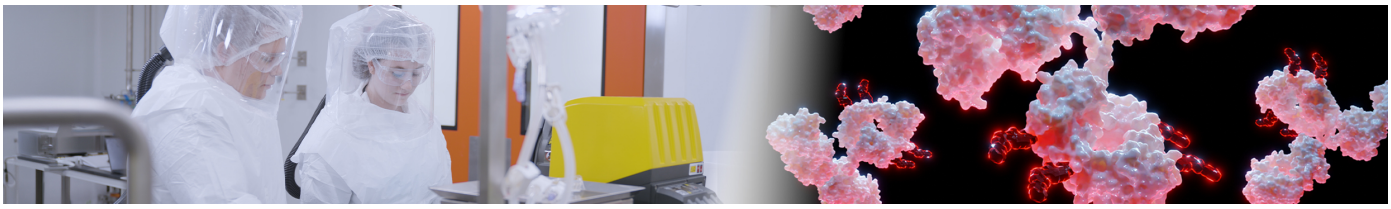
WHITE PAPER

Improvements in ADC Efficacy and Stability Through Proprietary Hydrophilic Linker Platform

SoluFlex Link™, enabling the next generation of ADC therapeutics

LOTTE BIOLOGICS
Possibilities Beyond Limits



Overview

Antibody-drug conjugates (ADCs) are reshaping the oncology landscape by combining the targeting precision of monoclonal antibodies with the potency of cytotoxic payloads. However, as ADC payloads become increasingly potent and hydrophobic, developers are encountering growing challenges that affect both drug performance and manufacturability, including aggregation, reduced solubility, and instability.

These issues are frequently observed during ADC process development and scale-up. Across multiple ADC programs, payload-driven hydrophobicity can impact conjugation efficiency, product stability, purification behavior, and overall process robustness, making it a key factor influencing the developability and manufacturability of next-generation ADCs.
As biotech companies pursue alternatives that can improve the pharmacokinetic profiles of today's more potent therapeutics, linkers with better physicochemical properties than the conventional linkers that were mainstays in early ADC applications are attracting attention. As a result, hydrophilic linkers capable of counteracting some of the inherent hydrophobicity of ADC payloads have emerged as enabling solutions for advancing increasingly complex, and highly hydrophobic payloads.

Hydrophobicity, which has the potential to negatively impact both a drug's developability and its ultimate safety and potency, has become a growing concern in ADC development as organizations work to conjugate more hydrophobic cytotoxic payloads to a single antibody. Low DAR can reduce payload delivery per antibody and compromise potency, whereas excessively high DAR may worsen physicochemical properties (e.g. hydrophobicity/aggregation), leading to faster systemic clearance, reduced exposure, and an increased risk of toxicity and immunogenicity.

Designed to improve solubility and mitigate issues that can arise from payload-derived hydrophobicity, hydrophilic linkers have consequently proliferated in the market. Options such as polyethylene glycol (PEG)-based linkers can enhance ADC performance, paving the way for a wider pipeline and greater commercial potential.
Yet many of these linker formats come with their own challenges, including cost considerations, synthesis complexity, and biocompatibility, which can complicate development in unique ways.

As ADC pipelines expand, hydrophilic linker design has become central to optimization efforts. Designed to address both hydrophobicity in ADC development and overcome the challenges of other hydrophilic linkers, SoluFlex Link™ offers developers more favorable physicochemical and pharmacological properties for their therapeutics within an end-to-end ADC development platform.

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Hydrophobic Payloads as the Primary Driver of ADC Instability

In most ADC designs, hydrophobicity originates primarily from the payload rather than the linker itself. Many of the cytotoxic agents used in ADCs, including microtubule inhibitors and DNA-damaging agents, are inherently hydrophobic molecules.

This innate hydrophobicity is often advantageous at the cellular level, as it facilitates membrane permeability and intracellular activity, which positively impacts ADC efficacy through the bystander effect.

However, when multiple hydrophobic payload molecules are conjugated to a large protein such as an antibody, the cumulative hydrophobic effect can become a major determinant of the ADC's physicochemical behavior.

As DAR increases, the antibody surface gains new hydrophobic groups, raising the likelihood of intermolecular interactions that can lead to aggregation, reduced solubility, and conformational instability.

Even modest increases in DAR can disproportionately amplify hydrophobic behavior, particularly with highly hydrophobic payloads, a phenomenon that typically places practical limits on achievable DAR values. While higher DAR constructs theoretically deliver more payload per targeting event, they also introduce increased risks of instability and aggregation. In many cases, hydrophobicity becomes the primary constraint for payload loading.

Historically, developers often addressed these challenges by lowering DAR. Reduced DAR constructs typically exhibit improved stability and less aggregation, but this strategy comes with important trade-offs. Reducing DAR decreases the amount of payload deliver per antibody, which may reduce potency and require higher doses to achieve therapeutic effect, potentially increasing systemic toxicity.

SoluFlex Link™ as a Next-Generation Hydrophilic Linker Platform

One of the most important applications of hydrophilic linker technology is enabling high-DAR ADC constructs.

Achieving this requires careful control of conjugation efficiency, DAR distribution, and aggregate formation — all of which depend heavily on the optimized conjugation conditions, particularly antibody concentration, buffer composition, reaction duration, and drug-to-antibody ratio. PEG, a hydrophilic moiety already applied in approved ADCs, possesses an increased risk of accelerated blood clearance due to existing or induced anti-PEG antibodies. This is a reason for the emerging need for a new hydrophilic linker.

One of the hydrophilic polymer scaffolds used in ADC development, as a hydrophilic polymer scaffold, is characterized by its highly complex structure. The definition of polymer distribution and manufacturing process risks due to the polymer are pointed out as drawbacks. Our linker, with its lower structural complexity, offers significant advantages in this context.

SoluFlex Link™ is a next-generation hydrophilic linker platform designed to overcome the limitations of both traditional linkers and PEG-based systems. Although SoluFlex Link™ operates within the broader class of hydrophilic linkers, it is structurally distinct from PEG and delivers hydrophilicity through an alternative architecture. This structural distinction may offer immunogenicity advantages, as PEG-related immune responses have become a growing concern in biologic development.

By avoiding PEG-based structures, SoluFlex Link™ provides a hydrophilic alternative that may reduce immunogenicity risk while maintaining favorable physicochemical properties. Its primary function is to counterbalance the lipophilicity of cytotoxic payloads. By enhancing the hydrophilicity of the linker–payload complex, SoluFlex Link™ can improve stability and reduce aggregation.

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Developers must therefore balance multiple competing objectives: maximizing potency through sufficient payload loading while preserving safety, pharmacokinetics, and stability. Hydrophobicity sits at the center of this equation. Lowering DAR is therefore often used as a strategy to improve tolerability, but this approach does not fundamentally resolve the underlying constraints.

As a result, modern ADC development increasingly focuses on strategies that enable higher DAR constructs without compromising stability or safety. Hydrophilic linker technologies represent one of the most promising approaches to achieving this balance.

This effect becomes particularly important at higher DAR values, where hydrophobicity would otherwise limit ADC performance.
Beyond mitigating hydrophobic effects, SoluFlex Link™ enables ADC designs that would otherwise be impractical. By improving stability and manufacturability, this platform enables flexible process development for these applications.

> “Hydrophilic linkers are no longer viewed simply as solubility enhancers but as critical tools for optimizing ADC performance.”

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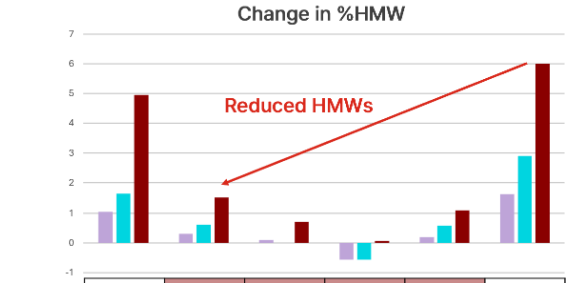
Case Study: Linker Comparison

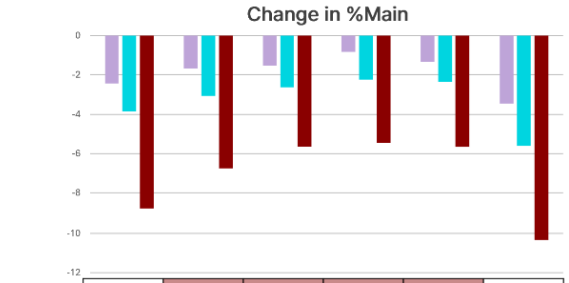
The thermal stability testing demonstrated that the ADCs incorporating the SoluFlex Link™ exhibited markedly suppressed %HMW formation relative to both the ADC without SoluFlex Link™ and the control ADC.
The observed suppression of %HMW formation supports that the linker effectively shields the hydrophobicity of the payload, thereby mitigating nonspecific intermolecular interactions and aggregation.

Comparing ADCs with various combinations of novel solubilizing linkers to conventional ADCs, those solubilized ADCs showed superior in vitro potency. In a study of HER-2-targeting ADCs, LOTTE Biologics found SoluFlex linkers improved antitumor activity of ADC, comparable to an approved ADC therapy for HER2-positive and HER2-low metastatic breast cancer.

Formulation buffer

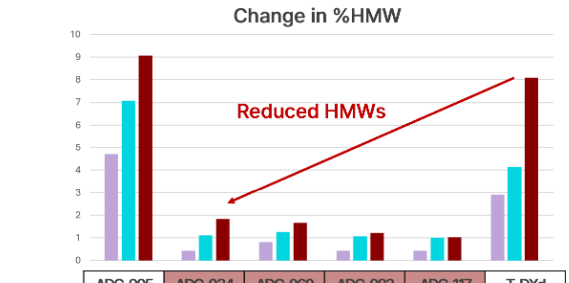


	ADC-005	ADC-034	ADC-060	ADC-082	ADC-117	T-DXd
40℃, 2W	1.04	0.31	0.09	-0.56	0.19	1.61
40℃, 4W	1.63	0.61	0	-0.56	0.58	2.89
40℃, 8W	4.96	1.5	0.7	0.06	1.1	6.01

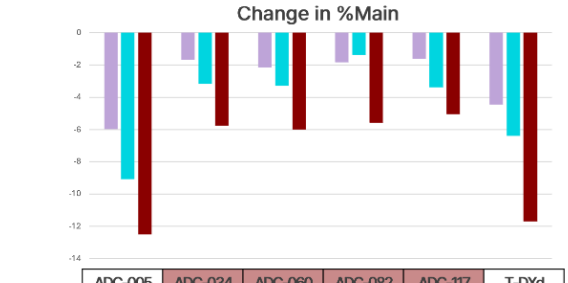


	ADC-005	ADC-034	ADC-060	ADC-082	ADC-117	T-DXd
40℃, 2W	-2.43	-1.67	-1.54	-0.82	-1.33	-3.44
40℃, 4W	-3.87	-3.05	-2.62	-2.23	-2.35	-5.62
40℃, 8W	-8.75	-6.75	-5.64	-5.44	-5.67	-10.35

PBS



	ADC-005	ADC-034	ADC-060	ADC-082	ADC-117	T-DXd
40℃, 2W	4.7	0.44	0.82	0.44	0.44	2.92
40℃, 4W	7.08	1.11	1.25	1.07	1.01	4.12
40℃, 8W	9.07	1.84	1.67	1.22	1.03	8.09



	ADC-005	ADC-034	ADC-060	ADC-082	ADC-117	T-DXd
40℃, 2W	-5.97	-1.69	-2.15	-1.82	-1.62	-4.45
40℃, 4W	-9.08	-3.17	-3.3	-1.38	-3.37	-6.39
40℃, 8W	-12.5	-5.74	-5.98	-5.57	-5.04	-11.69

- ADC-005; without solubilizing linker
- ADC-034, 060, 082, 117; with solubilizing linker

Figure 1: *ADCs with SoluFlex linkers showed a better thermal stability profile than control ADC. (ADC-005, without solubilizing linker; ADC-034, 060, 082, 117, with solubilizing linker; control ADC, an approved ADC).*

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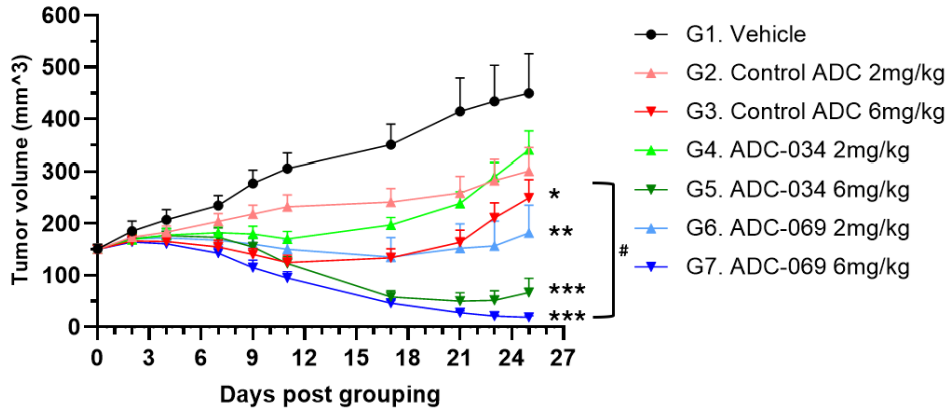
JIMT-1 model (HER2 +)



- *P* values are calculated using ordinary one-way ANOVA, *P* < 0.05, *, *P* < 0.01, **, *P* < 0.001, ***, *P* < 0.05, # vs. G3
- Tumor regression: ≥20% reduction in tumor volume compared to initial volume.

Treatment	TGI (%)	Tumor Regression
G1	-	-
G2	33.1	0/8 (0%)
G3	44.6	0/8 (0%)
G4	24.2	0/8 (0%)
G5	85.2	7/8 (87.5%)
G6	59.5	3/8 (37.5%)
G7	95.8	8/8 (100%)

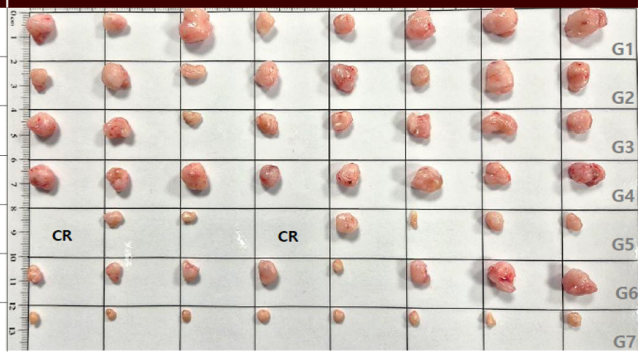


Figure 2: *ADCs with SoluFlex linkers-exatecan showed superior anti-tumor efficacy in a HER2 moderate JIMT-1 breast cancer model.*

The combined in vitro cytotoxicity and in vivo tumor inhibition data support the conclusion that hydrophilic linker design can enhance ADC efficacy by improving delivery and exposure without being compromised by the payload hydrophobicity. The increased hydrophilicity made possible with the SoluFlex linker indicates that the linker effectively shields the payload, which in turn can improve the physicochemical instability caused by the payload, thereby improving PK and efficacy. This finding underscores the value of hydrophilic linker strategies for challenging payloads and higher DAR constructs.

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Integration with End-to-End ADC Development and The Future of Hydrophilic Linker Design

The advantages of hydrophilic linker technologies extend beyond molecular design into the broader ADC development process. Successful ADC development requires careful integration of molecular design, process development, and manufacturing. End-to-end production, conjugation, analytical characterization, and fill–finish operations.

Integrated development environments facilitate smoother scale-up by ensuring continuity between development and manufacturing. When early-stage equipment and analytical methods align with later-stages processes, tech transfer becomes more predictable and efficient. Hydrophilic linker technologies can be particularly valuable in these integrated environments, as improved stability and manufacturability can simplify both development and scale-up.

As ADC technologies evolve, linker design has become a highly sophisticated discipline. Hydrophilic linkers are no longer viewed simply as solubility enhancers but as critical tools for optimizing ADC performance. Future designs will likely incorporate tighter control over hydrophilicity, flexibility, and spatial arrangement, expanding the range of payloads while allowing for flexible application of DAR.

Advancing ADC Performance Through Strategic Linker Innovation

Hydrophobicity remains one of the central challenges in modern ADC development, influencing stability, manufacturability, and therapeutic performance. While reducing DAR can mitigate some risks, it often comes at the cost of reduced efficacy. Hydrophilic linker technologies provide a more balanced approach by enabling higher DAR constructs while maintaining stability and manufacturability. Next-generation platforms such as SoluFlex Link™ offer an alternative to PEG-based systems, delivering hydrophilicity without the associated liabilities. As ADC pipelines continue to grow, linker technologies will likely play a critical role in shaping the next generation of ADC therapeutics by enabling the use of hydrophobic payloads without requiring chemical modifications to improve their properties.

> “By enhancing the hydrophilicity of the linker–payload complex, SoluFlex Link™ can improve stability and reduce aggregation.”

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About LOTTE Biologics

LOTTE Biologics is a global contract development and manufacturing organization delivering integrated biologics and bioconjugate services across the full product lifecycle.

With a unified Dual Hub Service model spanning the United States and South Korea, we strengthen supply chain security, enable scalable manufacturing pathways, and uphold consistent quality across regions.

Our capabilities encompass phase-appropriate drug substance manufacturing for mammalian-cell-based biologics, including monoclonal antibodies, fusion proteins, and multispecific modalities, as well as fully integrated Bioconjugate manufacturing supported by strategic investment in onsite conjugation facilities.

Guided by the vision "Possibilities Beyond Limits," LOTTE Biologics is committed to serving as a long-term, trusted leading global CDMO partner, supporting efficient scale-up, dependable manufacturing execution, and the continuous advancement of clients' therapeutic programs.

Syracuse Bio Campus ADC Facility

The LOTTE Biologics Syracuse Bio Campus is home to onsite end-to-end bioconjugation services. With capabilities spanning antibody manufacturing to conjugation and DS fill at one site, supported by in-house analytics, the Syracuse Bio Campus offers scalable, state-of-the-art manufacturing.

High-Potency API Safety

Industry-standard containment (OEL target 10ng/m^3) ensures safe handling of potent compounds

Quality & Compliance Excellence

In-house QC, extended characterization, and regulatory expertise for global compliance

Scalable cGMP Manufacturing

Flexible production of up to 1kL for clinical and commercial ADC drug substance

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