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The blood acid base and gastrointestinal response to three different forms of sodium citrate encapsulation

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ABSTRACT

Enterically coated (ENT) or delayed-release (DEL) capsules may lessen gastrointestinal symptoms (GIS) following acute sodium citrate (SC) ingestion, although the effects on blood acid-base balance are undetermined. Fourteen active males ingested 0.4 $g.kg^{-1}$ body mass (BM) SC, within gelatine (GEL), DEL and ENT capsules or 0.07 $g.kg^{-1}$ BM sodium chloride control (CON). Blood acid-base balance and GIS were measured for 4 h. Ingestion form had no significant effect on total GIS experienced (GEL: 2 ± 7; DEL: 1 ± 8; ENT: 1 ± 4 AU). Most (7/14) participants experienced zero symptoms throughout. Peak GIS typically emerged ≤100 min post-ingestion, with a similar time to reach peak GIS between ingestion form (GEL: 36 ± 70; DEL: 13 ± 28; ENT: 15 ± 33 AU). Blood [HCO_3^-] was significantly higher with ENT versus GEL (ENT: 29.0 ± 0.8; GEL: 28.5 ± 1.1 $mmol.L^{-1}$, $P = 0.037$). Acute ingestion of a reduced SC dose elicited minimal GIS, producing significant changes in blood [HCO_3^-] from rest, irrespective of ingestion form (GEL: 6.0 ± 0.9; DEL: 5.1 ± 1.0; ENT: 6.2 ± 0.8 $mmol.L^{-1}$). The necessity of individualized ingestion strategies is also challenged, with sustained increases in blood [HCO_3^-] of ≥4 $mmol.L^{-1}$ for up to 153 min highlighted. If commencing exercise at peak alkalosis augments subsequent performance above starting at a standardized time point where HCO_3^- is still elevated remains unclear.

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Bicarbonate; buffering; fatigue; peripheral

Introduction

High-intensity to endurance-intensive efforts (>6 s to 1+ min) is associated with high levels of glycolytic flux (van Loon *et al.*, 2001; Romjin *et al.*, 1993), simultaneous to reductions in both muscle and blood pH and [HCO_3^-] (Fitts, 1994). Elevated H^+ production versus removal rate may quickly exceed the limits of endogenous HCO_3^- buffering capacity, contributing to a decline in muscular contractile force and velocity, by interfering with multiple metabolic and contractile processes (Jarvis *et al.*, 2018; Sundberg *et al.*, 2018; Keyser, 2010; Allen, Lamb and Westerblad, 2008; Fitts, 1994). Exogenously

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administering extracellular buffers to increase [HCO_3^-] buffering capacity (Heibel et al., 2018) appears a logical method to support pH regulation during such intense efforts.

Theoretically, any increase in circulating [HCO_3^-] would lead to a corresponding increase in buffering capacity, with sodium citrate (SC) ingestion shown to elevate blood alkalosis when compared to baseline or placebo (Urwin et al., 2019). While further investigation is required to elucidate the minimal change in [HCO_3^-] necessary to induce a performance effect, de Oliveira et al. (2021) recently observed greater effects following increases of 4–6 mmol.L^{-1} from baseline. The ingestion of the recommended quantities of SC (0.4–0.5 g.kg^{-1} body mass (BM)) (Cerullo et al., 2020; Urwin et al., 2021) typically elicits changes in blood [HCO_3^-] of 5–8 mmol.L^{-1} (Urwin et al., 2019; Russell *et al*., 2014; Vaher *et al*., 2014). These doses are recommended to maximize blood alkalosis, with further increases providing limited additive ergogenic benefit while also increasing the risk of gastrointestinal symptoms (GIS) (McNaughton, 1990, 1991; Urwin et al., 2019, 2016).

Such large doses of SC are necessary as immediately post-ingestion it rapidly dissociates into Na^+ and citrate (Requena et al., 2005). Citrate is then removed from the plasma, unbalancing the electrical equilibrium (Devlin, 2010). Electrical neutrality is restored by a decrease in [H^+] and an increase in [HCO_3^-], creating the alkalotic response observed post-ingestion (Peacock et al., 2021; Urwin et al., 2019, 2021). At a dose of 0.4 g.kg^{-1} BM (28 g for a 70 kg individual) blood HCO_3^- may increase by ~5 mmol · L^{-1} (Cunha et al., 2019), equating to only 17% of the expected increase in HCO_3^- if the entire dose entered the blood (considering SC should increase [HCO_3^-] by ~29.6 mmol.L^{-1} in 5 L of blood). Following identical calculations for sodium bicarbonate (SB), de Oliveira et al. (2018) suggested that the majority of ingested HCO_3^- is neutralized in gastric acids or may be removed in faeces to a smaller degree. Logically, avoiding such losses of HCO_3^- would yield larger increases in [HCO_3^-] and mitigate GIS. An optimal SC ingestion protocol is then one which maximizes blood alkalosis (pH and/or HCO_3^-) and minimizes the potential of GIS (Cerullo et al., 2020 and Urwin *et al*., 2021). This may be addressed by manipulating ingested dose (McNaughton, 1990, 1991; Urwin et al., 2019, 2016) and/or timing (Gough et al., 2017, 2018; Miller et al., 2016), or more novel approaches such as the use of different delivery modes – capsules rather than solution.

Multiple forms of encapsulation have been trialled with the purpose of avoiding degradation in the stomach, achieved by utilizing the variable pH across the gastrointestinal (GI) tract, meaning degradation of "gastroresistant capsules" occurs primarily in the less acidic duodenum (pH 6–7 arbitrary units [AU]) (Barbosa et al., 2017). Gastric acid neutralization is therefore limited, lessening GIS that would otherwise develop alongside elevated CO_2 tension in the stomach (Hilton et al., 2020).

Hilton et al. (2019) observed reduced incidence/severity of GIS following the administration of delayed-release (DEL) SB, compared to aqueous delivery. Additionally, some individuals have benefitted from augmented bicarbonate bioavailability (≤2 mmol.L^{-1}), supporting the need for ingestion based on individual blood analyte responses. In the sole example, Peacock et al. (2021) recently compared the pharmacokinetic and GIS response to ingesting SB and SC in DEL capsules at an identical dose

(0.3 g.kg^{-1} BM). While both substances induced significant alkalosis, SB resulted in a greater change in blood [HCO_3^-]. SC ingestion was also associated with reduced GIS, although at a dose that has yet to consistently demonstrate ergogenicity. Given the value

of reduced GIS, there is a demand for future research to understand the minimum effective dose(s) (Peacock et al., 2021; Urwin *et al*., 2016).

Hilton et al. (2020) later demonstrated that enterically coated (ENT) capsules have the capacity to further attenuate GIS versus gelatine (GEL) and DEL capsules, providing an additional option for those who experience notable GIS, at an added financial cost. Moreover, changes in blood alkalosis

([HCO_3^-] and pH) were lower with ENT SB, possibly due to increased absorption across the intestinal mucosa (Turnberg et al., 1970) alongside declining absorption time (Hilton et al., 2020). Given that the level of induced alkalosis may limit performance effects following both SB and SC (de Oliveira et al., 2021), ENT capsules may improve the GIS response at the expense of performance (Hilton et al., 2020).

At present, no research has compared the blood acid-base and GIS response to SC ingestion between GEL, DEL or ENT capsules. Successfully minimizing GIS, while understanding the potential implications for performance (i.e., level of blood alkalosis induced) at an apparently ergogenic dose (0.4 $g.kg^{-1}$ BM) would be of high value to athletes and practitioners. Therefore, the aim of this study was to determine the blood acid-base and GIS responses to the ingestion of 0.4 $g.kg^{-1}$ BM SC, administered in GEL, DEL and ENT capsules.

Methods

Participants

Fourteen active males (age 27 ± 4, BM 81.4 ± 8.9 kg, peak oxygen uptake 41.43 ± 13.03 $mL.kg^{-1}min^{-1}$) were recruited for this study. Participants completed regular exercise training (≥3 d . $week^{-1}$) for at least 2 years and were free of GI-related issues. Exclusion criteria also required that participants were not following a salt-restricted diet or ingesting other buffering agents simultaneous to the current study. All experimental procedures were explained fully, with questions addressed before the provision of written, informed consent. Ethical approval was given by the institutional ethics committee (SPA-REC-2019-252R1).

Experimental overview

In a double-blind, randomized crossover design, participants attended the laboratory on five separate occasions. Following an initial visit (detailed below), experimental trials consisted of a control (CON) and three SC trials, wherein SC was ingested in gelatine (GEL), delayed-release (DEL) or enteric-coated (ENT) capsules. Experimental trials were counterbalanced using block randomization and completed at least 48 h apart to facilitate washout of residual blood HCO_3^- (Siegler et al., 2012). Participants abstained from alcohol or caffeine beverages (El-Sayed et al., 2005; Guest et al., 2021) for 12 h and strenuous exercise 24 h (Tornero-Aguilera et al., 2022) before each trial.

During the initial visit, peak VO_2 was determined using a previously outlined protocol (Deb et al., 2018), involving 5 min unloaded pedalling (no added resistance) into a ramped increase of 0.5 W · s^{-1} (30 W . min^{-1}), until volitional exhaustion was reached (Excalibur Sport, Lode, Netherlands). Experimental trials were completed at a similar time-of-day to

account for circadian variation (Ayala et al., 2021). Participants arrived at the laboratory following an overnight fast. Participants then ingested 0.4 $g.kg^{-1}$ BM SC in each either GEL, DEL or ENT capsules or the CON (0.07 $g.kg^{-1}$ BM sodium chloride) (Gough et al., 2017) which was administered in size 0 opaque (white) capsules. Capsules were provided in an opaque (black) tub to lessen the visual impact of the large numbers of capsules to be ingested.

All capsules were manually filled by a laboratory technician using a capsule filling device (Capsule Connection LLC, USA) with doses tested for accuracy regularly (Fisher, OHAUS^{TM}). Capsules were consumed with 500 ml of room temperature water (18°C). After ingestion, water was permitted *ad libitum* with consumption throughout the first trial recorded and replicated as accurately as possible in subsequent trials. Excluding toilet breaks, participants remained seated throughout.

Acid-base balance responses

The response to ingestion was determined based on the time course of blood [HCO_3^-] and pH changes over a 4 h sampling period. Fingertip capillary blood samples (95 µL) were obtained pre-ingestion and a further 14 times, spread equally over the 238 min window. Samples were collected in heparin-coated capillary tubes (Radiometer Medical Ltd, Denmark) and analysed immediately (Radiometer ABL800 BASIC, Denmark) for blood [HCO_3^-] and pH. Blood HCO_3^- measurements were then used to establish the key characteristics of each form of encapsulation, 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} is taken as the point at which blood [HCO_3^-] increased beyond normal daily fluctuation, established individually following ingestion of CON. Data describing individual responses for both blood HCO_3^- and pH is also provided.

Gastrointestinal symptoms

At each interval, a GI questionnaire was completed to assess the severity of a range of GI symptoms using a visual analogue scale ([VAS] where 0 = no symptom and 10 = most severe) (Gough et al., 2017). Symptoms include nausea, flatulence, stomach cramping, belching, stomach-ache, bowel urgency, diarrhoea, vomiting and stomach belching.

Results

Gastrointestinal symptoms

There was no significant effect of ingestion form on total GIS experienced ($F_{3,39} = 1.316$, $P = 0.283$, $\eta p2 = 0.092$). Total symptoms were also not significantly different in either GEL (6.7 ± 13.2 AU), DEL (4.8 ± 15.7 AU), ENT (1.9 ± 5.3 AU) or CON (0.3 ± 1.1 AU) ($F_{3,36} = 2.359$, $P = 0.148$, $\eta p2 = 0.164$). Seven of fourteen participants experienced no symptoms irrespective of ingestion form or sample time post-ingestion (Table 1).

Peak individual GIS typically occurred ≥100 min post-ingestion. Whilst the highest individual symptom occurred earlier following ENT (51 ± 48 min) compared to other ingestion forms (GEL = 102 ± 88 min; DEL 62 ± 20 min), ingestion form had no significant

Table 1. Individual peak GIS reported following different sodium citrate ingestion forms. Symptom scores are displayed in parentheses and are expressed as arbitrary units (AU).

Participant	GEL	DEL	ENT	CON
1	Nausea (3.0)	Flatulence (3.0)	Flatulence (1.0)	None (0.0)
2	Nausea (6.0)	None (0.0)	None (0.0)	None (0.0)
3	None (0.0)	None (0.0)	None (0.0)	None (0.0)
4	None (0.0)	None (0.0)	None (0.0)	None (0.0)
5	None (0.0)	None (0.0)	Flatulence (3.0)	None (0.0)
6	None (0.0)	None (0.0)	None (0.0)	None (0.0)
7	None (0.0)	None (0.0)	None (0.0)	None (0.0)
8	Flatulence (2.0)	Flatulence (3.0)	Flatulence (3.0)	None (0.0)
9	Bowel urgency (4.0)	None (0.0)	None (0.0)	None (0.0)
10	None (0.0)	None (0.0)	None (0.0)	None (0.0)
11	None (0.0)	None (0.0)	None (0.0)	Vomiting (4.0)
12	None (0.0)	None (0.0)	None (0.0)	None (0.0)
13	None (0.0)	None (0.0)	None (0.0)	None (0.0)
14	Bowel urgency (4.0)	Diarrhoea (8.0)	Bowel urgency (4.0)	None (0.0)

Peak symptoms were determined based on the earliest occurrence of the largest individual value reported (AU).

effect on the time-to-reach peak GIS ($F_{2,26} = 1.857$, $P = 0.176$, $\eta_p^2 = 0.125$). Only one participant experienced GIS at the point of T_{max} in the GEL trial (rated as 1/10 AU only), with no further instances of GIS at T^{max}. Furthermore, this participant appeared to display high GIS relative to the remaining sample, based on greater total symptom scores compared to mean values for GEL (7 vs 2 ± 7 AU).

Five of fourteen participants experienced at least one GIS in the GEL trial, whereas only three and four participants experienced GIS following DEL and ENT, respectively. One participant recorded GIS in the CON trial, which occurred around the time of ingestion. Flatulence (24.1%), stomach bloating (20.7%) and bowel urgency (19.0%) represented the most common GIS overall, with diarrhoea (5.3 ± 3.1), vomiting (4 ± 0) and bowel urgency (3.6 ± 1.2) providing the highest severity ratings overall (Table 2).

Acid-base responses

Ingestion form had a significant effect on blood [HCO_3^-] ($F_{2,12} = 5.1$, $P = 0.025$, $\eta_p^2 = 0.459$) but not on pH ($F_{1.6,6.3} = 1.7$, $P = 0.242$, $\eta_p^2 = 0.299$) and [Na^+] ($F_{2,8} = 1.51$, $P = 0.278$, $\eta_p^2 = 0.274$). Blood [HCO_3^-] was significantly higher with ENT versus GEL ($P = 0.037$). In the post-ingestion period, there were significant effects on blood [HCO_3^-] ($F_{14,84} = 254.72$, $P < 0.001$, $\eta_p^2 = 0.977$), pH ($F_{2.9,11.6} = 64.521$, $P < 0.001$, $\eta_p^2 = 0.942$) and [Na^+] ($F_{14,56} = 29.026$, $P = <0.001$, $\eta_p^2 = 0.879$). Blood [HCO_3^-] and pH were significantly elevated above baseline from 34 to 136 min post-ingestion and remained significantly elevated throughout the remaining sampling period. Blood [Na^+] was significantly elevated above baseline from 102- to-170 min post-ingestion. Significant trial × time interactions emerged for blood [HCO_3^-] ($F_{28,168} = 3.867$, $P < 0.001$, $\eta_p^2 = 0.942$) and [Na^+] ($F_{28,112} = 2.360$, $P < 0.001$, $\eta_p^2 = 0.371$). There were no significant trial × time interactions for blood pH ($F_{2.64,10.55} = 1.831$, $P = 0.204$, $\eta_p^2 = 0.314$). Time course responses for blood [HCO_3^-] and pH are presented in Figure 1.

After SC ingestion, ΔC_{max} was significantly higher in the ENT trial than DEL ($P = 0.027$), however, values were similar between ENT and GEL ($P = 0.794$) GEL and DEL ($P = 0.112$) (6.2 ± 0.8 versus 6.0 ± 0.9 mmol.L^{-1} and 6.0 ± 0.9 and 5.1 ± 1.0 mmol.L^{-1}, respectively)

Table 2. Frequency and severity of GIS reported following sodium citrate ingestion ($n = 14$). The most frequent and severe GIS are highlighted.

	Overall		GEL		DEL		ENT		CON	
Symptoms	%	*Mean ± SD*	%	*Mean ± SD*	%	*Mean ± SD*	%	*Mean ± SD*	%	*Mean ± SD*
Nausea	8.6	3.4 ± 1.9	**17.9**	**3.4 ± 1.9**	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0
Flatulence	**24.1**	2.6 ± 1.2	**17.9**	2.0 ± 0.0	**28.6**	**3.4 ± 1.7**	**33.3**	**2.0 ± 1.0**	0.0	0.0 ± 0.0
Stomach cramp	3.4	1.0 ± 0.0	0.0	0.0 ± 0.0	9.5	1.0 ± 0.0	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0
Bowel urgency	**19.0**	**3.6 ± 1.2**	**10.7**	**3.0 ± 1.0**	**23.8**	**4.2 ± 1.5**	**33.3**	**3.3 ± 0.6**	0.0	0.0 ± 0.0
Diarrhoea	5.2	**5.3 ± 3.1**	7.1	**4.0 ± 2.8**	4.8	**8.0 ± 0.0**	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0
Vomiting	1.7	**4.0 ± 0.0**	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	**100**	**4.0 ± 0.0**
Stomach bloating	**20.7**	2.4 ± 0.7	**17.9**	2.0 ± 0.0	**19.0**	2.8 ± 1.0	**33.3**	**2.7 ± 0.6**	0.0	0.0 ± 0.0
Belching	5.2	2.0 ± 0.0	7.1	2.0 ± 0.0	4.8	2.0 ± 0.0	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0
Stomach-ache	12.1	2.0 ± 0.6	**21.4**	2.3 ± 0.5	9.5	1.5 ± 0.7	0.0	0.0 ± 0.0	0.0	0.0 ± 0.0
Any	0.8	2.8 ± 1.3	1.5	2.7 ± 0.5	1.1	3.3 ± 0.7	0.5	2.7 ± 0.2	0.1	0.4 ± 0.0

Overall percentage includes those who reported GIS after at least one sodium citrate form. Any percentage describes instances of reported GIS relative to total scores reported.

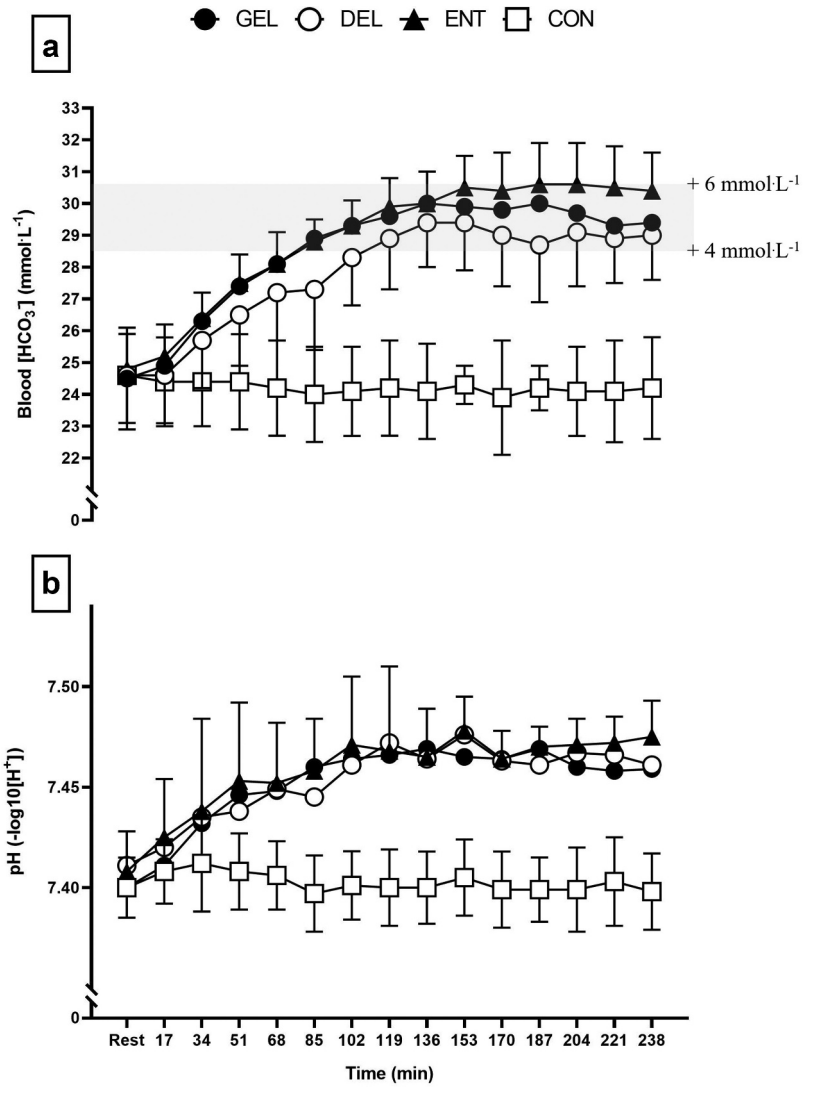

Figure 1. Mean (± standard deviation) blood [HCO_3-] (a) and pH (b) pre- and post-intgestion of 0.4 gKg^{-1} body mass sodium citrate, in gelatine (GEL), delayed-release (DEL) and entericcoated (ENT) capsules. The shaded area represents a 4-6 $mmol.L^{-1}$ increase in blood [HCO_3-] relative to basline levels. *Some error bars are omitted for clarity.

(Figure 2). T_{max} occurred significantly earlier following GEL compared to ENT ($P = 0.023$), while T_{max} values were otherwise similar between trials. Blood pH peaked at similar time points ($P > 0.05$) between GEL (153 ± 27 min), DEL (169 ± 42 min) and ENT (179 ± 33 min). Absolute changes in peak blood pH were also similar ($P > 0.05$) in GEL (0.084 ± 0.018), DEL (0.075 ± 0.032) and ENT (0.084 ± 0.022) trials. Blood HCO_3^- kinetics for each form of encapsulation are displayed in Table 3.

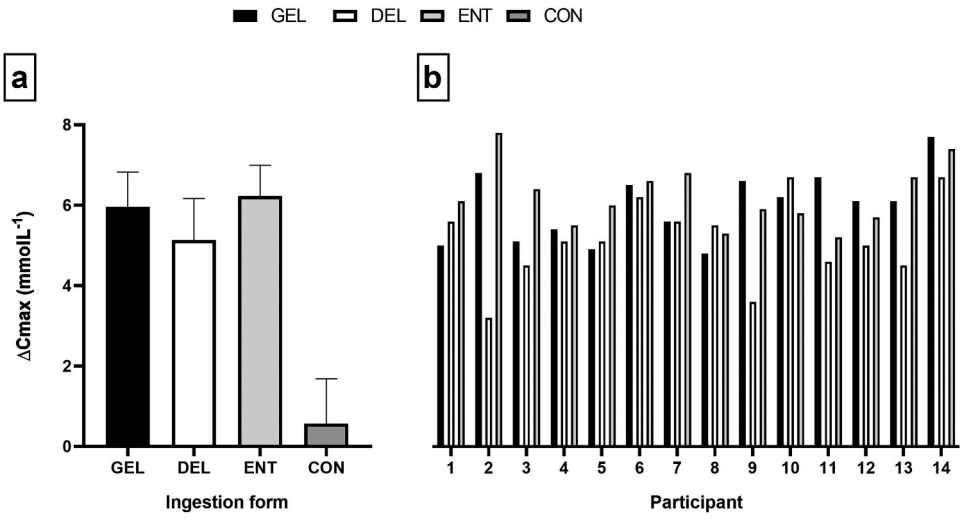

Figure 2. Mean (± SD) (a) and individual (b) changes in blood [HCO_3-] following ingestion of different sdium citrate ingrestion forms. *signification greated than PLA (P<0.05).

Table 3. Within trial variation in bicarbonate kinetic variables for different sodium citrate ingestion forms.

	GEL		DEL		ENT	
Variable	*Mean ± SD*	*CV*	*Mean ± SD*	*CV*	*Mean ± SD*	*CV*
T_{lag} (min)	31.0 ± 10.9	35.1	40.1 ± 21.7	54.2	34.1 ± 13.3	39.1
C_{max} (mmol.L^{-1})	30.4 ± 0.9	3.0	29.8 ± 1.6[c]	5.2	31 ± 1.1[b]	3.6
ΔCmax (mmol.L^{-1})	6.0 ± 0.9	14.4	5.1 ± 1.0[c]	20.1	6.2 ± 0.8[b]	12.3
T_{max} (mmol.L^{-1})	153 ± 27.4[c]	17.9	168.8 ± 42.4	25.1	178.5 ± 32.5[a]	18.2
AUC (mmol.min.L^{-1})	400.5 ± 10.0	2.5	390.5 ± 20.6	5.3	401.1 ± 20.1	5

GEL, gelatine; DEL, delayed-release; ENT, enteric-coated; CV, coefficient of variation; Tlag, lag time; Cmax, peak bicarbonate concentration; ΔCmax, change in peak bicarbonate concentration; Tmax, time to peak bicarbonate concentration; AUC, area under the curve, aSignificant from GEL trial (P < 0.05). bSignificant from DEL trial (P < 0.05). Significant from ENT trial (P < 0.05). CV calculated as 100 × (SD/m).

Discussion

This study represents the first investigation to compare the effects of capsule ingestion form on GIS and acid-base responses following individualized SC ingestion. The GIS and blood acid-base responses following the ingestion of SC in ENT capsules were also measured for the first time. Ingestion form had no significant effect on GIS, with GEL, DEL and ENT capsules eliciting similar average total symptom scores and TTP symptoms. Although ΔC_{max} was significantly higher following ENT versus DEL capsules, all forms of encapsulation promoted potentially meaningful changes in blood [HCO_3^-] of 4 + mmol.L^{-1} in all but two instances (ΔC_{max}: 3.2 and 3.6 mmol.L^{-1}). This aligns with the work of de Oliveira et al. (2021) who reported evidence of greater effects on exercise performance when ΔC_{max} was 4–6 mmol.L^{-1} versus ≤4 mmol.L^{-1}. Collectively, the necessity of different forms of SC encapsulation is challenged, with limited differences in GIS and blood acid-base kinetics.

Overall SC elicited minor GIS, with low frequency (0.8% of all possible instances) and severity (2.8 ± 1.3 AU) of symptoms reported throughout (Table 2). Half (7/14) of all participants reported zero GIS, supporting the notion that GIS following SC ingestion may induce reduced GIS, often discussed relative to SB (Maughan et al., 2018). Despite this, Urwin et al. (2022) recently observed no significant difference in GIS severity, reporting similarities in frequency of severe GIS (≥5 AU) of 9–10% of all cases, with 31–37% of all participants reporting one or more severe symptoms. Gastrointestinal symptoms (any score) were reported by 28.6% of all participants herein, which is lower than previous studies (Urwin et al., 2019, 2021, 2022). This may be partly explained by the use of a lower dose in the present study (0.4 compared to 0.5 $g.kg^{-1}$ BM). Further, direct comparison with GIS reported following the ingestion of SC is difficult, given the use of differing approaches to measuring GIS.

Flatulence, stomach bloating and bowel urgency represented the most common GIS overall, whereas the severity of diarrhoea, vomiting and bowel urgency were notably high. Frequency of symptoms reported did not exceed 1.5% across all capsule forms, with a greatest average severity of 3.3 ± 0.7 AU (Table 2). Whilst ENT SC resulted in a lesser average total symptom score (1.9 ± 5.3 AU) relative to DEL capsules (4.8 ± 15.7 AU) which, in turn, elicited fewer total symptoms than GEL capsules (6.7 ± 13.2 AU), these differences were not statistically significant. Interestingly, diarrhoea was not reported following ENT SC only, which may merit further consideration for practical application with athletes who may otherwise avoid supplementation. Mean GIS scores for SC ingested in DEL capsules were higher than previously reported (4.8 ± 15.7 versus 1.5 ± 1.8 AU) (Peacock et al., 2021), although a greater quantity was provided herein (0.4 versus 0.3 $g.kg^{-1}$ BM).

Use of multiple forms of encapsulation have been deployed with the purpose of avoiding degradation in the stomach, potentially lessening GIS that may arise alongside increased stomach CO_2 tension (Hilton et al., 2020), translating to changes in TTP blood alkalosis and potentially GIS (Hilton et al., 2019; Middlebrook et al., 2021; Peacock et al., 2021). Accordingly, it is unclear why a similar TTP GIS emerged between ingestion forms, typically occurring within 100 min of ingestion and in relative agreement with peak ratings ~60–90 min provided elsewhere (Urwin et al., 2021, 2022). Furthermore, how the severity of specific GIS may impact performance remains elusive, yet this may clarify why some studies have found GIS symptoms to limit performance (Cameron et al., 2010; Deb et al., 2018; Saunders et al., 2014), whereas others have not (Miller et al., 2016; Price & Simons, 2010). Future studies may aim to further clarify the relationship between GIS and willingness to commence/continue exercise (Urwin et al., 2022). Furthermore, only one participant experienced symptoms at the point of peak blood [HCO_3^-] (1 AU), suggesting that the peak alkalotic response may emerge somewhat separately to GIS.

Theoretically, any increase in circulating [HCO_3^-] following the ingestion of SC would lead to a corresponding increase in extracellular buffering capacity (Heibel et al., 2018). Whilst the minimal changes necessary to induce ergogenic effects are unclear, data suggest greater effects occurred when blood [HCO_3^-] increases were moderate (4–6 $mmol.L^{-1}$) to large (>6 $mmol.L^{-1}$) (de Oliveira et al., 2021). Whether absolute increases at TTP differ substantially from those at standardized time points is unknown. Indeed, the mean increase shown at time-to-peak by Gough et al. (2018) (+6.5 ± 1.3 $mmol.L^{-1}$) resembles increases shown at 60 min (+6.1 Froio de Araujo Dias et al., 2015; +5.1; Jones et al., 2016; +5.7; Gough et al., 2017), 90 min (+6.5 Jones et al.,

Table 4. Individual blood bicarbonate (HCO_3^-) and pH responses following the ingestion of 0.4 $g.kg^{-1}$ body mass sodium citrate, in gelatine (GEL), delayed-release (DEL) and enteric-coated (ENT) capsules.

	Participant													
GEL	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
HCO_3^- (mmol.L^{-1})														
Baseline	24.9	25.4	24.9	24.3	25.0	23.8	24.1	24.4	24.5	24.2	25.5	23.8	24.6	23.1
C_{max}	29.9	32.2	30.0	29.7	29.9	30.2	29.7	29.2	31.1	30.4	32.2	29.9	30.7	30.8
ΔC_{max}	5.0	6.8	5.1	5.4	4.9	6.5	5.6	4.8	6.6	6.2	6.7	6.1	6.1	7.7
T_{max} (min)	153	170	119	170	136	187	136	153	204	187	136	170	119	153
pH (-log10[H^+])														
Baseline	7.370	7.376	7.409	7.394	7.432	7.381	7.401	7.400	7.389	7.402	7.399	7.384	7.382	7.375
Peak	7.439	7.459	7.448	7.476	7.534	7.465	7.480	7.501	7.479	7.520	7.475	7.473	7.456	7.468
Absolute change	0.069	0.083	0.039	0.082	0.102	0.084	0.079	0.101	0.090	0.118	0.076	0.089	0.074	0.093
Time to peak (min)	204	170	153	153	136	170	102	102	170	187	136	170	170	204
DEL														
HCO_3^- (mmol.L^{-1})														
Baseline	26.4	26.4	20.8	24.4	24.2	24	23.7	23.9	27.2	22.8	26.2	24.6	25.1	24.9
C_{max}	32.0	29.6	25.3	29.5	29.3	30.2	29.3	29.4	30.8	29.5	30.8	29.6	29.6	31.6
ΔC_{max}	5.6	3.2	4.5	5.1	5.1	6.2	5.6	5.5	3.6	6.7	4.6	5.0	4.5	6.7
T_{max} (min)	153	204	153	136	119	238	136	119	238	204	136	136	204	187
pH (-log10[H^+])														
Baseline	7.403	7.432	7.418	7.410	7.396	7.400	7.418	7.412	7.411	7.390	7.427	7.409	7.407	7.410
Peak	7.488	7.454	7.459	7.494	7.478	7.482	7.502	7.560	7.472	7.511	7.471	7.486	7.478	7.464
Absolute change	0.085	0.022	0.041	0.084	0.082	0.082	0.084	0.148	0.061	0.121	0.044	0.077	0.071	0.054
Time to peak (min)	153	153	136	153	102	170	187	119	221	221	136	153	153	119
ENT														
HCO_3^- (mmol.L^{-1})														
Baseline	25.7	24.9	25.3	24.6	24.2	24.9	22.5	24.4	26.8	23.7	26.2	24.7	25.0	23.8
C_{max}	31.8	32.7	31.7	30.1	30.2	31.5	29.3	29.7	32.7	29.5	31.4	30.4	31.7	31.2
ΔC_{max}	6.1	7.8	6.4	5.5	6.0	6.6	6.8	5.3	5.9	5.8	5.2	5.7	6.7	7.4
T_{max} (min)	153	187	187	221	153	221	136	187	221	153	119	204	187	170
pH (-log10[H^+])														
Baseline	7.402	7.403	7.406	7.412	7.420	7.375	7.374	7.452	7.422	7.409	7.424	7.398	7.403	7.375
Peak	7.468	7.477	7.473	7.495	7.502	7.447	7.480	7.601	7.497	7.498	7.493	7.480	7.469	7.469
Absolute change	0.066	0.074	0.067	0.083	0.082	0.072	0.106	0.149	0.075	0.089	0.069	0.082	0.066	0.094
Time to peak (min)	221	136	238	119	153	136	102	119	238	187	238	153	238	204

2016; +6.1; Gough et al., 2017) and 120 min (+6.5 Jones et al., 2016; +5.6; Gough et al., 2017) with a matched 0.3 g.kg^{-1} BM aqueous dose of SB. Pertinent to the current study, blood HCO_3^- concentration was similar 60, 120 and 180 min post-ingestion in GEL capsules (Siegler et al., 2012).

Post ingestion of SC, ΔC_{max} was significantly higher following ENT SC compared to DEL, however ΔC_{max} between ingestion forms was otherwise similar (Figure 2). Across all forms, blood [HCO_3^-] was significantly elevated above baseline from 34-min post ingestion and throughout the remaining sampling period. Mean data revealed ΔC_{max} ≥4 mmol.L^{-1} after 85–102 min had elapsed, remaining elevated (GEL: +5.3 ± 0.8 mmol.L^{-1}; DEL: +5.0 ± 0.8 mmol.L^{-1}; ENT: +5.5 ± 0.8 mmol.L^{-1}) for up to 153 min (153, 136 and 136 min, respectively) post-ingestion. Notable inter-individual variance was evident for ΔC_{max} (GEL: 4.8–7.7; DEL: 3.2–6.7; ENT: 5.2–7.8, mmol.L^{-1}), although ΔC_{max} failed to exceed 4 mmol.L^{-1} on only two occasions, during the DEL trial (3.2 and 3.6 mmol.L^{-1}) (Table 4).

Collectively, it appears that SC in GEL, DEL or ENT capsule form could offer a "window of ergogenicity" that may equate to ~153 min or more, commencing after at least 85 min. Where TTP blood [HCO_3^-] has been proposed as a method of optimizing the ingestion of buffering agents (Gough et al., 2017; Miller et al., 2016), it would appear unnecessary given observations here. Contesting this, Boegman et al. (2020) recently demonstrated significant improvements in the rowing performance (200 m time trial) performance of 18/23 world class rowers, utilizing an individualized TTP strategy compared to a standardized approach (367.0 ± 10.5 s vs. = 369.0 ± 10.3 s). Improvements emerged with only a 0.5 mmol.L^{-1} difference (5.5 versus 6.0 mmol.L^{-1}) in resting HCO_3^-, suggesting that small changes in HCO_3^- may induce performance effects, or other mechanisms may be plausible (Newbury et al., 2021).

Conclusion

The ingestion of 0.4 g.kg^{-1} BM SC induces limited GIS, with no significant differences across GEL, DEL or ENT capsules, although minor differences may require practical consideration. While small differences in HCO_3^- kinetics are highlighted between capsule type, meaningful and sustained changes in blood [HCO_3^-] beyond potentially ergogenic thresholds were observed across all. Taken together, SC may offer a large(r) "window of ergogenicity" relative to SB, with limited GIS. Although the utility of an individualized approach to SC ingestion remains to be elucidated, the data presented here represent a potential alternative for SC, particularly when determining individual TTP is not possible. Future investigations should seek to translate GIS and blood acid-base responses provided here to exercise contexts, comparing both generalized and individualized approaches.

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