating, abdominal pain and vomiting (Carr et al., 2011a). Given the adverse side-effects experienced by some athletes, $NaHCO_3$ ingestion may not be practical during competition despite its potential performance-enhancing effects, which may deter athletes from supplementation (Heibel et al., 2018). Furthermore, previous findings suggest that GI symptoms can negate the performance-enhancing effects of $NaHCO_3$ (Carr et al., 2011b), and in some cases, may even be ergolytic (Cameron et al., 2010; Froio de Araujo Dias et al., 2015; Saunders et al., 2014). Irrespective of performance, little is known about the acute and chronic consequences of regular GI disturbances, which may be detrimental to health. Previous investigations have examined the efficacy of various ingestion strategies such as multiday dosing (Mueller et al., 2013), split-dosing (Sale et al., 2011) and carbohydrate co-ingestion (Carr et al., 2011a) to reduce GI disturbances. However, regardless of adopting these strategies, GI disturbances remain problematic in some individuals following ingestion, therefore emphasising the need for alternative ingestion strategies (Lancha Junior et al., 2015).

Enteric-formulated capsules can reduce side-effects associated with the ingestion of acid-sensitive compounds such as

$NaHCO_3$ (Barbosa et al., 2017). Through encapsulation in a polymer barrier, which is less soluble at high acidity (Mazarati et al., 2016), capsules resist disintegration in the stomach and compounds are released in the small intestine, therefore preventing GI disturbances. Recent evidence suggests that delayed-release $NaHCO_3$, which contained an enteric-coating within the shell, minimises GI symptoms in comparison to an oral solution while inducing comparable acid-base balance (Hilton et al., 2019). There is however speculation as to how the site of disintegration may alter the bioavailability of bicarbonate, which is thought to be a factor modulating its ergogenic effects (Heibel et al., 2018). Whilst minimising the loss of bicarbonate anions in the stomach may augment blood concentrations (Oliveira et al., 2018), delaying absorption also decreases GI transit time; which in turn may reduce changes in blood bicarbonate. These considerations suggest that bioavailability may be complex; one factor relates to GI transit time while another to the degree of neutralisation. Therefore, overall bioavailability is dependent upon on the balance between bicarbonate losses through neutralisation and GI transit time which is determined by the ingestion form. While previous research has compared the effects of administering $NaHCO_3$ in gelatine (Carr et al., 2011a) and delayed-release capsules in comparison to an oral solution (Hilton et al., 2019), research has yet to compare the effects of different capsule ingestion forms. Consequently, little is currently known regarding how enteric coatings may affect GI symptoms and bicarbonate kinetics following $NaHCO_3$ supplementation. Furthermore, there is a notable lack of data regarding the efficacy of commercially available capsule formulations, despite this being a potential form of ingestion for athletes.

The primary aim of the present study was to determine the optimal ingestion form to minimise GI disturbances following $NaHCO_3$ ingestion. The secondary aim was to examine the bioavailability of bicarbonate anions following $NaHCO_3$ ingestion across different ingestion forms.

METHODS

Participants

Fourteen trained (according to DePauw et al., 2013) males (age 23.6 ± 4.9 years, BM 80.9 ± 11.5 kg, maximal oxygen uptake 57.7 ± 5.3 $mL \cdot kg^{-1} \cdot min^{-1}$) volunteered for the study. All participants performed regular exercise training (≥ 3 $d \cdot week^{-1}$) for at least two years and were free of GI-related disorders. Exclusion criteria included those with hypertension, renal impairment or following a salt-restricted diet, and no participants were ingesting buffering agents or medications at the time of the study. Protocols were explained in full and questions were answered before the participants gave written, informed consent to participate in the study. Ethical approval was granted by the institutional research ethics committee.

Experimental overview

In a double-blind, placebo-controlled, randomised crossover design, participants attended the laboratory on five separate occasions. After an initial visit, experimental trials consisted of a placebo (PLA) and three $NaHCO_3$ trials, whereby 300 $mg \cdot kg^{-1}$ BM $NaHCO_3$ was administered in either gelatine (GEL), delayed-release (DEL) or enteric-coated (ENT) capsules. According to the manufacturer, the DEL capsules (DRcaps™) were embedded with a polymer barrier

(Hypromellose) within the shell, whereas the ENT capsules (Bicarbi™) were spray-coated with the same ingredient. Experimental trials were counterbalanced (balanced Latin-square) in the order of administration and conducted at least 48 h apart to allow for blood bicarbonate concentration ($[HCO_3^-]$) to return to 'normal' values. Participants were required to abstain from alcohol or caffeine-containing beverages for 12 h, and strenuous exercise 24 h before each laboratory visit.

During the initial visit, semi-nude BM was measured (BOD POD®, COSMED, Italy) before participants performed an incremental exercise test to volitional exhaustion on an electromagnetically-braked cycle ergometer (Excalibur Sport, Lode, Netherlands). This involved a standardised warm-up (5 min at 70 W) before the workload increased by 1 W every 2 s (30 $W \cdot min^{-1}$) until volitional exhaustion was reached.

Experimental trials took place under standardised laboratory conditions (temperature 20-22 °C, humidity 50 ± 5 %) and commenced at the same time of day to account for circadian rhythms (Reilly et al., 1990). Participants arrived at the laboratory after an overnight fast (~ 12 h) which was verbally confirmed upon arrival. Participants then ingested 300 $mg \cdot kg^{-1}$ BM $NaHCO_3$ or PLA (cornflour) which were administered in size 0 opaque (white) capsules. Each experimental capsule contained 650 mg $NaHCO_3$ therefore doses were administered to the nearest whole capsule. Capsules were manually filled by the same individual using a capsule filling device (Capsule Connection LLC, USA) and doses were tested for accuracy (Fisher, OHAUS™). Supplements were ingested with an equal volume (6 $mL \cdot kg^{-1}$ BM) of water (Evian®, France) within 5 min while the timing commenced at the start of ingestion (Stannard et al., 2016). Given that water was

permitted *ad libitum* post-ingestion, volumes were recorded on the first trial and replicated thereafter. Participants remained seated throughout although toilet breaks were permitted.

Assessment of acid-base balance

During each trial, the exposure-response was established by determining the time course of blood [HCO_3^-] and potential hydrogen (pH). Fingertip capillary blood samples (95 µL) were obtained pre-ingestion and then every 20 min for 180 min post-ingestion, with 10 min sampling from 80 to 140 min. Samples were collected in heparin-coated glass capillary tubes (Radiometer Medical Ltd, Denmark) using an aseptic technique and were analysed immediately (Radiometer ABL800 BASIC, Denmark) for blood [HCO_3^-] and pH. Blood bicarbonate kinetics were used to determine characteristics of the ingestion forms, including lag time (T_{lag}), peak blood [HCO_3^-] (C_{max}), change in C_{max} (ΔC_{max}), time-to-reach C_{max} (T_{max}) and area under the curve (AUC). Bicarbonate T_{lag} was defined as the point at which blood [HCO_3^-] increased beyond normal daily fluctuation; established individually following ingestion of PLA.

Gastrointestinal symptoms

Symptoms of GI distress were recorded at the same time points using a 9-item questionnaire (adapted from Carr et al., 2011a) including nausea, flatulence, stomach cramping, belching, stomach ache, bowel urgency, diarrhoea, vomiting, and stomach bloating. Symptoms were self-measured on a 10 cm visual analogue scale ranging from "0, no symptom" to "10, severe symptom" (Miller et al., 2016). Symptom

terminology was explained to participants before the experimental trials commenced to ensure consistency in the reporting of symptoms.

Statistical analysis

Data were assessed for normality using standard graphical methods prior to analyses (Grafen & Hails, 2002). Blood [HCO_3^-], pH and aggregated GI symptom scores were analysed using two-way (trial × time) analysis of variance (ANOVA) with repeated-measures. Where a significant main effect was found, Bonferroni post-hoc pair-wise comparisons were determined (Atkinson, 2002). One-way ANOVA with repeated measures were used to compare peak GI symptom scores, T_{lag}, C_{max}, Δ C_{max}, T_{max} and AUC between trials. Effect sizes were calculated using partial eta squared (η_p^2) and were described as trivial (<0.20 AU), small (0.20-0.49 AU), moderate (0.50-0.79 AU) or large (≥ 0.80 AU) as previously suggested (Cohen, 1988). The α-level of statistical significance was set at $P < 0.05$ and values for P of "0.000" given by the statistical package were corrected to "< 0.0005" (Kinnear & Gray, 1995). Relationships between peak GI symptom scores were determined using Pearson's correlation coefficients. Descriptive data are presented as mean ± standard deviation (SD) unless stated otherwise. Data were analysed using the Statistical Package for the Social Sciences (SPSS®) version 25 software.

RESULTS

Gastrointestinal symptoms

Ingestion form had a significant effect on GI symptoms ($F_{1.4, 17.7} = 10.3$, $P = 0.003$, $\eta_p^2 = 0.44$) with lower GI symptom scores observed during PLA compared to the GEL ($P = 0.011$), DEL ($P = 0.005$) and ENT (P

= 0.02) trials (Figure 1). The ENT trial also resulted in significantly lower GI symptom scores compared to GEL (4.8 ± 1.4 AU; 95% CI 1.0-8.6 AU; $P = 0.025$) but not DEL ($P = 0.211$) post-ingestion. Time had no effect on GI symptoms ($F_{1.8, 23.8} = 2.1$, $P = 0.148$, $\eta_p^2 = 0.14$) and there was no significant trial × time interaction ($F_{2.6, 34.0} = 1.8$, $P = 0.180$, $\eta_p^2 = 0.12$).

[INSERT FIGURE 1 NEAR HERE]

The highest individual GI symptom (Table 2) occurred at ~ 60 to 90 min (GEL 94 ± 58 min, DEL 91 ± 21 min, ENT 73 ± 34 min) and was significantly earlier with ENT than in the GEL ($P = 0.028$) trial. No other differences were observed in the time to reach peak GI symptom scores ($P > 0.05$) between trials. In total, eleven participants experienced GI symptoms at the point of T_{max} in the GEL trial compared with seven and one in the DEL and ENT trials respectively, although these were rated as less than 3/10 AU throughout. Significant relationships were observed between peak GI symptoms in the DEL trial with all other $NaHCO_3$ trials (GEL $r = 0.78$, $P = 0.001$; ENT $r = 0.64$, $P = 0.014$). No other relationships were observed in peak GI symptoms between trials.

All fourteen participants experienced at least one GI symptom in the GEL trial, compared to twelve participants in the DEL and ENT trials (Table 2). Only two participants reported any GI symptoms in the PLA trial. Stomach bloating (100.0%), belching (92.9%) and bowel urgency (92.9%) were the most common GI symptoms overall, whereas diarrhoea (7.8 ± 3.1 AU), bowel urgency (5.9 ± 3.0 AU) and

flatulence (4.4 ± 2.7 AU) had the highest severity rating overall (Table 1).

Acid-base responses

Ingestion form had a significant effect on blood [HCO_3^-] ($F_{3.0, 39.0}$ = 53.6, $P < 0.0005$, $\eta_p^2 = 0.81$) and pH ($F_{3.0, 39.0} = 50.7$, $P < 0.0005$, $\eta_p^2 = 0.80$) (Figure 2). Blood [HCO_3^-] and pH were significantly lower with ENT than with GEL and DEL in the post-ingestion phase. In the post-ingestion time period, there were significant effects on blood [HCO_3^-] ($F_{3.4, 44.1} = 143.8$, $P < 0.0005$, $\eta_p^2 = 0.92$) and pH ($F_{5.3, 68.5} = 36.3$, $P < 0.0005$, $\eta_p^2 = 0.74$). Blood [HCO_3^-] at 110 min was significantly higher than at baseline, 20 and 40 min ($P < 0.0005$). Blood pH was significantly higher at 140 min than at baseline and 20 min ($P < 0.0005$). Significant trial × time interactions were observed for blood [HCO_3^-] ($F_{5.2, 67.3} = 28.9$, $P < 0.0005$, $\eta_p^2 = 0.69$) and pH ($F_{8.3, 108.3} = 6.0$, $P < 0.0005$, $\eta_p^2 = 0.32$) (Figure 2 for significant differences between trials at each time point). No changes in blood [HCO_3^-] or pH were observed for PLA throughout the post-ingestion phase ($P > 0.05$).

[INSERT FIGURE 2 NEAR HERE]

After $NaHCO_3$ ingestion, ΔC_{max} was lower in the ENT trial than in the GEL ($P = 0.001$) and DEL ($P < 0.0005$) trials (Figure 3) however, the values were similar during the GEL and DEL trials (6.5 ± 1.2 mmol·L^{-1} and 6.0 ± 1.3 mmol·L^{-1}, respectively; $P = 0.116$). During the GEL trial T_{max} occurred within 60 to 90 min post-ingestion for most participants ($n = 9$) although this was not the case for DEL ($n = 2$) and ENT ($n = 3$). Blood pH peaked at similar time points across

trials (GEL 101 ± 30 min, DEL 119 ± 23 min, ENT 113 ± 32 min; $P >$ 0.05), with no significant differences between trials. Changes in peak blood pH were similar in the GEL (0.08 ± 0.02 AU) and DEL (0.08 ± 0.02 AU) trials, whereas changes with ENT (0.06 ± 0.02) were significantly lower than with GEL ($P = 0.047$) and DEL ($P = 0.047$) $NaHCO_3$.

[INSERT FIGURE 3 NEAR HERE]

DISCUSSION

The present study is the first to investigate the effects of capsule ingestion form on GI disturbances and acid-base balance following $NaHCO_3$ ingestion. The key finding is that enteric-coated $NaHCO_3$ results in fewer and less severe GI symptoms compared to both the gelatine and delayed-release capsules. Furthermore, enteric-coated $NaHCO_3$ resulted in very few participants experiencing GI symptoms at the point of peak blood [HCO_3^-]; a time when exercise is likely to be scheduled for athletes using individualised ingestion strategies (Heibel et al., 2018). Interestingly, blood [HCO_3^-] was increased above 5 $mmol \cdot L^{-1}$ for longer with delayed-release $NaHCO_3$ compared to the gelatine capsules (Figure 2), which may provide a greater 'ergogenic window' following supplementation (Carr et al., 2011b), although this has yet to be confirmed. Altogether, these data suggest that enteric-coated capsules are more effective at attenuating GI symptoms following $NaHCO_3$ ingestion however, delayed-release $NaHCO_3$ maximises extracellular buffering capacity.

In the present study GI symptoms were reported by 85.7% of the participants across all $NaHCO_3$ ingestion trials, which is higher

than some studies have previously reported (Driller et al., 2012; Sale et al., 2011; Saunders et al., 2014). Stomach bloating, belching and bowel urgency were the most common reported GI symptoms overall and although less frequent, the severity of diarrhoea was particularly high (Table 1). As expected, GI symptoms decreased following delayed-release and enteric-coated $NaHCO_3$ ingestion compared to the gelatine capsules, therefore suggesting that bypassing the stomach can alleviate many of the symptoms associated with acute bicarbonate loading (Oliveira et al., 2018). In relation to causes of GI symptoms, these are unlikely to be due to the large number of capsules ingested since only minor symptoms were experienced with the placebo. Instead, GI symptoms can be attributed to the $NaHCO_3$ alone, which also highlights that in some athletes, symptoms are likely to occur with oral delivery despite substantially fewer side-effects with enteric-formulated capsules. Given the relationships observed for GI symptoms between ingestion forms, it appears that some individuals are more prone to GI disturbances than others, although the reasons for this are currently unclear.

Exercise timed with peak alkalosis may optimise performance benefits (Gough et al., 2018), therefore it is prudent to consider which GI symptoms will occur at this timepoint. While all participants reported at least one GI symptom post-ingestion, only three participants reported GI symptoms at the point when exercise would likely commence. Of these participants, all were experiencing severe diarrhoea (10.0 AU) at the point of peak alkalosis, which may negatively affect subsequent exercise performance (Deb et al., 2018; Saunders et al., 2014). Nevertheless, it is difficult to suggest which GI symptoms may adversely affect exercise performance based on the

current data. Since very few exercise-based studies have quantified GI symptoms, it may be the severity that modulates the effects on performance, rather than GI symptoms per se. This may also explain why some studies have found GI symptoms to have deleterious effects on performance with $NaHCO_3$ supplementation (Deb et al., 2018; Cameron et al., 2010; Saunders et al., 2014) whereas others have not (Miller et al., 2016; Price & Simons, 2010). To elucidate the effects of GI disturbances on performance, future studies should look to describe the GI symptoms experienced immediately prior to exercise, as well as the athletes perceived readiness to commence.

Blood [HCO_3^-] and pH corresponded to increases typically observed with 300 mg·kg BM $NaHCO_3$ (Matson & Tran, 1993), however this was not observed with enteric-coated $NaHCO_3$. Indeed, enteric-coated capsules reduced the bioavailability of bicarbonate with changes of ~ 4 $mmol \cdot L^{-1}$ post-ingestion, which may hinder the effect on exercise performance. Bicarbonate anions are actively transported across the intestinal mucosa rather than passively and become saturated (Turnberg, 1970), which could explain why blood concentrations are reduced with enteric-coated $NaHCO_3$. Furthermore, as enteric-coated capsules do not disintegrate until reaching the small intestine, overall GI transit time is decreased which may have contributed to reduced blood concentrations. Similar to previous work (Gough et al., 2017), changes in blood [HCO_3^-] and pH demonstrated a high degree of inter-individual variability following $NaHCO_3$ ingestion (Table 3). Interestingly, changes in blood [HCO_3^-] were less variable with enteric-coated capsules which suggests that much of the variation derives from the degree of neutralisation in the stomach. Although blood [HCO_3^-] was similar between gelatine and delayed-

334 released $NaHCO_3$, concentrations were elevated for longer in the
335 delayed-release form. Similarly, more participants reached
336 concentrations that are associated with performance-enhancing effects
337 (Carr et al., 2011b). Given that higher pre-exercise blood [HCO_3^-] is
338 associated with greater performance enhancements (Carr et al., 2011b;
339 Matson & Tran, 1993), ingestion form may alter the ergogenic
340 potential of $NaHCO_3$.

341 In conclusion, the ingestion of $NaHCO_3$ in delayed-release or
342 enteric-coated capsules attenuates GI disturbances following $NaHCO_3$
343 ingestion. Enteric-coated $NaHCO_3$ is optimal for minimising GI
344 symptoms and may be favourable for those who report GI disturbances
345 following supplementation, even in those who have tried alternative
346 ingestion strategies. Given the dramatic variation in the timing of peak
347 blood [HCO_3^-] (60-180 min) across ingestion forms, it is
348 recommended that athletes continue to adopt an individualised
349 ingestion strategy. Gelatine capsules can be ingested 90 min prior to
350 exercise for athletes without access to a blood-gas analyser, whereas
351 delayed-release and enteric-coated $NaHCO_3$ can be ingested 120 min
352 before exercise commences. Given that blood buffering capacity was
353 blunted with enteric-coated $NaHCO_3$, future research should look to
354 determine the effects of enteric-coated $NaHCO_3$ on exercise
355 performance.
356

357 **Acknowledgements**

358 We thank all of those who gave their time to participate in the study.
359 We also thank Capsugel® (France) and Nephcentric© (USA) who
360 kindly provided us with the delayed-release (DRcaps™) and enteric-
361 coated (Bicarbi™) capsules free of charge.

362

363 **Authorships**

364 The study was designed by NH, LM and AS. Data were collected by
365 NH and NL. The manuscript was written by NH with feedback
366 provided by LM, AS and MC. All authors approved the final version
367 of the manuscript.

368

369 **Funding**

370 No funding was received for this study.

371

372 **Conflicts of interest**

373 NH, NL, MC, AS and LM can confirm that there are no competing
374 interests.

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520 **Tables**

Table 1. Frequency and severity of GI symptoms following $NaHCO_3$ ingestion (n = 14). The most frequent and severe GI symptoms are highlighted in bold.

	Overall		PLA		GEL		DEL		ENT	
Symptoms	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD
Stomach bloating	**100.0**	4.4 ± 1.9	0.0	0.0 ± 0.0	**85.7**	3.7 ± 1.8	**78.6**	3.6 ± 2.2	50.0	2.9 ± 1.2
Belching	92.9	3.5 ± 1.4	7.1	**2.0 ± 0.0**	**85.7**	3.4 ± 1.6	64.3	2.3 ± 1.4	**57.1**	2.3 ± 0.9
Bowel urgency	92.9	5.9 ± 3.0	0.0	0.0 ± 0.0	**85.7**	5.9 ± 3.1	71.4	3.8 ± 2.3	21.4	3.3 ± 1.5
Stomach ache	85.7	3.5 ± 2.3	**14.3**	1.5 ± 0.7	71.4	3.5 ± 2.6	57.1	2.2 ± 1.5	14.3	1.0 ± 0.0
Stomach cramps	78.6	4.0 ± 2.2	0.0	0.0 ± 0.0	64.3	4.4 ± 2.3	28.6	2.1 ± 0.7	7.1	3.0 ± 0.0
Flatulence	71.4	4.4 ± 2.7	0.0	0.0 ± 0.0	57.1	3.6 ± 2.9	28.6	3.0 ± 1.2	35.7	3.8 ± 2.2
Diarrhoea	64.3	**7.8 ± 3.1**	0.0	0.0 ± 0.0	50.0	**8.2 ± 3.4**	42.9	**6.2 ± 2.7**	7.1	**5.0** ± 0.0
Nausea	57.1	3.0 ± 2.4	0.0	0.0 ± 0.0	35.7	3.6 ± 2.7	35.7	1.6 ± 1.3	7.1	4.0 ± 0.0
Vomiting	14.3	1.0 ± 1.0	0.0	0.0 ± 0.0	7.1	1.0 ± 0.0	7.1	2.0 ± 0.0	0.0	0.0 ± 0.0
Any	100.0	4.2 ± 0.8	14.3	1.8 ± 0.4	100.0	4.1 ± 1.0	85.7	3.0 ± 1.4	92.9	2.8 ± 1.5

Notes: Overall percentage includes those who reported GI symptoms after at least one $NaHCO_3$ ingestion form.

522 **Table 2.** Individual peak GI symptom reported following different $NaHCO_3$ ingestion forms. Symptom scores are displayed in parentheses and are expressed as arbitrary units (AU).

Participant	PLA	GEL	DEL	ENT
1	Nil (0.0)	Bowel urgency (7.0)	Stomach bloating (3.0)	Belching (2.0)
2	Nil (0.0)	Diarrhoea (10.0)	Diarrhoea (7.0)	Belching (1.0)
3	Nil (0.0)	Stomach bloating (4.0)	Diarrhoea (5.5)	Diarrhoea (5.0)
4	Nil (0.0)	Bowel urgency (6.0)	Flatulence (5.0)	Bowel urgency (3.0)
5	Nil (0.0)	Stomach cramp (6.0)	Bowel urgency (2.0)	Belching (3.0)
6	Stomach ache (2.0)	Diarrhoea (10.0)	Stomach ache (4.5)	Nausea (3.0)
7	Nil (0.0)	Diarrhoea (10.0)	Diarrhoea (8.0)	Bowel urgency (5.0)
8	Nil (0.0)	Bowel urgency (4.0)	Stomach cramp (1.2)	Stomach bloating (3.0)
9	Nil (0.0)	Diarrhoea (10.0)	Stomach bloating (8.0)	Flatulence (6.0)
10	Nil (0.0)	Nausea (8.0)	Diarrhoea (7.0)	Belching (2.0)
11	Belching (1.0)	Belching (5.0)	Bowel urgency (2.0)	Belching (1.0)
12	Nil (0.0)	Stomach bloating (4.3)	Nil (0.0)	Nil (0.0)
13	Nil (0.0)	Diarrhoea (10.0)	Diarrhoea (8.5)	Flatulence (5.0)
14	Nil (0.0)	Stomach cramp (4.0)	Stomach bloating (3.0)	Nil (0.0)

Table 3. Within-trial variation in bicarbonate kinetic variables for different $NaHCO_3$ ingestion forms.

	GEL		DEL		ENT	
Variable	Mean ± SD	CV	Mean ± SD	CV	Mean ± SD	CV
T_{lag} (min)	21.4 ± 5.3[b,c]	24.9	30.0 ± 10.4[a]	34.6	31.4 ± 12.9[a]	41.1
C_{max} (mmol·L^{-1})	30.5 ± 1.9[c]	6.1	31.3 ± 1.4[c]	4.5	28.2 ± 0.9[a,b]	3.3
ΔC_{max} (mmol·L^{-1})	6.0 ± 1.3[c]	22.1	6.5 ± 1.2[c]	17.8	4.4 ± 0.5[a,b]	12.0
T_{max} (mmol·L^{-1})	95.0 ± 31.8[b]	33.5	119.3 ± 24.3[a]	20.4	120.0 ± 35.1	29.2
AUC (mmol·min·L^{-1})	687.6 ± 307.1[c]	44.7	741.3 ± 237.3[c]	32.0	342.7 ± 190.0[a,b]	55.5

Notes: GEL, gelatine; DEL, delayed-release; ENT, enteric-coated; CV, coefficient of variation; 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]Significant from GEL trial ($P < 0.05$). [b]Significant from DEL trial ($P < 0.05$). [c]Significant from ENT trial ($P < 0.05$). CV was calculated as 100 × (SD/μ).

524 **Figure legends**

525 **Figure 1.** Aggregated GI symptom scores (A) and mean (± SD) peak GI symptom (B) experienced following ingestion of PLA
526 and $NaHCO_3$ ingestion forms. Aggregated GI symptom scores include those who reported no symptoms (i.e. "0.0"). Error bars
527 are removed for clarity. Peak GI symptom refers to the highest individual symptom reported up to 3 h post-ingestion.
528 *Significantly greater than PLA ($P < 0.05$).

529 **Figure 2.** Mean (± standard error of the mean) blood [HCO_3^-] (A) and pH (B) pre- and post-ingestion. *Significant from GEL
530 trial ($P < 0.05$). †Significant from DEL trial ($P < 0.05$). Blood [HCO_3^-] is significantly greater ($P < 0.05$) than PLA from 20
531 min with GEL and 40 min in the DEL and ENT trials. Blood pH is significantly greater ($P < 0.05$) than PLA from 40 min in
532 the GEL and DEL trials and from 80 min with ENT.

533 **Figure 3.** Mean (± SD) (A) and individual (B) changes in blood [HCO_3^-] following ingestion of different $NaHCO_3$ ingestion
534 forms. *Significantly greater than PLA ($P < 0.05$).

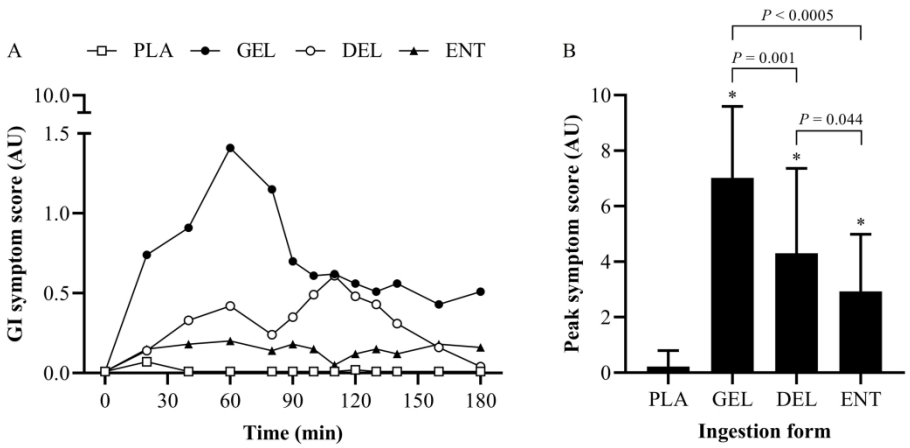

Figure 1. Aggregated GI symptom scores (A) and mean (± SD) peak GI symptom (B) experienced following ingestion of PLA and NaHCO3 ingestion forms. Aggregated GI symptom scores include those who reported no symptoms (i.e. "0.0"). Error bars are removed for clarity. Peak GI symptom refers to the highest individual symptom reported up to 3 h post-ingestion.*Significantly greater than PLA (P < 0.05).

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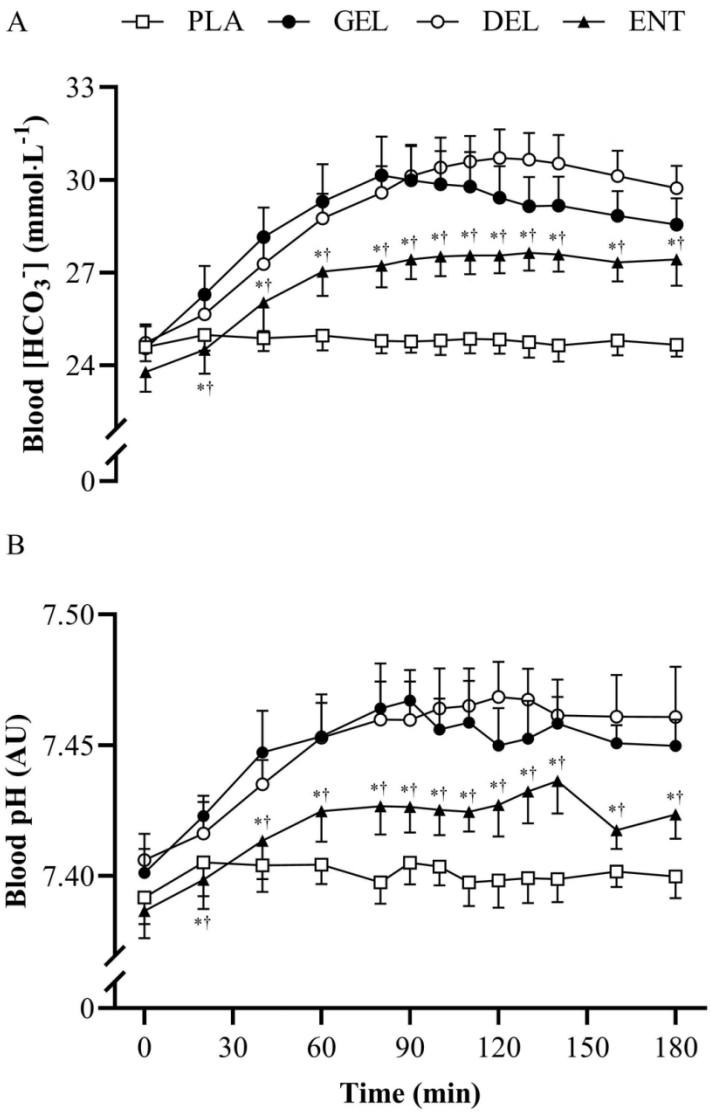

Figure 2. Mean (± standard error of the mean) blood [HCO3−] (A) and pH (B) pre- and post-ingestion. *Significant from GEL trial (P < 0.05). †Significant from DEL trial (P < 0.05). Blood [HCO3−] is significantly greater (P < 0.05) than PLA from 20 min with GEL and 40 min in the DEL and ENT trials. Blood pH is significantly greater (P < 0.05) than PLA from 40 min in the GEL and DEL trials and from 80 min with ENT.

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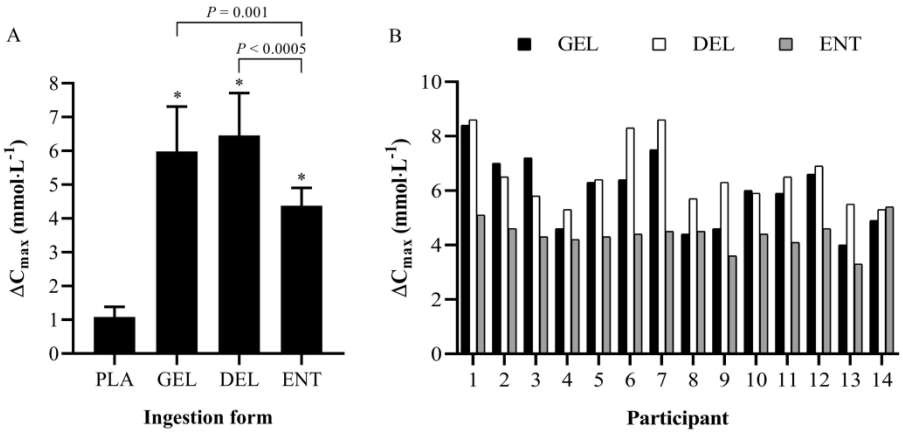

Figure 3. Mean (± SD) (A) and individual (B) changes in blood [HCO3−] following ingestion of different NaHCO3 ingestion forms. *Significantly greater than PLA (P < 0.05).

268x131mm (300 x 300 DPI)