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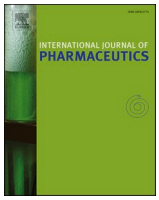

Expert insights into the development of large-volume subcutaneous drugs with permeation enhancers: A survey examining challenges, alternatives, and future directions

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ABSTRACT

Permeation enhancers (PE) such as hyaluronidase are increasingly incorporated into subcutaneous (SC) biologic drug formulations to improve drug absorption. However, there remain gaps in our understanding of the intricacies of their co-formulation with drugs, including their impact on formulation development, manufacturing processes, and SC administration volume limits. This global, online, anonymous survey of 100 formulation experts familiar or experienced with co-formulating drugs with PE was conducted from 25 April to 6 May 2024 to gain more insights into these gaps and explore the perspectives of drug formulation stakeholders. The survey consisted of 11 screening questions and 25 questions related to the process of developing SC drugs co-formulated with PE. The mean duration of experience was 13.7 years and 46 % of participants were currently or previously employed by a company that markets PE for co-formulation with drugs. The biophysical aspects of hyaluronidase were considered moderately/very/extremely challenging by 89 % of respondents, particularly the high drug-interaction potential, temperature sensitivity, and pH sensitivity. Incompatibility between drug and PE was reported to occur in 36 % of cases (weighted mean; mode: 31–40 %). The most common stages where challenges occurred were quality and stability testing and co-formulation development. Despite a lack of data demonstrating improvements in SC drug bioavailability with PE, 90 % of respondents believed that PE positively impacts drug bioavailability. These findings may assist stakeholders in making informed decisions regarding co-formulation of drugs with PE.

1. Introduction

Biologic drugs such as monoclonal antibodies (mAbs) have revolutionized the treatment of cancer and autoimmune diseases, with a rapid increase in the number of options in recent years and expansion into multiple therapeutic areas (Martins et al., 2023). While most biologics are administered intravenously (IV) by healthcare professionals, there has been an increasing focus on subcutaneous (SC) formulations. Compared to IV formulations, these SC formulations may have several advantages, such as faster administration, better tolerability (particularly by reducing infusion-related reactions), potential for fewer dosing errors, self-administration, and patient preference (Desai et al., 2023; Jackisch et al., 2015; Overton et al., 2021; Pivot et al., 2014; Usmani et al., 2022).

SC formulations are delivered to the SC extracellular space, where they disperse into the local area before being absorbed into the lymphatic system or local capillaries. As such, bioavailability with SC may be lower than with IV formulations (Richter et al., 2012), so the total dose is usually adjusted to compensate for this (Desai et al., 2023). A larger dose requirement often necessitates a larger drug volume for

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delivery, especially when the drug cannot be highly concentrated. While several options exist for SC biologic drug delivery, fewer options are available for volumes exceeding 3 mL. Common approaches to large-volume SC delivery include pumps, on-body injectors (OBIs), and co-formulations with permeation enhancers (PEs). PEs such as hyaluronidase (recombinant human hyaluronidase [rHuPH20]) temporarily break down hyaluronan, a gel-like substance in the skin, creating more space in the SC tissue (Kang et al., 2021). This enhances drug dispersion and allows for faster injection. It should be noted that hyaluronidase is referred to here as a PE due to familiarity with this term within the industry and drug development community, as well as the widespread adoption of the term, largely influenced by the educational narratives promoted by hyaluronidase developers over the past decade. However, to be precise, hyaluronidase facilitates dispersion through the SC space rather than increasing permeability across a membrane. Companies licensing modified hyaluronidase for large-volume SC delivery include Halozyme, the first company to initiate co-formulations with PEs, as well as Alteogen and Huonslab (Jacquot et al., 2024; Kim & Byun, 2024; Takeda Pharmaceuticals Inc., 2024). Fortunately, large-volume SC delivery technologies can be combined. By using an OBI with a drug co-formulated with hyaluronidase, manufacturers can strike a balance between delivery speed and patient comfort, optimizing the SC administration of biologic therapies.

Co-formulations of biologics and PEs may present specific challenges due to the sensitivity of hyaluronidase to pH and temperature. While hyaluronidase is active at a neutral pH (~7), its peak enzymatic performance occurs at a pH range of 4.5–5.5 (Chen et al., 2016). However, most mAb formulations require a narrow pH range near neutral to maintain stability and prevent issues like aggregation or chemical degradation (Ghosh et al., 2023). This balance becomes even more critical given that even brief exposure of an IgG1 antibody to a pH outside of its optimal range can cause small amounts of aggregation (Ghosh et al., 2023). Excipient and buffer compatibility add another layer of complexity, as mAbs and hyaluronidase may require distinct stabilizers, such as surfactants, sugars, or buffers. The excipients optimal for one component might negatively affect the other, necessitating iterative testing to identify a stable formulation. This further complicates the development of these combination formulations.

In regards to the temperature stability of hyaluronidase, a 2015 patent highlights that the “uber-thermophile” modified variant retains at least 50 % of its enzymatic activity after incubation at 52 °C (125.6 °F) for 10 min at a neutral pH (Halozyme Inc., 2015), whereas the unmodified variant exhibits significantly reduced activity under similar conditions (Chen et al., 2016). However, the patent does not provide information on how temperature stability changes outside of a neutral pH, and it is not currently clear which variant is used in commercialized formulations. As a temperature-sensitive enzyme, hyaluronidase requires careful handling during manufacturing to prevent heat-induced denaturation. Processes like sterilization, which may involve elevated temperatures, could inactivate the enzyme, necessitating stringent temperature controls to preserve the functionality of the final product.

Despite the drug absorption benefits of PEs, evidence supporting their impact on drug bioavailability is inconsistent or incomplete (Dolton et al., 2021; Nolan & Printz, 2024). The belief that co-formulation with hyaluronidase increases the bioavailability of SC drugs appears to be mainly based on the mechanism of action of hyaluronidase rather than robust clinical data. A recent publication investigating whether there are bioavailability improvements with hyaluronidase reported a range of 0–20 % improvement for 10 monoclonal antibodies co-administered with hyaluronidase (Nolan & Printz, 2024). However, these findings were derived from computational modelling rather than clinical studies in humans for five of the 10 antibodies; moreover, for five of the 10 antibodies, bioavailability data were only available for the SC formulation with hyaluronidase, with no comparative data for formulations without it, making comparison in these antibodies impossible. Table 1 summarizes the publicly available bioavailability data for these 10 antibodies, including modelled and experimental data. While modelling provides valuable insights, exclusive reliance on modelling rather than clinical data diminishes the credibility and practical utility of the results, as computational predictions cannot fully replicate the complexities of human physiological processes influencing bioavailability.

Nolan et al. also state that the addition of hyaluronidase increased the bioavailability of SC amivantamab by 20 % from a modelled 62 % to a modelled 82 % (Nolan & Printz, 2024). However, data from the Phase 1 PALOMA study reported a bioavailability of 65 % for SC amivantamab *with* hyaluronidase, meaning a negligible bioavailability increase of only 3 % with hyaluronidase (Krebs et al., 2022). Moreover, the bioavailability of SC tocilizumab appears to vary substantially by dose, yet recently modelled values do not appear to consider this or to draw on the full clinical data available, some of which were published $>$ 10 years prior. As shown in Table 1, tocilizumab bioavailability at a 162 mg dose was modelled at 90 % with the addition of hyaluronidase (single dose) (Nolan & Printz, 2024), but a much earlier study published in 2013 found that a four-fold higher dose of tocilizumab (648 mg, single dose) plus hyaluronidase resulted in a lower-than-modelled bioavailability of 83 %. Furthermore, bioavailability was 76 % at twice the modelled dose (324 mg, single dose) (Morcos et al., 2013). In the Phase 3 trial data, the bioavailability of SC tocilizumab without hyaluronidase was 80 % with the 162 mg dose (weekly to bi-weekly dosing) (Abdallah et al., 2017), but a Phase 1 study reported a bioavailability of only 49 % for SC tocilizumab at the same dose (single dose) and of 23 % with an 81 mg SC dose (single dose) (Zhang et al., 2013). These discrepancies further underscore the limitations of computational modelling for accurately predicting bioavailability values and highlights the variability often observed in measured bioavailability across studies (Table 1). While improvements in bioavailability have been reported when injecting human SC immune globulin 10 % after a separate injection of hyaluronidase, it should be noted that this was a rare case, as the injection volumes were extremely large (up to 600 mL) (Wasserman et al., 2012), far exceeding the $\leq$ 20 mL volumes typical of other biologics co-formulated with hyaluronidase (**Table S1**). Therefore, it remains uncertain whether improvements in bioavailability conferred by co-formulation with hyaluronidase are only clinically meaningful for drugs administered in extremely large volumes (i.e., >100 mL) and those with extremely low SC bioavailability before co-formulation.

The clinical significance of small increases in bioavailability is currently unknown for many drugs. For example, changes of 5–10 % in bioavailability would not be considered clinically relevant according to the US Food and Drug Administration (FDA) criteria for determining bioequivalence between a generic drug product and a reference drug, either by the $\pm$ 20 rule (average bioavailability of the generic is within $\pm$ 20 % of that of the reference formulation) or by the 80/125 rule (average bioavailability of the generic formulation is within 80–125 % of the reference formulation). In addition, where bioavailability has been shown to be increased by more than this threshold, the clinical impact depends on factors such as the drug’s therapeutic index, dosing, mechanism of action, pharmacokinetics, and other variables necessitating further consideration to determine the minimum increase required for a meaningful difference (Bass et al., 2018; Bhosle et al., 2017; Chow, 2014).

The focus on developing SC formulations with PE has also contributed to confusion regarding injection volumes, with a prevailing misconception that SC volumes are limited to 2–3 mL without a PE, leading to the development of high-concentration, small-volume formulations that are costly to develop and associated with additional challenges, such as protein–protein interactions (Desai et al., 2023). This misconception regarding injection volume limits is surprising as large-volume SC formulations have been available long before the use of PE. In addition, there have been several recent drug approvals of SC formulations without PE that have similar or larger volumes to those co-formulated with hyaluronidase (Alexion Pharmaceuticals Inc., 2024;

Table 1
Bioavailability data for biologic therapies with and without hyaluronidase.

Drug	Trastuzumab	Daratumumab	Rituximab	Atezolizumab	Pertuzumab	Crenezumab	Tocilizumab	Bococizumab	Adalimumab	Amivantamab
Drug target	HER2	CD38	CD20	PD-L1	HER2	Aβ40	IL6R	PCSK9	TNFα	EGFR-MET
Target location	Cell membrane	Cell membrane	Cell membrane	Soluble and cell membrane	Cell membrane	Soluble	Soluble and cell membrane	Soluble	Soluble	Cellular
SC Bioavailability, fraction (data source)	N/A	N/A	N/A	N/A	N/A	0.80 (Modelled using single ascending dose data of 600–7200 mg)(Nolan & Printz, 2024)	0.80 (SUMMACTA/ BREVACTA trial data using 162 mg weekly/bi-weekly dosing)(Abdallah et al., 2017)0.49 (healthy volunteer trial data using 162 mg single dosing) (Zhang et al., 2013)	0.30 (modelled using 300 mg single dosing)(Nolan & Printz, 2024)	0.70 (modelled using 40 mg single dosing)(Nolan & Printz, 2024)	0.62 (modelled using 1050 mg weekly-bi-weekly dosing)(Nolan & Printz, 2024)
SC bioavailability with hyaluronidase (data source)	0.77 (HannaH trial data using 600 mg Q3W dosing)[a] (Quartino et al., 2016)	0.70 (multitrial data using 1800 mg weekly-to-Q4W dosing)[a] (Luo et al., 2021)	0.63 (multitrial data using doses up to 2200 mg monthly)[a] (Gibiansky et al., 2021)	0.7 (trial data using 1800 mg dosing Q3W in the abdomen)0.83 (trial data using 1800 mg single dosing or 1200 mg bi-weekly dosing in the thigh)[a,b] (Felip et al., 2021)	0.71 (FeDeriCa trial data using x1 dose of 1200 mg followed by 600 mg Q3W)[a] (Wang et al., 2021)	0.80 (modelled using single ascending dose data of 600–7200 mg) (Nolan & Printz, 2024)	0.90 (modelled using 162 mg single dosing) (Nolan & Printz, 2024)0.83 (healthy volunteer trial data using 648 mg single dosing) (Morcos et al., 2013) 0.76 (healthy volunteer trial data using 324 mg single dosing) (Morcos et al., 2013)	0.33 (modelled using 150–450 mg single) (Nolan & Printz, 2024)	0.85 (modelled) (Nolan & Printz, 2024)	0.82 (modelled) (Nolan & Printz, 2024)0.65 (PALOMA trial data using 1050 mg dosing weekly-bi-weekly)(Krebs et al., 2022)
Date of initial FDA approval for use with hyaluronidase	2019	2020	2017	2024	2020	Not approved	Not approved for use with hyaluronidase	Not approved	Not approved for use with hyaluronidase	In trials for use with hyaluronidase

[a] No comparator without hyaluronidase was included in trial. [b]Bioavailability was reported as 0.829 following injection in the thigh and 0.711 following injection in the abdomen for an average bioavailability of 0.77.
Abbreviations: Aβ40, amyloid β; EGFR-MET, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PCSK9, Proprotein convertase subtilisin/kexin type 9; PD-L1, programmed cell death ligand 1; QxW, every x weeks; TNFα, tumour necrosis factor alpha.

Amgen Inc., 2021; Apellis Pharmaceuticals, 2024; Argenx BV, 2024; CSL Behring, 2010, 2017, 2022, 2023; Desai et al., 2023; Genentech Inc, 2024; Genentech Inc., 2020, 2021, 2024a, 2024b, 2024c; Janssen Biotech Inc., 2024; Takeda Pharmaceuticals Inc., 2024; UCB, 2024) (Table 2). It is important to note that while hyaluronidase can increase flow rate, achieving the fastest flow rates with co-formulated drugs necessitates a larger needle diameter, which independently contributes to increased flow. This effect may have been mistakenly attributed solely to the PE, when in fact, the larger needle diameter plays a substantial role (Shahriar et al., 2021; Watt et al., 2019).

In summary, there are currently limited publicly available data regarding the challenges that PEs present for formulation development and manufacturing. There is also limited information available about stakeholder perspectives on the benefits that PEs provide. This gap in understanding presents a challenge for organisations in balancing the potential benefits and limitations of these PE co-formulations, making it difficult to make informed decisions about their use versus other options. To address this gap, we conducted a survey of drug formulation experts with experience in developing drugs with PE co-formulations. These experts provided insights into both the perceived value and the challenges associated with PE use, drawing from their experience with formulation design, stability testing, and manufacturing considerations.

2. Methods

2.1. Study design

This was a global, online, anonymous survey conducted from 25 April to 6 May 2024 of Chemistry, Manufacturing, and Controls (CMC) and formulation experts familiar or experienced with co-formulating

Table 2
Approved large-volume biologic drug formulations for SC delivery.

Therapeutic Agent	Approval Year	Volume and Time	Hyaluronidase Dose	Indication	Needle Size	Delivery System	Reference(s)
Immune Globulin Subcutaneous (Human), 20 %	2010	Up to 400 mL (50 mL/site) based on indication and body weight	N/A	CIDP, PI	24G	Syringe pump	(CSL Behring, 2010, 2023)
Immune Globulin Subcutaneous 10 % (Human) with HYAL	2014	Requires a separate administration step with HYAL before SC infusion of immune globulin	0.5 mL rHuPH20 solution per 10 mL Immune Globulin	CIDP, PI	24G	Manual syringe & syringe pump	(Takeda Pharmaceuticals Inc., 2024)
Evolocumab	2015	3.5 mL over 5 mins	N/A	Selected patients with CVD or MACCE risk	29G	OBI	(Amgen Inc., 2021; Desai et al., 2023)
Rituximab/HYAL	2017	11.7 mL over ~ 5 mins 13.4 mL over ~ 7 mins	23,400 units	CLL, DLBCL, FL	25–30G	Manual syringe	(Genentech Inc., 2021; Melaragno, 2017)
Plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH)	2017	~8.6 mL (lyophilized drug with weight-based dosing for a 75 kg male)	N/A	HAE	Not Listed	Manual syringe	(CSL Behring, 2017, 2022)
Trastuzumab/HYAL	2019	5 mL over 2–5 mins	10,000 units per 5 mL	Breast cancer	25G	Manual syringe	(Desai et al., 2023; Genentech Inc, 2024)
Pertuzumab/trastuzumab/HYAL	2020	10 mL over 5 mins 15 mL over 8 mins	30,000 units per 15 mL or 20,000 units per 10 mL	Breast cancer	25–27G	Manual syringe	(Genentech Inc., 2020)
Daratumumab/HYAL	2020	15 mL over 3–5 mins	30,000 units	light chain amyloidosis, MM	23G	Manual syringe	(Desai et al., 2023; Janssen Biotech Inc., 2024)
Pegcetocoplan	2021	20 mL over 30–60 mins	N/A	C3G, primary IC-MPGN, PNH	29G	OBI	(Apellis Pharmaceuticals, 2024; Desai et al., 2023)
Ravulizumab	2022	7 mL over 10 mins	N/A	aHUS, gMG, PNH, NMOSD, STEC-HUS,	29G	OBI	(Alexion Pharmaceuticals Inc., 2024; Desai et al., 2023)
Rozanolixizumab	2023	3–6 mL up to 18 mins	N/A	gMG	26G +	Manual syringe	(UCB, 2024)
Efgartigimod/HYAL	2023	5.6 mL over 30–90 secs	10,000 (prefilled syringe) or 11,200 units (vial)	CIDP, gMG	25G	Manual syringe	(Argenx BV, 2024)
Atezolizumab/HYAL	2024	15 mL over 7 mins	30,000 units per 15 mL	ASPS, HCC, melanoma, NSCLC, SCLC	23–25G	Manual syringe	(Genentech Inc., 2024c)
Ocrelizumab/HYAL	2024	23 mL over 10 mins	23,000 units per 23 mL	MS	24–26G	Manual syringe	(Genentech Inc., 2024a)
Crovalimab	2024	4–6 mL between 2 and 3 injections if bodyweight > 100 kg	N/A	PNH	25–27G	Multiple manual syringes	(Genentech Inc., 2024b)

Shaded cells indicate biologics without hyaluronidase co-formulation. Table adapted with modification from: Desai M et al. mAbs 2023;15(1). Doi: 10.1080/19420862.2023.2285277) under the terms of the Creative Commons Attribution-NonCommercial License https://creativecommons.org/licenses/by-nc/4.0/. Abbreviations: aHUS, atypical hemolytic uremic syndrome; ASPS, alveolar soft part sarcoma; C3G, C3 glomerulopathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CLL, chronic lymphocytic leukaemia; CVD, cardiovascular disease; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; G, gauge; gMG, generalized myasthenia gravis; HAE, hereditary angioedema; HCC, hepatocellular carcinoma; HYAL, hyaluronidase; IC-MPGN, immune complex membranoproliferative glomerulonephritis; kg, kilograms; mAb, monoclonal antibody; MACCE, major adverse cardiac and cerebrovascular events; mins, minutes; mL, millilitres; MM, multiple myeloma; MS, multiple sclerosis; N/A, not applicable; NMOSD, neuromyelitis optica spectrum disorder; NSCLC, non-small cell lung cancer; OBI, on-body injector; PI, primary immunodeficiency; PNH, paroxysmal nocturnal hemoglobinuria; secs, seconds; SCLC, small cell lung cancer; STEC-HUS, Shiga toxin *E. coli* related hemolytic uremic syndrome.

drugs with PE. Prospective participants were identified from a large, global, third-party life sciences database that includes several biotechnology and pharmaceutical industry experts in various functions. Respondents were excluded if their specialization was in clinical development, medical affairs, commercial, or any other category outside of CMC; if they had less than two years of experience in their specialization; if they were not familiar with hyaluronidase; if they reported no direct experience with hyaluronidase and also indicated no or uncertain involvement with it; if they reported direct experience but had spent less than 5 % of their time on it and also indicated no or uncertain involvement; or if they were unsure about their role in decision making regarding SC drug products co-formulated with hyaluronidase. The survey included 11 questions related to participant demographics and 25 questions about the development of large-volume SC drugs co-formulated with PE, including benefits, challenges, and alternatives. Questions were a mix of multiple-choice, 4- or 5-point Likert scales from 1 (lowest) to 4 or 5 (highest), and free-text options.

2.2. Ethics

Institutional review board approval and informed consent were not required for this non-interventional study. All participants provided consent for data to be used for research purposes.

2.3. Data analysis

Responses to survey questions were tabulated and basic descriptive statistics were calculated. Results for questions asked with Likert scale response options are presented as mean (standard deviation [SD]) or as the number and percentage of participants (n [%]) choosing each category. Results for questions with binary responses are presented as number and percentage of respondents selecting each response. There was no formal sample size calculation and no formal hypothesis testing.

3. Results

3.1. Survey respondents

A total of 100 responses were analysed in the final data set. Most respondents were based in North America (all within the United States; 45 %), followed by Europe (34 %) and Asia (19 %) (Table 3).

3.2. Participant experience with PE

Overall, 91 % of respondents were employed by biotechnology or pharmaceutical companies, with 67 % of respondents working for mid-to-large-capacity organisations (e.g., $2–10 billion market capitalisation and >$10 billion market capitalisation, respectively; Table 3). Nearly half of respondents (46 %) were currently or previously employed by a company that directly markets PE such as hyaluronidase for co-formulation with drugs and most (95 %) were either the decision-maker or involved in the decision-making process. The mean (SD) duration of experience was 13.7 (5.9) years. All participants were experienced with hyaluronidase, with 89 % indicating that they were 'extremely familiar' or 'very familiar' with it. Most participants (70 %) had worked on between one and five SC drugs co-formulated with hyaluronidase during their career (mean [SD] number of co-formulated drugs, 5.1 [4.8]), although four respondents had worked on ≥ 16 co-formulations. Oncology was the most represented therapeutic area of experience for co-formulating drugs with hyaluronidase; this was expected, as most approved hyaluronidase-co-formulated therapies are within oncology (Table 3). Responses to survey questions from CMC experts with current/previous employment by a company that manufactures PE (n = 46) and from those without (n = 54) were found to be generally consistent, although there were slight differences in responses for certain aspects of co-formulation challenges; these differences are described in the following sections.

Table 3
Characteristics of survey respondents.

Characteristic, n (%)	Total (N = 100)
Region of residence/work	45 (45)
North America	34 (34)
Europe	19 (19)
Asia	2 (2)
Middle East	
Type of organisation	24 (24)
Large-capacity biotech/pharma[a]	43 (43)
Mid-capacity biotech/pharma[b]	17 (17)
Small capacity biotech/pharma[c]	7 (7)
Micro-capacity biotech/pharma[d]	6 (6)
CMC vendor	2 (2)
CRO	1 (1)
Independent CMC consultant	
Years of relevant experience	22 (22)
<10	55 (55)
10–20	23 (23)
≥20	
Familiarity with hyaluronidase	
Familiar	11 (11)
Very Familiar	34 (34)
Extremely familiar	55 (55)
Number of SC drugs co-formulated with hyaluronidase directly worked on during career	
0	2 (2)
1–10	88 (88)
11–20	8 (8)
>21	2 (2)
Involvement in projects or roles where hyaluronidase was a component (direct or indirect)	
Yes	94 (94)
No	3 (3)
Unsure	3 (3)
Current or previous employment by a company that manufactures PE	46 (46)
Proportion of time spent working directly on the development of SC drugs co-formulated with hyaluronidase	
<15 %	12 (11.8)
15–45 %	63 (61.7)
>45	23 (23.5)
Involvement in decision-making for SC drug products co-formulated with hyaluronidase	
Decision-maker	38 (38)
Involved in decision-making process	57 (57)
Not involved	5 (5)
Main area of experience in SC products co-formulated with hyaluronidase	
Oncology	51 (51)
Dermatology	17 (17)
Rheumatology	13 (13)
Neurology	10 (10)
Endocrinology	3 (3)
Gastroenterology	2 (2)
Other[e]	4 (4)

Data presented as n (%) unless otherwise noted. [a]>$10 billion market capitalization; [b]$2–10 billion market capitalization; [c]$250 million-$2 billion market capitalization; [d]<$250 million market capitalization; [e]"Other" included nephrology (n = 1), benign haematology (n = 1), primary care (n = 1) and immuno-oncology (n = 1). Abbreviations: CMC, Chemistry, Manufacturing, and Controls; CRO, contract research organisation; PE, permeation enhancers; SC, subcutaneous.

3.3. Challenges of PE

A total of 89 % of respondents considered the biophysical aspects of hyaluronidase to be moderately/very/extremely challenging (Table 4). The aspects of PE considered moderately to extremely problematic for development (i.e., compatibility, cost, timelines) were high drug interaction potential, temperature sensitivity, and pH sensitivity (Fig. 1).

Table 4
Responses to survey questions related to experiences with PE and opinions/beliefs around co-formulations.

Survey Question / Response	Total (N = 100)
How challenging are the biophysical properties of hyaluronidase when working with it before co-formulation with a drug product	
Not at all challenging	0
Slightly	11 (11)
Moderately	57 (57)
Very	29 (29)
Extremely	3 (3)
Time (months) to develop SC drug co-formulated with hyaluronidase	
0–3	0
4–6	5 (5)
7–9	18 (18)
10–12	32 (32)
13–15	21 (21)
16–18	24 (24)
Additional time (months) to develop a SC drug co-formulated with hyaluronidase versus a high concentration (>100 mg/mL) SC formulation without hyaluronidase	
0–6	10 (10)
7–12	34 (34)
13–24	28 (28)
>24	27 (27)
Other[a]	1 (1)
Weighted mean	16.7 months
Additional time (months) to develop a SC drug co-formulated with hyaluronidase versus a low concentration SC formulation without hyaluronidase	
0–6	18 (18)
7–12	37 (37)
13–24	29 (29)
>24	16 (16)
Weighted mean	13.9 months
Estimated increase in direct costs[b] (million USD) associated with co-formulating a SC drug with vs. without hyaluronidase	
<1	2 (2)
1–3	22 (22)
>3–6	51 (51)
>6–9	10 (10)
>9	15 (15)
Weighted mean	5.1 million USD
Top three most-selected challenging aspects of the manufacturing process for a drug co-formulated with hyaluronidase	
Complexity of CMC process	75 (25.0)
Analytical challenges/specifications	65 (21.7)
Formulation development costs/timelines	61 (20.3)
Perceived maximum concentration (IU/mL) of hyaluronidase in a co-formulated drug	
1000	6 (6)
2000	39 (39)
5000	32 (32)
10,000	8 (8)
No upper limit	15 (15)
Perceived maximum drug volume (mL) that can be administered SC as an immediate bolus without hyaluronidase	
<2	24 (24)
2–3	41 (41)
3–6	25 (25)
6–10	6 (6)
>10	4 (4)
Reason for maximum injection volume selected for SC bolus without hyaluronidase	
Peer-reviewed literature	31 (31)
Familiarity with commercialized biologics	44 (44)
Expert or colleague opinion	17 (17)
Lecture at conference/seminar	7 (7)
Other[c]	1 (1)
Perceived maximum drug volume (mL) that can be administered SC over several minutes (SC infusion) without hyaluronidase	
<2	10 (10)
2–3	32 (32)
4–6	40 (40)
7–10	13 (13)
>10	5 (5)
Reason for maximum injection volume selected for SC infusion without hyaluronidase	
Peer-reviewed literature	30 (30)
Familiarity with commercialised biologics	42 (42)
Expert or colleague opinion	22 (22)
Lecture at conference/seminar	6 (6)
Agreement with statement: 'Bioavailability is increased with the addition of hyaluronidase'	
Strongly disagree (1)	2 (2)
Disagree (2)	8 (8)
Agree (3)	78 (78)
Strongly agree (4)	12 (12)
Perceived impact of hyaluronidase on drug bioavailability	
≤10 %	14 (13.7)
11–15 %	24 (24.5)
16–20 %	29 (29.6)
21–30 %	20 (19.6)
>30 %	11 (11.2)
Perceived impact of hyaluronidase on drug bioavailability in respondents with current/previous experience in a company that manufactures PE (n = 45)	
≤10 %	6 (13.3)
11–15 %	11 (24.4)
16–20 %	10 (22.2)
21–30 %	11 (24.4)
>30 %	7 (15.6)
Perceived impact of hyaluronidase on drug bioavailability in respondents without current/previous experience in a company that manufactures PE (n = 53)	
≤10 %	8 (15.1)
11–15 %	13 (24.5)
16–20 %	19 (35.8)
21–30 %	9 (17.0)
>30 %	4 (7.5)
Changed beliefs regarding impact of hyaluronidase on drug bioavailability	
Overall	74 (74.7)
Participants with current/previous experience in a company that manufactures PE	40 (87.0)
Participants without current/previous experience in a company that manufactures PE	34 (64.2)

All data presented as n (%). [a]Free-text response from one participant stated that the time taken was 'the same' (i.e., no additional time was required for development of a co-formulation). [b]Such as development costs, drug product, engineering runs, line changes, etc., and excluding royalties, milestones or any other aspects of the deal structure. [c]Free-text response from one participant: 'limitations of products that administer' (i.e., the delivery device). Abbreviations: CMC, Chemistry, Manufacturing, and Controls; FDA, US Food and Drug Administration; PE, permeation enhancer; SC, subcutaneous; USD, United States Dollars.

3.4. Co-formulation challenges

For respondents indicating that hyaluronidase pH or temperature sensitivity is moderately/very/extremely problematic for development (n = 99), the top four challenges related to pH or temperature sensitivity during the co-formulation process were 'compatibility with the drug' (22.9 %), 'chemical stability' (20.5 %), 'manufacturing complexities' (15.2 %), and 'long-term storage conditions' (15.2 %) (Fig. 2). For respondents who indicated that the viscosity of hyaluronidase is slightly-to-very problematic (n = 93), the top identified challenges were 'healthcare professional (HCP) administration', 'product manufacturing processes', 'product stability', and 'patient pain during administration' (Fig. 2).

Incompatibility between drug product and PE during the feasibility stage of co-formulation was reported to be frequent; 29 % of participants reported that incompatibility occurred in a weighted mean of 36 % of cases (mode: 31–40 % of cases; Fig. 3a). Risk of failure was reported at

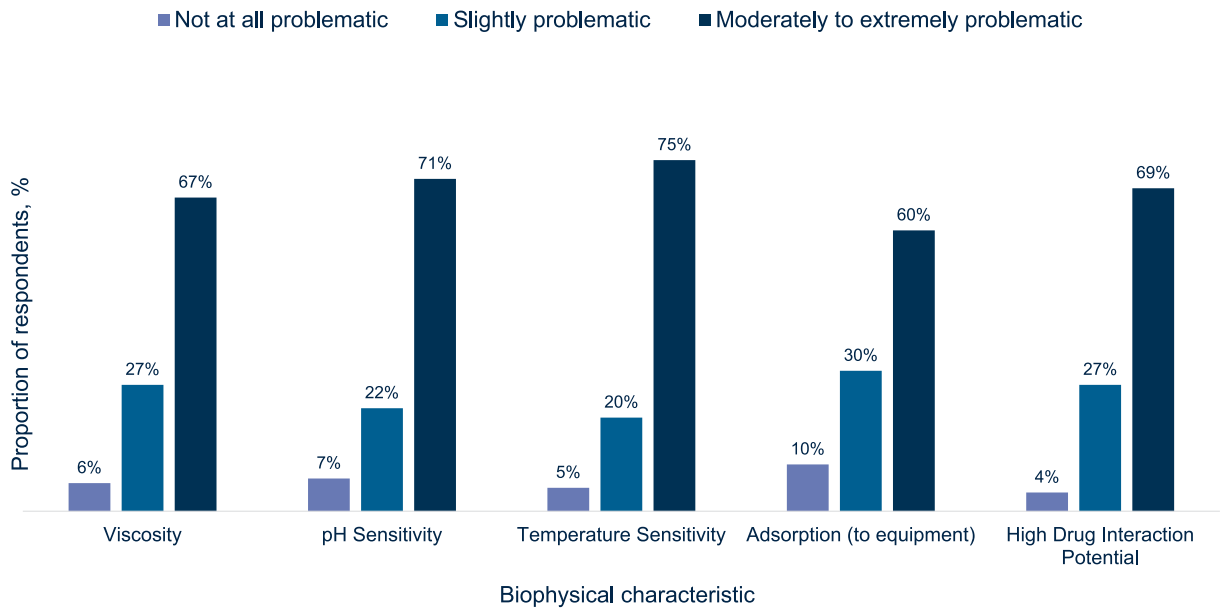

Fig. 1. Challenges of biophysical characteristics of PE in development (all respondents, N = 100). Abbreviations: PE, permeation enhancer. Fig. 1 **alt text:** Clustered bar graph showing the biophysical characteristics of permeation enhancers that survey respondents considered 'not at all problematic', 'slightly problematic', or 'moderately to extremely problematic'. Viscosity, pH sensitivity, temperature sensitivity, adsorption (to equipment), and high drug interaction potential were all considered 'moderately to extremely problematic' by ≥ 60 % of respondents.

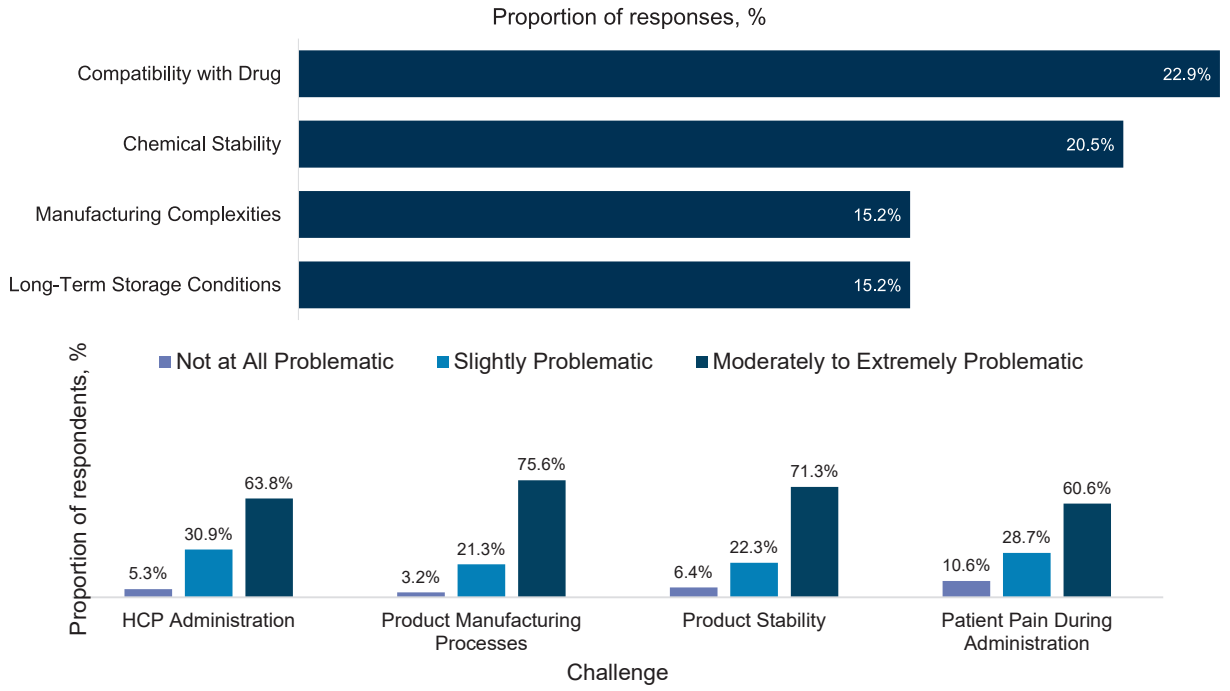

Fig. 2. Top four challenges associated with PE pH and temperature sensitivity during co-formulation (n = 99) (A) and challenges with viscosity in PE co-formulations (n = 93) (B). A: Respondents were included if they indicated that hyaluronidase temperature or pH sensitivity were moderately/very/extremely problematic in terms of development risk (survey question 3). B: Respondents were included if they indicated that hyaluronidase viscosity was slightly/moderately/very/extremely problematic in terms of development risk (survey question 3). Abbreviations: HCP, healthcare professional; PE, permeation enhancer. Fig. 2 **alt text:** Two bar graphs labelled A and B. Graph A shows the challenges during co-formulation development associated with the pH and temperature sensitivity of permeation enhancers, with the four most common being compatibility with drug, chemical stability, manufacturing complexities, and long-term storage conditions. Graph B shows the challenges associated with viscosity in permeation enhancer co-formulations, with ≥ 60.6 % of respondents indicating that HCP administration, product manufacturing processes, product stability, and patient pain during administration were 'moderately to extremely problematic'.

all stages; however, the two stages of development that posed the highest probability of failure were quality/stability testing (selected by 38 % of respondents) and co-formulation development (selected by 31 % of respondents; Fig. 3b). Participants with current or prior employment by a PE company reported incompatibility in a weighted mean of 45 % of cases at the feasibility stage (mode: 31–40 %), while those without such experience reported incompatibility in a weighted mean of 40.2 % of cases (mode: 31–40 %).

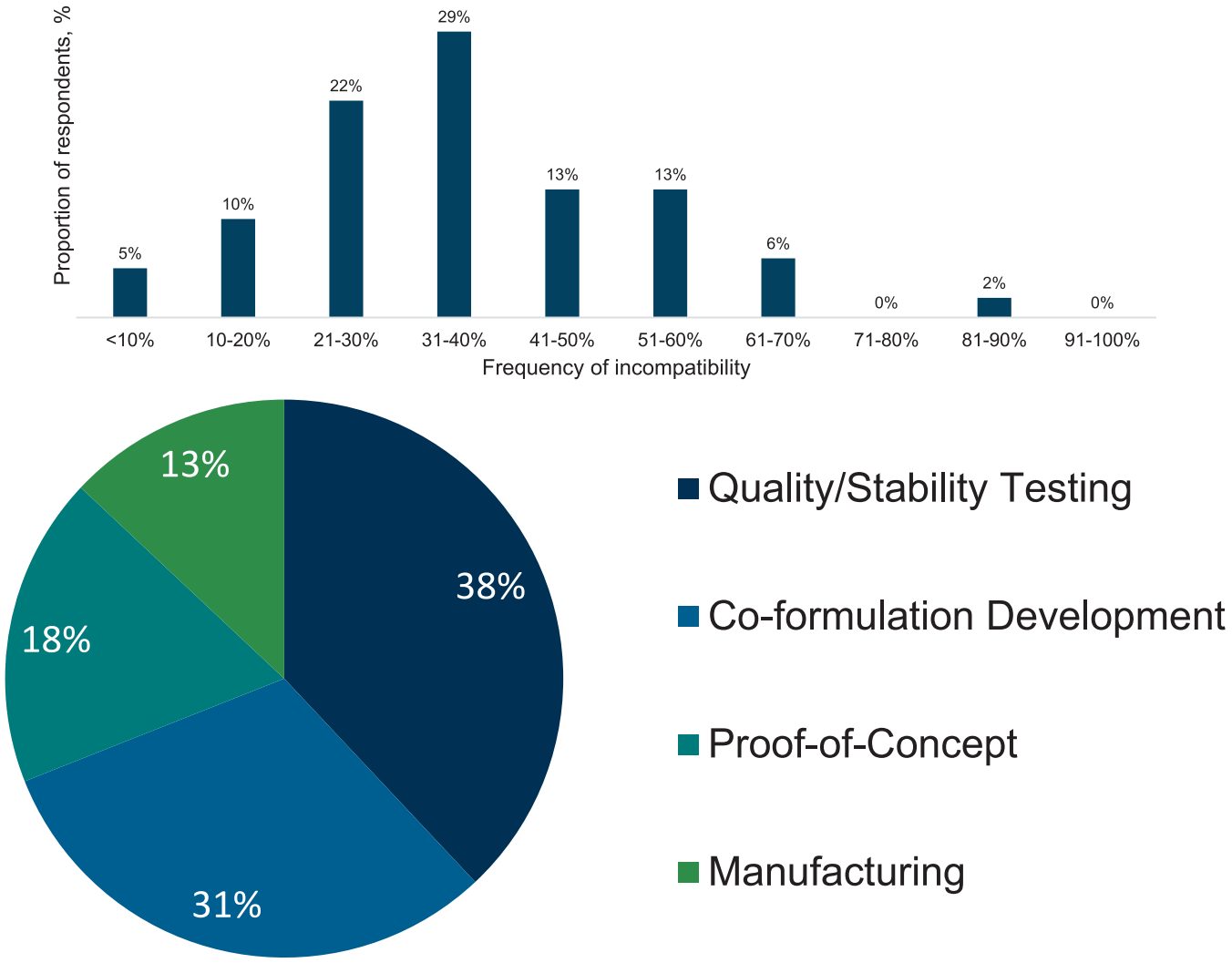

Fig. 3. Frequency of incompatibility encountered between drug product and PE during feasibility stage of co-formulation (A) and stage of development for SC co-formulated with PE that poses the highest risk of failure (B) (all respondents; N = 100). Abbreviations: PE, permeation enhancer. Fig. 3 **alt text:** Two graphs labelled A and B. Graph A is a bar chart showing the reported frequency of incompatibility between drug and permeation enhancer during the feasibility stage of co-formulation development, with 29% of respondents indicating that incompatibility occurs in 31–40% of cases. Graph B shows a pie chart with the stage of co-formulation development (quality/stability testing, co-formulation development, proof-of-concept, manufacturing) respondents judged to pose the greatest risk of failure. A total of 38% of respondents judged quality/stability testing and 31% of respondents judged co-formulation development to be the stage with the highest risk of failure.

Several features of monoclonal antibodies were identified as more favourable for compatibility and stability when co-formulating with hyaluronidase; these included low concentration (<100 mg/mL; rated 'extremely favourable' by 26 %), single-agent drug (rated 'extremely favourable' by 23 %), humanised (rated 'extremely favourable' by 21 %), and monospecific (rated 'extremely favourable' by 19 %) (**Fig. S1**). Respondents indicated that a single, monospecific drug is more stable and predictable with less risk of incompatibility. Use of a humanised drug was perceived to reduce immunogenicity and adverse drug pharmacokinetics. Low-concentration formulations were favoured as they allow for reduced viscosity, easing drug administration and manufacturing while providing more formulation stability.

The time required to develop a SC drug co-formulated with hyaluronidase varies depending on the characteristics of the drug, company resources, and previous expertise with PE. However, respondents indicated that co-formulating a drug with hyaluronidase increased the time to trial readiness compared with a low-concentration drug formulation by a weighted mean of 13.9 months (mode 7–12 months), with 66 % of respondents reporting an increase of between seven and 24 months (Table 4) and 16 % of respondents estimated the increased time required to be > 24 months. Hyaluronidase co-formulations were also associated with increased direct formulation development costs (e.g., costs of development, drug product, engineering runs, and production line modifications) in addition to costs related to aspects of the licensing agreement structure. The weighted mean increase in direct formulation development costs was reported to be 5.1 million USD (mode > 3–6 million USD), with 15 % of respondents indicating that direct formulation development cost increases were > 9 million USD (Table 4).

The biophysical properties of a drug were reported to be the most influential factor impacting the decision to continue with drug co-formulation: 84 % rated biophysical properties as moderately or highly influential (**Fig. S2**). However, development timelines and costs during the decision-making process for SC co-formulations were also rated as moderately or highly influential by 78 % and 76 % of respondents, respectively.

3.5. Manufacturing challenges

The top challenges during the manufacturing process for a drug co-formulated with hyaluronidase were the complexity of the CMC processes, analytical challenges and specifications, and formulation development costs and timelines (Table 4). The pH and temperature sensitivity of PE were also reported to affect SC product development beyond compatibility, with impact on product storage identified as a key problem (Fig. 4). Three respondents indicated other areas beyond coformulation where pH and temperature may impact development; these were 'regulatory requirements', 'batch variation', and side effects such as 'allergic reactions after administration'.

3.6. Perceptions of SC volume administration capacity

A total of 65 % of respondents believed that 3 mL was the maximum SC drug volume feasible as a bolus (autoinjector) without hyaluronidase and 58 % of respondents selected a larger volume of > 3 mL if administering over several minutes as a SC infusion (pump or OBI) without hyaluronidase. These selections were largely reported to be based on personal experience: familiarity with commercialised biologics was reported as the reason for beliefs regarding bolus injections in 44 % of participants and was the reason for beliefs regarding SC infusions in 42 % of participants. Peer-reviewed literature was the second most frequent reason, reported by 31 % of respondents in relation to bolus injections and 30 % of respondents in relation to infusions (Table 4).

Responses from participants with current and/or previous employment by a company that manufactures PE and those without current or previous employment by a company that manufactures PE appeared to be similar. For example, 61 % and 68 % of respondents with and without current and/or prior employment by a company manufacturing PE, respectively, selected 3 mL as the maximum volume that can be injected without a bolus. When administered over several minutes as a SC infusion, 59 % and 57 % indicated that the volume of the SC drug can exceed 3 mL.

3.7. Perceptions of hyaluronidase co-formulations

In terms of drug concentrations, most participants selected 2000 IU/mL or 5000 IU/mL as the upper limit concentration of hyaluronidase when co-formulated with a drug (Table 4). Hyaluronidase was perceived by 90 % of respondents to increase SC drug bioavailability, with 31.6 % (31/98) selecting the increase in bioavailability to be > 20 % (Table 4). When presented with a data table showing reported changes in bioavailability (**Table S1**), most respondents (74/99, 74.7 %) reported that the data changed their belief about hyaluronidase's impact on bioavailability (Table 4). For respondents who indicated that the data did not change their beliefs, an overarching factor was the lack of published, peer-reviewed data and the large number of unknowns as all drugs except one have unpublished data. Bioavailability enhancement was perceived to vary by product, requiring a case-by-case evaluation with clinical data. For some respondents, the data were consistent with their existing understanding.

Of the 45 respondents with current and/or previous employment in a

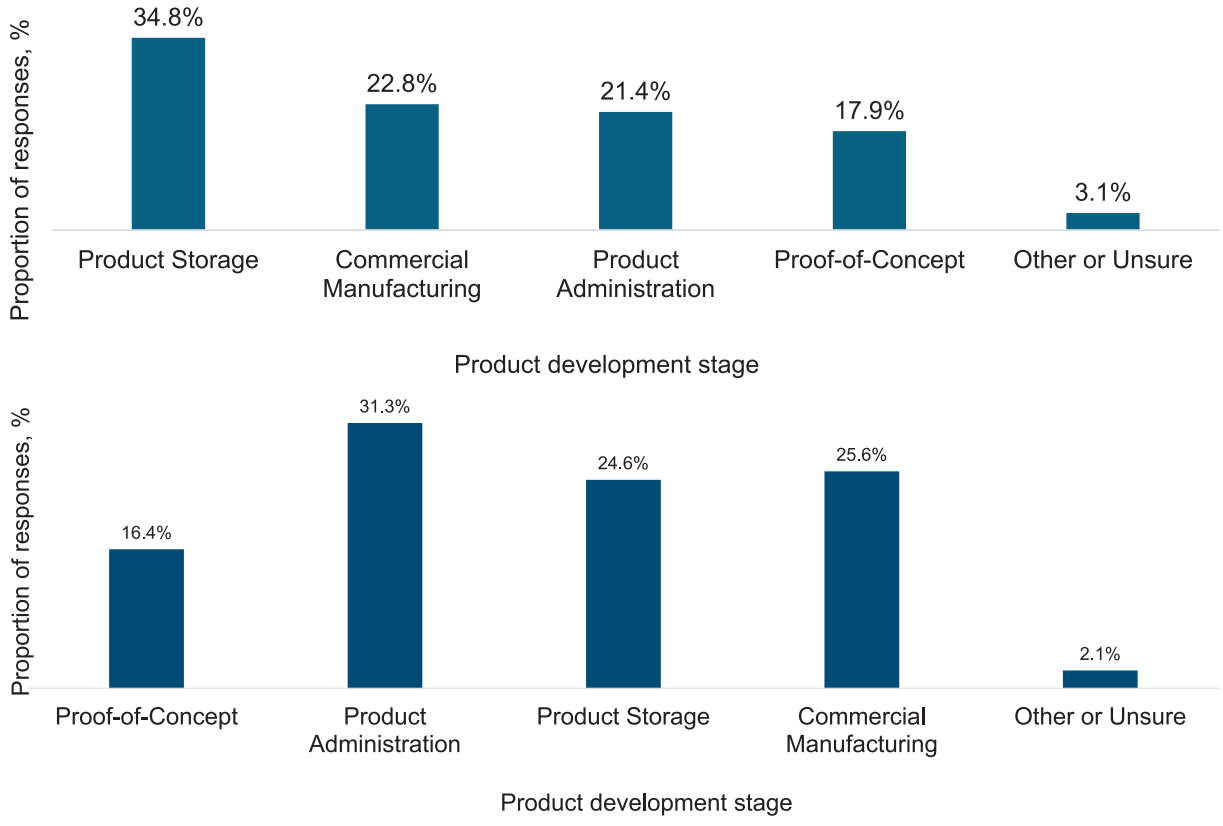

Fig. 4. Impact of PE pH and temperature sensitivity (n = 99) (A) and PE drug formulation viscosity (n = 93) (B) on SC product development beyond compatibility. A: Respondents were included if they indicated that hyaluronidase temperature or pH sensitivity were moderately/very/extremely problematic in terms of development risk (survey question 3). B: Respondents were included if they indicated that hyaluronidase viscosity was slightly/moderately/very/extremely problematic in terms of development risk (survey question 3). Abbreviations: PE, permeation enhancer; SC, subcutaneous. Fig. 4 **alt text:** Two bar graphs labelled A and B. Graph A shows the product development stage most impacted by the pH and temperature sensitivity of permeation enhancers (product storage, commercial manufacturing, product administration, proof-of-concept, and other/unsure), with 34.8% (largest proportion) of respondents indicating that product storage is most impacted. Graph B shows the product development stage most impacted by the viscosity of permeation enhancers (product storage, commercial manufacturing, product administration, proof-of-concept, and other/unsure), with 31.3% (largest proportion) of respondents indicating that product administration is most impacted.

company that manufactures PE, 40.0 % (18/45) indicated that hyaluronidase increases bioavailability by > 20 %. In contrast, 24.5 % (13/53) of respondents without this employment history selected an increase in bioavailability with hyaluronidase of > 20 %. When presented with bioavailability data, 87 % of the respondents with current and/or previous PE company employment reported that they would change their beliefs regarding bioavailability, versus only 64.2 % of the respondents without experience in a company that markets PE (Table 4).

4. Discussion

This survey of CMC and formulation science experts experienced in co-formulation development highlights several challenges associated with PE. The pH and temperature sensitivity, adsorption to equipment, and high drug interaction potential during co-formulation were identified as particularly problematic aspects of hyaluronidase during drug co-formulation, while pH and temperature sensitivity were identified as presenting specific challenges during co-formulation and manufacturing, particularly for drug compatibility and chemical stability. While PE can enhance drug dispersion facilitating faster injections, co-formulations with PE were reported to carry a notable risk of failure, especially during stages such as co-formulation development and quality and stability testing.

Hyaluronidase is known to be particularly sensitive to pH and temperature (Chen et al., 2016), requiring careful handling and storage. Our survey study demonstrates how the addition of hyaluronidase adds complexity to the drug development process from co-formulation development and manufacturing to storage and administration. The optimal pH of ~ 5 and temperature of 4 °C for co-formulations with hyaluronidase can be challenging to implement, since commercial monoclonal antibodies typically have a pH of 4.8 to 8.0 and pH impacts protein charge and formulation stability as well as administration site pain, indeed a physiologic pH is recommended to minimize pain associated with injection (Chen et al., 2016; Cheney et al., 1991; Desai et al., 2023; Talley & Alexov, 2010). Incompatibility between drug and PE was reported to occur in around a third of cases in our survey. Stricter temperature requirements not only impact manufacturing and development but may also impact patients doing drug self-administration (Desai et al., 2023; Eisenberg, 2021).

Publicly available data regarding the increased costs of co-formulation with PE are lacking. Respondents indicated that, in their experience, co-formulations are associated with increased costs, with 15 % reporting this increase to be more than $9 million USD. These costs are highly speculative, since not all experts involved in drug formulation development have oversight of costs. In fact, it is likely that only the final decision-maker has full oversight (38 % of respondents to this survey indicated that they were the decision-maker). Some of the increased costs may be attributed to the need to source on-patent drugs for co-formulation development. In addition, co-formulations frequently led to delays in clinical trial readiness by an average of 13.9 months, with 27 % of respondents reporting delays of more than two years. Considering that development costs and timelines were identified as pertinent factors when deciding whether to proceed with drug development, challenges with PE should be considered carefully as they could have notable implications for launch-readiness. This was recently observed with the SC formulation of the complement inhibitor, ravulizumab, which was announced in 2017 as being developed with hyaluronidase (Alexion Pharmaceuticals Inc., 2017) but was approved nearly five years later in July 2022 by the US FDA as a total 7 mL dose without hyaluronidase, delivered via two on-body injectors (Alexion Pharmaceuticals Inc., 2024). Interestingly, all currently approved SC complement inhibitors are large-volumesdelivered without a PE: ravulizumab (Alexion Pharmaceuticals Inc., 2024), crovalimab (up to 6 mL using multiple injections) (Genentech Inc., 2024b), and pegcetacoplan (20 mL via syringe pump or on-body injector) (Apellis Pharmaceuticals, 2024). This may imply that there are potential drug class-related incompatibilities with PE (in this case with injectable complement therapeutics). Delays were also observed with the SC formulations of efgartigimod (Argenx BV, 2023a), pembrolizumab (Reuters, 2022), rybrevant (Endpoints News, 2024) atezolizumab (Fierce Pharma, 2024), and nivolumab (US Food and Drug Administration, 2024) all of which include hyaluronidase. In 2017, Bristol Myers Squibb were commencing development of SC co-formulations with hyaluronidase for eleven products (Bristol-Myers Squibb, 2017); however, there has only been one approval to date, and co-formulations of BMS-986179 or BMS-986258 with hyaluronidase have not progressed beyond Phase 1 (NCT02754141; NCT03446040). Moreover, work on a SC autoinjector was later abandoned (BioPharmaDive, 2023; Fierce Pharma, 2023). However, an important point to highlight is that companies with considerable prior experience in co-formulations with PE likely possess the resources and expertise needed to navigate the additional challenges it presents (Endpoints News, 2024).

Some experts in our survey highlighted challenges with hyaluronidase during the clinical trial phase (i.e., proof of concept), reinforcing the risks associated with transitioning from IV to SC administration via co-formulation. While this strategy is often pursued as a low-risk lifecycle management approach, there have been failures. For example, one manufacturer of hyaluronidase reported that they have a 100 % Phase 3 to regulatory approval success rate (Fusion Media Limited, 2024), but this figure does not account for the failure of a co-formulation of efgartigimod alfa and hyaluronidase in a Phase 3 trial treating patients with primary immune thrombocytopenia (NCT04687072) or a Phase 3 trial in patients with pemphigus (NCT04598451). Remarkably, the trial in primary immune thrombocytopenia not only failed to meet the primary endpoint but also demonstrated inferior efficacy compared to placebo (Argenx BV, 2023b). As for the IV formulation of efgartigimod, it demonstrated positive top-line results (Broome et al., 2023), has secured approval in Japan (GlobeNewswire, 2024), and is undergoing an additional trial pursuing FDA approval. This underscores the reality that while SC co-formulations may offer commercial advantages, they also introduce scientific and regulatory risks that can affect drug development timelines and market viability. Greater transparency in co-formulation development and manufacturing could help companies make more informed decisions, reducing the likelihood of costly delays or failed programs.

Respondents selected several features of monoclonal antibodies as more favourable for compatibility and stability when co-formulating with hyaluronidase, including ‘single-agent drug’. This likely reflects experience with co-formulation development to date, as co-formulations have largely been developed for single-agent mAbs (Nolan & Printz, 2024). More recently, there has been a shift toward developing bispecific and multidrug therapies for immuno-oncology indications. Further research is needed to explore how these newer modalities may integrate with hyaluronidase in the future (Maccagno et al., 2024).

Overall, 42 % of respondents selected 3 mL as the upper limit for drugs administered over several minutes as a SC infusion without hyaluronidase despite the availability of larger-volume SC formulations without PE (Desai et al., 2023) (Table 2). For SC injections as an immediate bolus without hyaluronidase, 65 % of respondents selected 3 mL as the upper limit, while around 35 % of respondents thought that a volume of > 3 mL could be administered (Desai et al., 2023; Roethlisberger et al., 2017). A recent systematic review explored the range of volumes used for large-volume SC formulations of investigational and approved therapeutics (Green et al., 2024). For the 182 identified large-volume formulations, volumes ranged from 2–5 mL to > 30 mL. In the 2–5 mL range, non-oncology indications were more frequent, while in the range of > 5 to 30 mL, oncology indications were more frequent. Indeed, large-volume preparations without PE for SC use are approved for Immune Globulin Subcutaneous (Human), 20 % (CSL Behring, 2010, 2023), evolocumab (3.5 mL) (Amgen Inc., 2020), and more recently pegcetacoplan (20 mL) (Swedish Orphan Biovitrum Ltd., 2022), ravulizumab (7 mL) (Alexion Pharmaceuticals Inc., 2024), and

rozanolixizumab (3–6 mL) (UCB, 2024) (Table 2). As more than half of the respondents in this survey study were experienced in developing SC products for oncology indications, this may explain the misperception regarding volume limitations, particularly considering the high proportion of respondents who based their understanding of SC volume limits on their familiarity with commercialized biologics. Understanding of volume limits may therefore vary depending on area of experience. Overall, our survey indicated that around 40 % of CMC and formulation science experts did not understand SC volume limits for a bolus SC injection versus a SC infusion.

Several publications fail to clarify the distinction between SC bolus and SC infusion (Bookbinder et al., 2006; Connor et al., 2020; Davis et al., 2024; Ghosh et al., 2023; Grea et al., 2024; Locke et al., 2019; Shi et al., 2021). This oversight subtly reinforces the misconception that certain volumes, such as 2 or 3 mL, represent fixed limits for SC delivery irrespective of whether the administration is a bolus over several seconds or an infusion over several minutes. This finding is concerning, as it stifles innovation and could hinder both the development of large-volume SC drug candidates and the adoption of advanced drug delivery technologies such as pumps and OBIs that are specifically designed to enable large-volume SC administration without co-formulation. Indeed, a recent survey of oncology drug development experts indicated that more than 90 % of respondents had observed deprioritization or abandonment of a drug due to challenges in achieving volumes of $\leq$ 3 mL for SC administration (M. Desai, O. Rahman, et al., 2025). This volume misconception also drives companies to pursue high-concentration SC formulations, which can increase development time, cost, and risk (M. Desai, A. Kundu, et al., 2025). In a recent survey of drug formulation experts, high-concentration formulation development was associated with a weighted mean delay of 11.3 months, with specific challenges including solubility, viscosity, and aggregation issues (M. Desai, A. Kundu, et al., 2025). Most respondents stated that they believe hyaluronidase increases drug bioavailability, with over 30 % selecting the increase to be $>$ 20 %. This is of concern since bioavailability data for SC formulations with versus without hyaluronidase show small differences, are comprised of values based on modelling, are inconsistent, or remain unpublished. However, the estimates provided here are broadly aligned with the limited data currently publicly available (Table 1), although the clinical relevance of these changes in bioavailability remains to be determined (Bass et al., 2018; Bhosle et al., 2017; Chow, 2014). The most common free-text statement indicated that drugs co-formulated with PE often lack published bioavailability data compared to SC formulations without PE, making it challenging to draw conclusions. Companies may intentionally choose not to publish bioavailability data, creating uncertainties that influence decision-making and allow for flexible interpretation. This perceived but often misleading benefit of improved bioavailability has likely contributed to public misconceptions on the topic. Encouragingly, approximately 75 % of participants who were presented with publicly available bioavailability data adjusted their beliefs, indicating a strong receptiveness to verifiable data and underscoring the importance of "trust but verify." These findings highlight the need for enhanced educational initiatives and improved data transparency.

Large-volume SC delivery technologies have the potential to address challenges associated with co-formulations while remaining compatible with drugs co-formulated with PEs. For example, respondents indicated that viscosity presented a challenge for HCP administration of co-formulated drugs. Devices such as OBIs and infusion pumps are designed for patient comfort and may simplify drug delivery by allowing for hands-free administration (Badkar et al., 2021; Canè Medical Technology, 2024; Enable Injections, 2024). It is worth emphasising that these technologies are not mutually exclusive. In fact, large-volume delivery devices such as OBIs can be integrated with PEs to enhance the experience for nurses, pharmacists, and, most importantly, patients. For nurses/HCPs, OBIs are often preferred, since they can improve clinic efficiency and reduce the risk of repetitive strain and needlestick injuries associated with manual syringe administration (M. F. Desai, B. et al., 2025; Parmar et al., 2025; Sanchez Avello et al., 2025). For pharmacists, it alleviates workload by enabling chairside preparation by a nurse, streamlining pharmacy operations, and minimising drug wastage (M. Desai, M. Blewett, et al., 2025). This is particularly beneficial in cases where a patient is discharged against medical advice or when therapy adjustments occur after drug mixing. For patients, this approach offers significant advantages over traditional syringes or syringe pumps. (Parmar et al., 2025) OBIs enhance convenience by allowing mobility during administration, incorporating a hidden needle mechanism for added safety, and offer greater ease-of-use (Wasserman et al., 2022).

This study has limitations. Respondents indicated that the viscosity of hyaluronidase presented a particular challenge. However, the viscosity-related survey questions were not framed tightly enough to isolate the viscosity of hyaluronidase specifically. All drugs currently co-formulated with hyaluronidase are high-concentration formulations ($\geq$100 mg/mL) which typically have a high viscosity. This may have led the CMC and formulation science experts to respond with respect to the viscosity of the overall formulation which does introduce several challenges. It is important to note that hyaluronidase itself is not a high-viscosity substance; this distinction should have been emphasised more clearly in the survey. Use of Likert scales may have limited responses and unique perspectives. In particular, there was no neutral response option to the question 'To what extent do you agree with the following statement: Bioavailability is increased with the addition of hyaluronidase (e.g., rHuPH20)?'. This may have led to some respondents selecting 'agree' due to assumptions based on the mechanism of action of hyaluronidase. Additionally, since the survey was anonymised, we were not able to collect more granular data, such as the individual drugs on which respondents had worked. However, to our knowledge, this is the first study to collect insights on PE and SC drug formulation from a global cohort of experts in CMC drug formulation with a cumulative experience of 1,372 years, including a large proportion of respondents with current or previous employment by a company that manufactures and licenses PE for drug development.

Data on perspectives and challenges regarding co-formulation of SC drugs with PE have historically been limited due to the scarcity of individuals with experience with SC drugs co-formulated with PE as well as the difficulty with reporting information restricted by corporate confidentiality agreements. Additionally, while information on formulation challenges and bioavailability exists, there is a lack of transparency in publication. The companies do not publicly discuss challenges with drug co-formulation, and most published bioavailability data comparing formulations with and without PE have been modelled rather than derived from clinical trial results. This anonymous survey allowed us to report this expertise without breaching corporate policies and provides valuable insights. Moreover, our cohort of CMC experts is representative of currently approved hyaluronidase co-formulations, all of which have been developed by large- to mid-capacity pharmaceutical companies and most of which have been for oncology indications, which was the most represented area of co-formulation experience in our sample.

The challenges associated with co-formulating biologics with hyaluronidase take on added significance in light of the FDA's recent public release of Complete Response Letters, which revealed that over 70 % of rejections were due to CMC issues such as facility readiness, process validation, and stability (Slabodkin, 2025). Given that hyaluronidase co-formulations involve introducing a second agent, they are already associated with heightened CMC risk compared with single-agent products. As such, developers considering the use of hyaluronidase should carefully weigh the potential risks to development timelines and regulatory success before proceeding.

5. Conclusions

Co-formulating SC drugs with PE poses challenges during early

development, with incompatibility reported in around a third of cases. These challenges extend downstream due to the biophysical properties of PE, which are inherent and therefore challenging to circumvent. The common yet misleading belief that SC drug delivery is limited to ≤ 3 mL, along with the occasional incompatibility between hyaluronidase and biologic drugs, has likely led to the deprioritization of promising therapeutic candidates and a tendency to overlook alternative large-volume SC delivery methods such as OBIs and infusion pumps. While the value proposition of hyaluronidase in enhancing bioavailability remains unclear given that available data are unpublished, inconsistent, nonsignificant, or based on modelling, our findings indicate that CMC and formulation science experts are receptive to verifiable data. Thus, targeted educational efforts could be instrumental in dispelling misconceptions and broadening the landscape of SC drug development. Moreover, the distinction between SC bolus and SC infusion must be clearly defined when discussing volume limits. Conflating these terms not only perpetuates misunderstandings but may also stifle innovation in drug delivery and impede progress in drug development. By addressing these misconceptions regarding PE and volume limitations and exploring available large-volume SC delivery strategies, the industry can ensure that promising therapeutics are not unnecessarily restricted due to perceived volume limitations. Most importantly, large-volume SC delivery technologies such as PEs and OBIs can be integrated to optimise both injection speed and patient comfort, enhancing the patient and HCP experience and providing pharmaceutical companies with greater flexibility in lifecycle management.

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CRediT authorship contribution statement

Mehul Desai: Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Srini Tenjarla:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Michael Hageman:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Hao Lou:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Changquan Calvin Sun:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Feng Zhang:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Omar Rahman:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Wei Chen:** Conceptualization, Data curation, Formal analysis, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mehul Desai reports a relationship with Enable Injections Inc that includes: employment. Omar Rahman reports a relationship with Enable Injections Inc that includes: employment. Srini Tenjarla reports a relationship with Serina Therapeutics Inc that includes: employment. Feng Zhang reports a relationship with US Food and Drug Administration that includes: funding grants. Feng Zhang reports a relationship with Ashland Inc that includes: consulting or advisory. Wei Chen reports a relationship with WuXi Biologics, USA that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

MD, ST, MH, HL, CCS, FZ, OR, and WC were responsible for conceptualisation, data curation, formal analysis or interpretation, reviewing and critically revising the manuscript, and approving the final draft, and agree to be accountable for the accuracy and integrity of this manuscript.

Role of the funding source

The study sponsor, Enable Injections, Inc. (OH, USA), was involved in the study design, data collection and analysis, decision to publish, and preparation of the manuscript.

Disclosure of interest

MD is an employee of Enable Injections, Inc. OR is a former employee of Enable Injections. ST is an employee of Serina Therapeutics Inc. WC is an employee of WuXi Biologics, USA. FZ reports grants or contracts from the US Food and Drug Administration and consulting fees from Ashland Inc. MH, CCS and HL have no potential competing interests to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2025.126515.

Data availability

The data used to develop this manuscript are available from the corresponding author upon reasonable request.

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Glossary

CMC: Chemistry, Manufacturing and Controls
FDA: US Food and Drug Administration
HCP: healthcare professional
IgG: immunoglobulin G isotype
IU: international units
IV: intravenous
mAb: monoclonal antibody
OBI: on-body injector
PE: permeation enhancer
rHuPH20: recombinant human hyaluronidase
SC: subcutaneous
SD: standard deviation
USD: United States dollar