FEATURE ARTICLE

Current Understanding of Sodium N-(8-[2-Hydroxylbenzoyl] Amino) Caprylate (SNAC) as an Absorption Enhancer: The Oral Semaglutide Experience

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Oral administration of peptide therapeutics faces challenges because of the distinct environment of the gastrointestinal tract. An oral formulation of semaglutide, a glucagon-like peptide 1 receptor agonist, was approved by the U.S. Food and Drug Administration in 2019 as a peptide therapy for the treatment of type 2 diabetes. Oral semaglutide uses sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) technology to enhance the absorption of semaglutide in the stomach and protect it from degradation by gastric enzymes. This article presents a summary of studies investigating SNAC technology as an absorption enhancer for a number of molecules and, in particular, explores how SNAC, once coformulated with oral semaglutide, facilitates increased absorption and bioavailability. Practical advice and dispensing information for pharmacists is also provided.

KEY POINTS

- Oral delivery of protein and peptide therapeutics can be challenging because of obstacles presented by the gastrointestinal tract environment.
- Sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC) technology has been used to enhance the absorption of semaglutide and protect it from degradation by gastric enzymes when administered orally, leading to its approval as the first oral glucagon-like peptide 1 receptor agonist for the treatment of type 2 diabetes.
- Co-formulation of semaglutide with SNAC does not have any appreciable effects on half-life, efficacy, or safety compared with the subcutaneous formulation of semaglutide.

Peptide and protein therapeutics is a rapidly expanding area of pharmaceutical research (1). However, most of these therapies are only available for injectable administration, despite oral administration being desirable for many patients (1).

Oral drug delivery can be challenging because of various obstacles presented by the gastrointestinal (GI) tract, including complex pH environments, digestive enzymes, mucus barriers, and epithelial permeability (2). These obstacles are multiplied for peptide and protein therapeutics, which are unstable in acidic environments and susceptible to proteolysis by GI enzymes, and their absorption may be affected by their size (1). To overcome these obstacles, an oral formulation of a protein or peptide drug must preserve the drug's structure, protect it from proteolysis, and allow its absorption into the bloodstream (1).

Various methods have been proposed to enable oral delivery of protein and peptide therapeutics, including coadministration of compounds that alter the physiology of the GI tract, drug modifications, and delivery of the drug via a carrier, which was reviewed by Wagner et al. (1). More recently, approaches based on physical interactions (e.g., magnetic, acoustic, and mechanical forces) have shown promise in improving drug permeability, as reviewed by Luo et al. (3).

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Peptide therapeutics are important in the treatment of type 2 diabetes, with insulin required by many patients (4). Glucagon-like peptide 1 (GLP-1) receptor agonists have also become well-established peptide therapies for the treatment of type 2 diabetes and are an efficacious treatment option, offering effective glycemic control, weight loss, and a low risk of hypoglycemia (4). According to American Diabetes Association guidelines, GLP-1 receptor agonists are among the preferred glucose-lowering treatment options for people with type 2 diabetes who have not achieved their A1C target, as well as those who would benefit from weight management (4). Some GLP-1 receptor agonists (as well as sodium–glucose cotransporter 2 inhibitors) may be of particular benefit in people with type 2 diabetes who have established, or are at high risk of, cardiovascular disease (4). GLP-1 receptor agonists are generally administered subcutaneously; however, the first oral GLP-1 receptor agonist (semaglutide) was approved by the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of type 2 diabetes (5). Oral semaglutide has the potential to address some of the challenges associated with injectable therapies, such as easing administration issues and suboptimal patient adherence, which is associated with poor glycemic control, and increased health care resource use and medical costs (6).

This review discusses the importance of the availability of an oral GLP-1 receptor agonist for people with type 2 diabetes and prescribers. It will explore the role of the innovative sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) technology in facilitating absorption and bioavailability of oral semaglutide and other therapies. In addition, it will provide practical information for dispensing pharmacists regarding appropriate drug administration parameters, the effects of food on oral semaglutide absorption and bioavailability, and potential drug-drug interactions (DDIs).

Overview of SNAC as a Drug-Delivery Technology

Various compounds, including surfactants, bile salts, bacterial toxins, chelating agents, and medium-chain fatty acids, have proven effective as absorption enhancers in vitro and in vivo (7). Some of the most widely tested absorption enhancers in clinical trials are the Eligen carriers, a library of absorption-enhancing compounds (7). Among these carriers is SNAC, an N-acetylated amino acid derivative of salicylic acid (Figure 1*A*) (7). Despite the structural similarity between SNAC and salicylic acid, evidence from preclinical models and early-stage clinical studies suggests that SNAC has no antiplatelet effect (8–10).

SNAC technology has been explored as an absorption enhancer for a number of molecules, including heparin, vitamin B12, and ibandronate, leading to increased absorption after oral administration (Table 1) (10–25). A vitamin B12-SNAC coformulation has been approved as a medical food and granted "generally recognized as safe" status as part of this process (7).

More recently, SNAC technology has been investigated as an absorption enhancer for the GLP-1 receptor agonists liraglutide and semaglutide (15). Plasma exposure was significantly lower for liraglutide than for semaglutide when coformulated with SNAC, which may be the result of the membrane-binding properties of liraglutide and its proneness to form sizeable oligomers, thus hindering its transcellular passage and subsequent absorption (15). An oral formulation of liraglutide has, therefore, not been investigated further. In contrast, coformulation with SNAC enables effective absorption of semaglutide (discussed in detail later in this review) (15), which has led to oral semaglutide being the first FDA-approved peptide drug coformulated with SNAC.

Development of an Oral GLP-1 Receptor Agonist Formulation for Treatment of Type 2 Diabetes

Six GLP-1 receptor agonists are FDA-approved for the treatment of type 2 diabetes (4,26–32). The GLP-1 receptor agonist class comprises modified synthetic forms of the peptide exendin-4 (exenatide, exenatide extended-release, and lixisenatide) and modified GLP-1 analogs (liraglutide, dulaglutide, and semaglutide), as reviewed in Aroda (33) and Lau et al. (34). The modified GLP-1 analogs have evolved from once-daily liraglutide with 97% homology to native GLP-1 to the development of analogs for once-weekly administration achieved through the use of an Fc fusion protein (dulaglutide) or advances in fatty acid acylation–based protraction technology (semaglutide) to extend the half-life (15,33,34).

Semaglutide has 94% homology with native GLP-1, with three key modifications to extend the half-life: an amino acid substitution to protect against dipeptidyl peptidase 4 degradation, the attachment of a linker and C18 fatty dicarboxylic acid chain to provide strong binding to albumin, and an amino acid substitution to prevent C18 fatty acid binding at the wrong site (Figure 1*B*) (35). Fatty acid acylation extends the half-life of

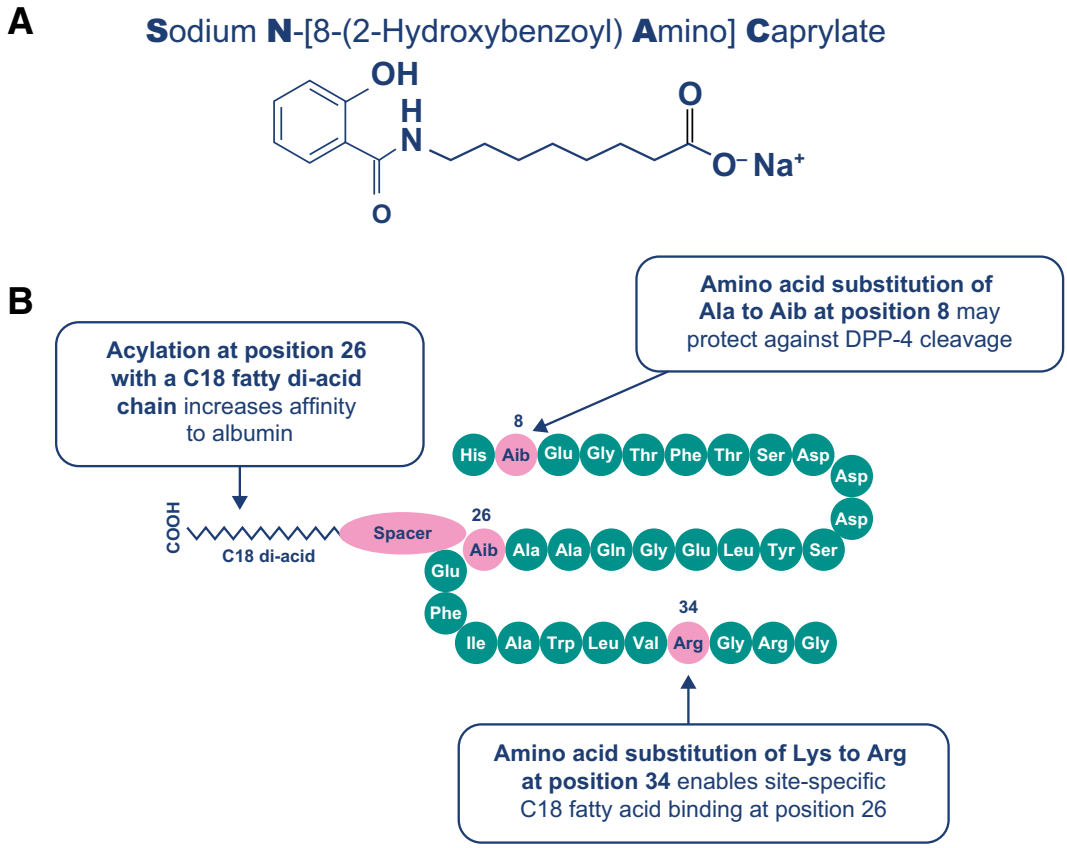

FIGURE 1 Structure of SNAC (*A*) and semaglutide (*B*). The unmodified molecule in *B* represents native GLP-1. Aib, aminoisobutyric acid; Ala, alanine; Arg, arginine; Asp, aspartic acid; COOH, carboxyl group; di-acid, dicarboxylic acid; DPP-4, dipeptidyl peptidase 4; Gln, glutamine; Glu, glutamic acid; Gly, glycine; His, histidine; Ile, isoleucine; Leu, leucine; Phe, phenylalanine; Ser, serine; Thr, threonine; Trp, tryptophan; Tyr, tyrosine; Val, valine. Adapted from Twarog et al. (7) and Kalra and Sahay (35). Both articles are published under a Creative Commons CC BY license (https://creativecommons.org/licenses/by-nc/4.0).

semaglutide with no impact on its function (15). This, in addition to the small size of semaglutide (36), makes semaglutide well suited for oral administration when coformulated with an absorption enhancer (15).

Understanding the Mechanism of SNAC-Facilitated Oral Semaglutide Absorption

The coformulation of semaglutide with SNAC enables site-directed release and absorption in the stomach, as documented by γ scintigraphy (15). This process was confirmed in preclinical mechanistic studies in dogs using pyloric ligation and venous effluent analysis, which demonstrated that the stomach is the predominant site of absorption (15).

SNAC increases drug absorption in the stomach by several mechanisms. First, SNAC acts as a localized buffer to neutralize the pH of the microenvironment surrounding the semaglutide tablet, stabilizing semaglutide on exposure to gastric fluids and providing protection from degradation by gastric enzymes (Figure 2*A*) (15).

Second, SNAC reduces oligomerization of semaglutide, which could affect absorption (Figure 2*B*) (15). Finally, SNAC interacts with and fluidizes lipid membranes, thus increasing their permeability and enhancing the transcellular passage of semaglutide, with no appreciable effect on tight junction complexes of GI epithelia (Figure 2*C*) (15). Semaglutide relies on close proximity to SNAC for exposure to and efficient absorption at the GI epithelium, where coformulation of the two molecules allows for corelease and therefore spatial proximity (15). Importantly, the absorption-enhancing effects of SNAC are transient and fully reversible (with permeability returning toward baseline from 30 minutes after exposure to SNAC) and do not affect the absorption of other molecules that are coadministered (rather than coformulated) with SNAC (15).

Pharmacokinetics of SNAC and Oral Semaglutide

The pharmacokinetics of oral semaglutide have been assessed in healthy individuals and people with type 2

TABLE 1 Summary of Studies Investigating SNAC as an Absorption Enhancer for Molecules Other Than Oral Semaglutide

Test Molecules	Preparation/Population	Assessments/Treatment(s)	Observations	Success
Preclinical studies				
BER with SNAC microspheres (11)	Caco-2 cells and Sprague-Dawley rats	Assessed transport across the Caco-2 cell monolayer by measuring transepithelial electrical resistance of the Caco-2 cell monolayer before and after treatment with BER and BER with SNAC; the PK profile of BER in rats after oral BER, BER with SNAC, and BER-SNAC–loaded microspheres was also assessed.	SNAC significantly enhanced permeability of BER two- to threefold; the P_{app} of BER mixed with SNAC (1:1) and BER mixed with SNAC (2:3) improved by 2.11- and 2.64-fold. PK studies demonstrated a 9.87-fold increase in AUC of BER mixed with SNAC and a 14.14-fold increase in AUC of microspheres compared with BER alone.	✓*
Cromolyn with SNAC (12)	Caco-2 cells	Assessed transport of cromolyn across Caco-2 cell monolayers with various SNAC concentrations	Absorption of cromolyn was enhanced markedly by SNAC. Cromolyn was undetectable in the basolateral solutions of Caco-2 monolayers incubated with cromolyn alone or with cromolyn and 17–51 mmol/L SNAC. Cromolyn permeation with 67 and 83 mmol/L SNAC was measurable and increased with SNAC concentration (statistically significant with 83 mmol/L SNAC; $P < 0.05$).	✓†
Cromolyn with SNAC (13)	Caco-2 cells	Evaluated the effect of SNAC on cromolyn lipophilicity and changes in Caco-2 cell membrane fluidity	SNAC had no influence on the lipophilicity of cromolyn. SNAC increased the membrane fluidity of Caco-2 cells in a concentration-dependent manner. The increase in fluidity with SNAC was seen in the presence and absence of cromolyn, and the presence of cromolyn did not augment the effect of SNAC on membrane fluidity.	✓†
Exendin-4 with SNAC, D-octaarginine–linked PNVA-co-AA, or sodium caprate (14)	Mouse nasal mucosa	Assessed plasma concentration–time profiles of exendin-4 after its nasal administration with or without absorption enhancers (including SNAC)	A nonsignificant increase in nasal absorption of exendin-4 was observed when coadministered with SNAC (2.3 mg/mouse).	✗
Liraglutide (GLP-1 receptor agonist) with SNAC (15)	Sprague-Dawley rats	Compared the arithmetic mean of liraglutide and semaglutide plasma concentration–time profiles after oral dosing with SNAC	$AUC_{0-180min}$ was lower for liraglutide vs. semaglutide ($P = 0.002$) as tested by a two-tailed Student *t* test.	✗‡

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TABLE 1 Summary of Studies Investigating SNAC as an Absorption Enhancer for Molecules Other Than Oral Semaglutide (Continued)

Test Molecules	Preparation/Population	Assessments/Treatment(s)	Observations	Success
Octreotide with SNAC (16)	Rat and human intestinal mucosae	Assessed the effects of SNAC on the apparent P_{app} of [^{3}H]-octreotide across isolated rat intestinal tissue mucosae from five regions and from colonic human mucosae mounted in Ussing chambers	Addition of 20 mmol/L SNAC increased the P_{app} across rat tissue: colon (by 3.2-fold) > ileum (3.4-fold) > upper jejunum (2.3-fold) > duodenum (1.4-fold) > stomach (1.4-fold). 20 and 40 mmol/L SNAC also increased the P_{app} by 1.5- and 2.1-fold, respectively, across human colonic mucosae.	✓†
Octreotide, lixisenatide, or somatropin administered with SNAC or tetraglycine-L-octaarginine–linked hyaluronic acid (17)	Mouse nasal mucosa	Plasma concentration–time profiles of exendin-4 after nasal administration of exendin-4, octreotide, lixisenatide, and somatropin with or without absorption enhancers (including SNAC)	SNAC enhanced nasal absorption of octreotide and lixisenatide. No significant difference in AUC or bioavailability of somatotropin was observed between mice treated with or without SNAC.	✓ for octreotide and lixisenatide ✗ for somatotropin
Clinical studies				
GLP-1 with SNAC (18)	Randomized, double-blind, two-way crossover study in healthy males (n = 16)	PK/PD effects of a single dose (2 mg GLP-1 + SNAC) of oral GLP-1 administered prior to an OGTT, compared with SNAC alone	After administration of oral GLP-1 + SNAC, 10-fold higher plasma concentrations were obtained compared with controls. GLP-1 + SNAC significantly stimulated basal insulin release (P <0.027), with marked effects on glucose levels.	✓
GLP-1, PYY3–36 with SNAC (19)	Randomized, double-blind, four-way crossover study in healthy males (n = 12)	Participants received 2.0 mg GLP-1, 1.0 mg PYY3–36, or 2.0 mg GLP-1 + 1.0 mg PYY3–36, all mixed with SNAC	Both GLP-1 and PYY3–36 were rapidly absorbed from the gut, leading to plasma concentrations several times higher than those of endogenous peptides in response to a normal meal.	✓
Ibandronate with SNAC, coadministered with metformin (20)	Exploratory PK study in healthy individuals (n = 22)	Individuals received metformin 500 mg on days 1–6. On day 7, individuals received metformin concomitantly with ibandronate/SNAC (25/125 mg dose).	Exposure to metformin was slightly increased on day 7 when coadministered with ibandronate/SNAC compared with day 6 when administered alone; however, the change was not considered clinically relevant.	▬
Ibandronate with SNAC (21)	Randomized, four-way crossover, open-label study in four cohorts of 28, 21, 19, and 29 healthy volunteers	Within each cohort, different oral formulations with one dose of ibandronate (30 mg) and three different ratios of ibandronate:SNAC (1:5, 1:10, and 1:20) were compared with the approved oral ibandronate tablet	The highest mean ibandronate exposure was achieved with a capsule formulation containing drug-coated beadlets and an ibandronate:SNAC ratio of 1:5. AUC_{last} and C_{max} of ibandronate were	✓

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TABLE 1 Summary of Studies Investigating SNAC as an Absorption Enhancer for Molecules Other Than Oral Semaglutide (Continued)

Test Molecules	Preparation/Population	Assessments/Treatment(s)	Observations	Success
		formulations (150 and 50 mg ibandronate).	approximately 1.3- and 2.2-fold higher compared with the reference treatment (150 mg ibandronate without SNAC).	
Insulin with SNAC (22)	Healthy males (*n* = 16)	Twelve volunteers without diabetes received capsules containing SNAC (2,100 or 2,800 mg) and insulin (given in a dose escalation format). In addition, four control volunteers received either 2,100 mg SNAC or 350 units of insulin alone.	Fasting volunteers without diabetes given increasing doses of insulin (200–400 units) orally with SNAC (2,100 mg) showed a decrease in glucose levels. There was no change in glucose levels with SNAC or insulin alone.	✓
Unfractionated heparin with SNAC (10)	Healthy volunteers (*n* = 30)	Individuals were randomly assigned to receive ascending doses (1.4–10.5 g) of SNAC by gavage (group 1), 10,000 units heparin with ascending doses (1.4–10.5 g) of SNAC (group 2), or 20,000 or 30,000 units heparin with a fixed dose (10.5 g) of SNAC (group 3).	Increases in APTT, antifactors IIa and Xa, and tissue factor pathway inhibitor concentrations were detected in healthy volunteers when heparin + SNAC was administered orally.	✓
Unfractionated heparin with SNAC (23)	Phase 1 PK study in healthy volunteers (*n* = 24) and phase 2 double-blind, randomized study of hip replacement patients (*n* = 123)	The phase 1 study compared oral heparin/SNAC (90,000 units heparin) with subcutaneous unfractionated heparin (5,000 units). The phase 2 study compared unfractionated heparin (5,000 units) with oral heparin/SNAC at either 60,000 or 90,000 units heparin.	In the phase 1 study, anti-FXa activity was comparable between oral heparin/SNAC and subcutaneous heparin. In the phase 2 study, no change in major bleeding and VTE was observed for oral heparin/SNAC compared with subcutaneous heparin.	✓
Unfractionated heparin with SNAC (24)	Randomized, single-dose, three-way crossover, open-label study in healthy males (*n* = 16)	Individuals were assigned to one of four treatment groups, to receive: *A*) two capsules of unfractionated heparin/SNAC capsules (total dose of 75,000 units heparin sodium); *B*) 1 mL of heparin sodium USP parenteral 10,000 units/mL via subcutaneous injection; *C*) 75,000 units heparin sodium milled powder for oral solution; or *D*) 0.5 mL of heparin sodium USP parenteral 10,000 units/mL solution via intravenous bolus.	Combining unfractionated heparin with SNAC markedly increased the gastrointestinal absorption of heparin.	✓

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TABLE 1 Summary of Studies Investigating SNAC as an Absorption Enhancer for Molecules Other Than Oral Semaglutide (Continued)

Test Molecules	Preparation/Population	Assessments/Treatment(s)	Observations	Success
Vitamin B12 with SNAC (25)	Open-label, randomized study in healthy males (n = 20)	Individuals were assigned to one of four treatment groups, to receive: *A*) two tablets, each with 5 mg of vitamin B12 with 100 mg of SNAC; *B*) one tablet of 5 mg of vitamin B12 with 100 mg of SNAC; *C*) one commercial tablet of 5 mg of vitamin B12; or *D*) 1 mg of vitamin B12 via intravenous injection.	Vitamin B12 in combination with SNAC achieved higher absolute bioavailability compared with the commercial oral formulation (5 vs. 2%). No adverse effects were reported.	✓

*Clinical studies still to be conducted. †In vivo studies still to be conducted. ‡Suboptimal interplay between SNAC and liraglutide. APTT, activated partial thromboplastin time; $AUC_{0–180min}$, AUC from time zero to 180 minutes; AUC_{last}, AUC from time zero to the last observable concentration; BER, berberine hydrochloride; OGTT, oral glucose tolerance test; P_{app}, permeability coefficient; PD, pharmacodynamic; PK, pharmacokinetic; PNVA-co-AA, poly(N-vinylacetamide-coacrylic acid); PYY, peptide YY; USP, United States Pharmacopeia; VTE, venous thromboembolism.

diabetes (15,37,38). After a single-dose administration of oral semaglutide (10 mg with 300 mg SNAC) in healthy individuals, complete tablet erosion (CTE) occurred in the stomach in ∼1 hour (15). Early systemic absorption of semaglutide was observed with a slow elimination phase, whereas, for SNAC, absorption started early, but elimination was rapid (15). SNAC is metabolized via β-oxidation and glucuronidation and is primarily eliminated in the urine (39), with a half-life of 2 hours (40).

Studies investigating different coformulations of semaglutide and SNAC in healthy individuals showed that exposure of semaglutide 5 or 10 mg was higher with 300 mg SNAC compared with 150 or 600 mg, demonstrating that 300 mg SNAC is the optimal amount of SNAC to enhance the absorption of semaglutide (15,37). It has been suggested that using 300 mg SNAC avoids the precipitation that may occur with higher amounts (15). In contrast, SNAC exposure (area under the curve [AUC] from time zero to 24 hours [$AUC_{0–24h}$]) and maximum concentration (C_{max}) increased with increasing amounts of SNAC, whereas the time to maximum concentration (t_{max}) for SNAC was similar between groups (37). When varying the amount of semaglutide with a fixed amount of 300 mg SNAC, semaglutide exposure increased with increasing doses of 2–10 mg (37).

In a multiple-dose study of oral semaglutide (coformulated with 300 mg SNAC), semaglutide exposure was approximately twofold higher at steady state with oral semaglutide 40 vs. 20 mg in healthy individuals (37). There was no difference in semaglutide exposure between healthy individuals and people with type 2 diabetes receiving 40 mg. The half-life of semaglutide was ∼1 week for all groups (37). At steady state, absorption of SNAC was rapid, and nearly complete elimination occurred within 12 hours (37). SNAC exposure did not vary between treatment groups, but the t_{max} was longer in people with type 2 diabetes (1.43 hours) compared with healthy individuals receiving either oral semaglutide dose (0.5 hour in both groups) (37).

Regarding variability of oral semaglutide at steady state, after a single dose, a trial of 107 people reported no measurable semaglutide in the plasma of some participants, and researchers hypothesized that this could be partially explained by a degree of variability after exposure (37). Decreased day-to-day variability is expected with multiple doses of oral semaglutide because of its long half-life. After multiple doses of oral semaglutide, the within-subject day-to-day variability

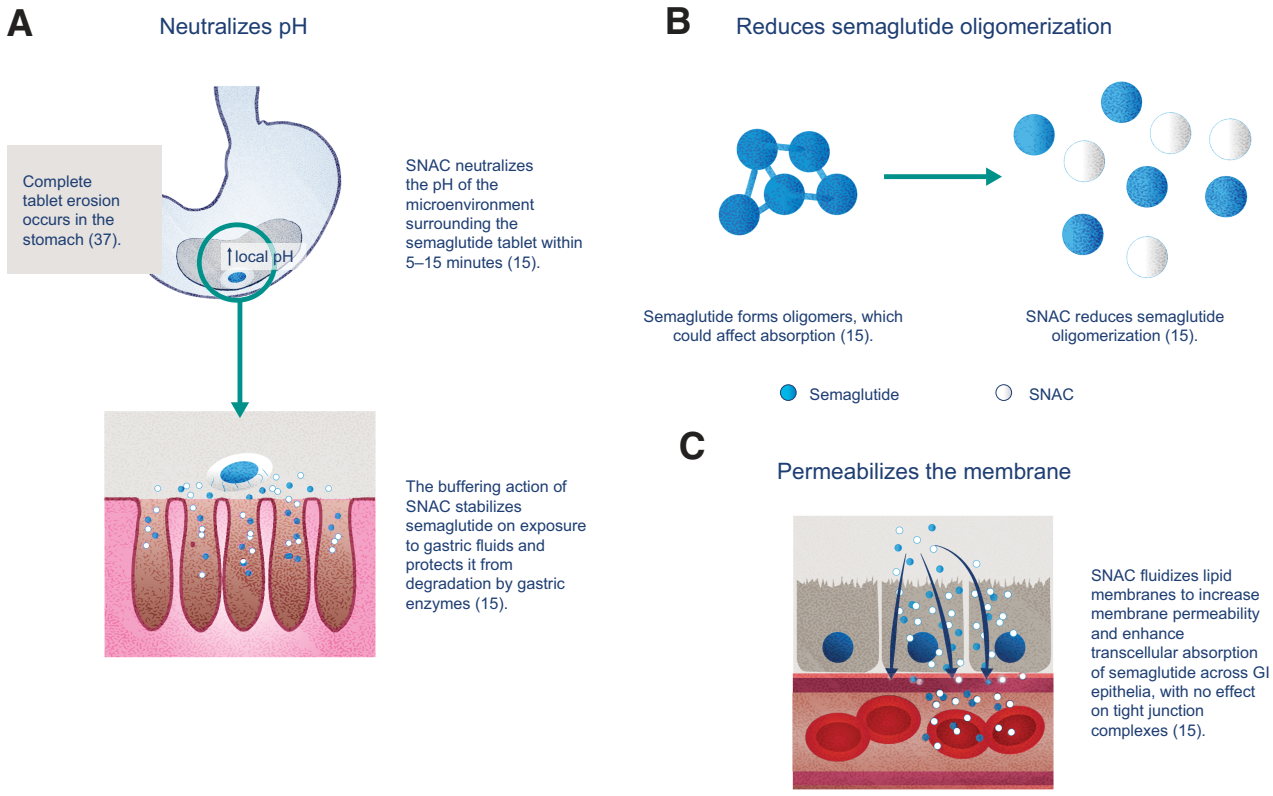

FIGURE 2 Mechanisms of SNAC absorption. SNAC neutralizes the local pH to stabilize semaglutide in the highly acidic environment in the stomach and to protect it from degradation by gastric enzymes (*A*). SNAC reduces semaglutide oligomerization, which could affect absorption (*B*). SNAC increases membrane permeability to enhance transcellular absorption of semaglutide (*C*) (15,37).

was 20–35% at steady state, with a higher total variability (consisting of within-subject day-to-day and between-subject variability) of up to 85%, suggesting some between-subject variability during oral semaglutide absorption (37). Semaglutide effectively reduced A1C across multiple subgroups that differed in terms of age and race (41).

A model-based analysis suggests that coformulation of semaglutide with SNAC does not alter the pharmacokinetics of semaglutide once absorbed, with oral and subcutaneous formulations of semaglutide distributed, metabolized, and eliminated in the same way (42). For both oral and subcutaneous semaglutide, distribution and elimination are characterized by two-compartment pharmacokinetics and first-order elimination (42). However, the absorption of oral semaglutide is faster and bioavailability is lower (0.8%) than with subcutaneous semaglutide (42). These findings support the use of SNAC as an absorption enhancer for oral semaglutide.

Administration of Oral Semaglutide

Single- and multiple-dose pharmacokinetic studies in healthy individuals and people with type 2 diabetes have informed the administration schedule and conditions for oral semaglutide (15,37,38). Although the half-life of oral semaglutide is ∼1 week, once-daily administration of oral semaglutide is required to achieve therapeutic steady-state activity and to mitigate the low bioavailability and high variability in semaglutide exposure after a single oral dose (15,37).

The absorption of oral semaglutide in the stomach is hindered by the presence of food (15). In a study of healthy individuals receiving once-daily oral semaglutide, more than half who were dosed in the fed state had no measurable semaglutide exposure, with limited exposure for the remaining individuals (15). In contrast, all individuals who received oral semaglutide in the fasting state had measurable semaglutide exposure, highlighting the need for administration of oral semaglutide in the fasting state (15).

The volume of water administered with oral semaglutide also affects its pharmacokinetics (38). In a study of healthy individuals who received single doses of oral semaglutide 10 mg with either 50 or 240 mL water, the t_{max} for semaglutide did not differ between water volumes; however, $AUC_{0–24h}$ and C_{max} were ∼70%

higher when oral semaglutide was administered with 50 versus 240 mL water (38). In contrast, for SNAC, AUC from time zero to 6 hours and C_{max} were lower with 50 versus 240 mL water, whereas t_{max} was unaffected by water volume (38). CTE occurred in the stomach regardless of water volume, although time to CTE was numerically longer after dosing with the smaller volume of water (38). It has been suggested that the impact of food and/or liquid intake on oral semaglutide pharmacokinetics could be the result of a dilution of SNAC and semaglutide, preventing the establishment of the concentration gradient required for enhanced absorption (15).

Based on these and other studies, patients should be advised to take oral semaglutide in the fasting state (before the first food, beverage, or other oral medications of the day), with no more than 120 mL (4 oz) of plain water, followed by a post-dose fasting period of at least 30 minutes (30). Administration of once-daily oral semaglutide under these conditions in healthy individuals for 10 days has been shown to result in clinically relevant semaglutide exposure (43).

It should be noted that, at steady state, single deviations in oral semaglutide dosing (such as a missed or double dose, a shorter or longer post-dose fasting time, or a dose taken with a larger volume of water) are likely to result in only minor and transient changes in exposure (42). However, exposure may change over time if persistent deviations in dosing conditions occur (42).

Use of Concomitant Medication With Oral Semaglutide

Polypharmacy is common in people with type 2 diabetes for the management of both type 2 diabetes and associated comorbidities (44,45). It has been suggested that oral semaglutide may alter the absorption of coadministered oral drugs because of the action of SNAC, as a result of delayed gastric emptying caused by semaglutide, or through other mechanisms (46). It is, therefore, crucial to understand any DDIs that may occur. DDIs with oral semaglutide have been reviewed in detail previously (47); therefore, this review will focus on DDIs with SNAC, including any differences compared with oral semaglutide.

Oral semaglutide has been shown to increase the total, but not maximum, exposure of levothyroxine by 33%, an effect not observed with SNAC alone (48). No change in clinical practice is required, but routine monitoring of thyroid parameters should be considered in patients treated with both oral semaglutide and levothyroxine (48).

Coadministration of oral semaglutide with omeprazole causes a small, nonstatistically significant increase in semaglutide exposure, while omeprazole treatment has no substantial impact on the exposure of SNAC (49). This increase was not considered clinically relevant, and dose adjustment of oral semaglutide is unlikely to be required in patients treated with omeprazole (49).

Studies have shown that treatment with either oral semaglutide or SNAC alone does not affect the exposure of lisinopril, *S*-warfarin, *R*-warfarin, digoxin, or oral contraceptives (46,50). Treatment with oral semaglutide has been shown to cause a small increase in the exposure of metformin, furosemide, and rosuvastatin (46,50). This effect was not reported with SNAC alone, although C_{max} for furosemide was slightly decreased (46,50). These increases are unlikely to be of clinical relevance, and no dose adjustment is likely to be required for patients treated with oral semaglutide and these other drugs (46,50). As a general reminder, patients should be counseled to take oral semaglutide 30 minutes before taking any other medication (30).

Oral Semaglutide in Special Populations

The pharmacokinetics of oral semaglutide has been assessed in a number of special populations, including in people with hepatic impairment, renal impairment, or upper GI disease (39,51,52).

A study assessing the pharmacokinetics of once-daily oral semaglutide for 10 days showed no apparent effect of hepatic impairment on semaglutide pharmacokinetics regardless of the severity of hepatic dysfunction (39). In contrast, SNAC exposure and C_{max} increased with decreasing hepatic function, while total apparent clearance decreased. This did not lead to SNAC accumulation or increased adverse events (39).

Renal impairment or hemodialysis also had no impact on the pharmacokinetics of oral semaglutide when administered once daily for 10 days (51). SNAC renal clearance decreased with severe renal impairment, and the AUC from time zero to 24 hours after the tenth dose increased with increasing levels of renal impairment, except for the group with end-stage renal disease (ESRD). Because the difference between the ESRD and severe groups was small and the number of participants was low ($n = 71$), these data should be interpreted

with caution (51). These effects were not considered clinically relevant (51). In the phase 3a PIONEER (Peptide Innovation for Early Diabetes Therapy) 5 study in people with type 2 diabetes and moderate renal impairment, oral semaglutide demonstrated efficacy in terms of reductions in A1C and body weight, with safety, including renal safety, consistent with the GLP-1 receptor agonist class (53).

In a toxicity study of SNAC in rats, high doses of SNAC (≥500 mg/kg/day) were associated with slightly higher liver and kidney weights (9). This finding was not associated with clinical pathology or histopathological changes and, as such, was not considered toxicologically significant (9). Also, it should be noted that the doses used were many times higher than that used in oral semaglutide, supporting the renal and hepatic safety of SNAC in this context.

Because the main site of absorption for oral semaglutide is the stomach, the pharmacokinetics of oral semaglutide in people with type 2 diabetes and upper GI disease (chronic gastritis and/or gastroesophageal reflux disease) was assessed in a phase 1, open-label, parallel-group trial (52). Semaglutide exposure and C_{max} were not significantly different in people with versus without upper GI disease, and similar t_{max} and half-life were reported (52).

Based on these findings, no dose adjustment of oral semaglutide is recommended for people with hepatic or renal impairment (30) or expected to be required for those with upper GI disease (52).

Clinical Efficacy and Safety of Oral Semaglutide

The efficacy and safety of oral semaglutide have been well characterized in the extensive PIONEER clinical program (PIONEER 1–10). The PIONEER program compared oral semaglutide with placebo and active comparators in patients from across the full treatment continuum of type 2 diabetes, recruiting people with newly diagnosed type 2 diabetes and long-term disease, drug-naive patients, and those receiving multiple drug therapies, including insulin (53–62). In these studies, oral semaglutide was superior to placebo and superior or similar to active comparators in terms of reductions in A1C and body weight (53–57,59–62). Early real-world data have confirmed the effectiveness of oral semaglutide in the reduction of A1C (63). In a propensity score–matched analysis of data from the PIONEER (oral semaglutide) and SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) (subcutaneous semaglutide) programs, exposure-response relationships for efficacy were consistent between oral and subcutaneous semaglutide (64).

The safety and tolerability of oral semaglutide are also similar to subcutaneous semaglutide, with GI adverse events (in particular nausea) among the most frequently reported (53–62,65). The exposure-response relationship for GI events (nausea and vomiting) has been shown to be consistent with oral and subcutaneous semaglutide (64). In a phase 2 dose-finding study, it was noted that fewer nausea events were reported among patients who started on a low dose of oral semaglutide, and the frequency of GI events was highest during the dose-escalation period (66), highlighting the importance of dose escalation when initiating semaglutide.

Pharmacists have an important role in ensuring that patients understand the adverse events (in particular GI events) associated with oral semaglutide treatment and how these can be minimized and managed, for example, by using a dose-escalating strategy for treatment initiation. The dose-escalation recommendations are to start oral semaglutide at 3 mg once daily for 30 days before increasing the dose to 7 mg once daily (30). If additional glycemic control is required after a further 30 days, the dose should be increased to 14 mg once daily (30).

It is also important for pharmacists to help patients (particularly those switching from a subcutaneous GLP-1 receptor agonist) understand that the formulation of oral semaglutide (i.e., coformulation with SNAC) facilitates absorption of this oral GLP-1 receptor agonist, so efficacy is not compromised versus subcutaneous options. The importance of taking oral semaglutide correctly (on an empty stomach, with no more than 4 oz of plain water, with no food or other medication for a minimum of 30 minutes) cannot be overemphasized.

Conclusion

SNAC fits a unique niche, increasing the absorption of semaglutide across the gastric epithelium, allowing adequate bioavailability and subsequent efficacy as an oral formulation.

Coformulation of semaglutide with SNAC does not appear to alter the pharmacokinetics of semaglutide once absorbed, and exposure-response relationships for efficacy and safety are consistent between oral and subcutaneous semaglutide. With the exception of

levothyroxine, oral semaglutide does not have any clinically relevant impact on the pharmacokinetics of other commonly used concomitant medications, and no dose adjustments are recommended in special populations (people with hepatic or renal impairment or those with upper GI disease). Taken together, this supports the use of SNAC as an absorption enhancer for semaglutide, allowing for its oral administration.

The approval of oral semaglutide is an important innovation in peptide delivery in the past decade, representing one of few successful examples of peptides that can be administered orally. Oral semaglutide is an important addition to the treatment armamentarium for people with type 2 diabetes, providing an oral option for GLP-1 receptor agonist therapy and a possible solution to the existing challenges posed by injectable GLP-1 receptor agonists.

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AUTHOR CONTRIBUTIONS

The manuscript was drafted by a medical writer under the direction of all authors. All authors edited and reviewed the manuscript and approved the final version for submission. C.T. is the guarantor of this work and, as such, had full access to all of the literature search results and references cited and takes responsibility for the integrity of the data and the accuracy of the analyses.

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