

Existing and Engineered Excipients as Product-Enabling Materials

Lessons from carbapenem stabilization, long-acting injectable suspensions, and ionizable lipids for RNA-encapsulating lipid nanoparticles. Highlighting excipients traversing the boundary from inactive to active agents.

Örn Almarsson, PhD ¹, Magali B. Hickey, PhD ²

¹ Axelyf, Inc., Brookline, Massachusetts, USA

² Beren Therapeutics, Inc., Thousand Oaks, California, USA

Received: May 6, 2026

Accepted: June 4, 2026

ABSTRACT

Review

Excipients are often discussed as inactive ingredients, implying to those unfamiliar with pharmaceutical development that their function is merely to accompany the active ingredient. It is less well known that many successful drug products depend on purpose-built excipient functions that directly control chemical stability, physical form, processability, solubility, delivery, and overall clinical usability. This review examines three product histories that illustrate some of these principles. First, bicarbonate-mediated carbon dioxide adduct formation provided a mechanistically elegant route to stabilize carbapenem antibiotics in solution: Harnessing the chemistry was a key enabling factor in the translation of unstable molecules such as meropenem and ertapenem into practical injectable products. Second, the long-acting injectable antipsychotic ARISTADA (aripiprazole lauroxil) illustrates how suspension performance can depend on deliberate surfactant-API interaction engineering, including the combined use of sorbitan monolaurate and polysorbate 20 to improve resuspendability, syringeability, and storage behavior. Third, the emergence of ionizable lipid nanoparticles demonstrates the rise of designer lipid excipients as core enabling delivery technologies for genetic medicines. The historical arc from early siRNA ionizable lipids such as Dlin-DMA-MC3 (MC3) to mRNA vaccine-era systems containing SM-102, ALC-315 and clinically validated companion lipids such as ALC-0159 illustrates how excipient design and selection have become inseparable from therapeutic innovation. Across these cases, the decisive variable is not excipient presence alone, but the chemistry-informed fit between drug, materials, dosage form, process and use scenario. A final product category examined is where materials are traversing the boundary between inactive excipient and active drugs for example, cyclodextrins. The next era of excipient research will increasingly reveal multifunctional materials engineered with product performance in mind from the outset, and additional examples of therapeutic uses of excipients are undoubtedly on the horizon.

KEY WORDS: Excipients; bicarbonate; carbapenems; ertapenem; meropenem; aripiprazole lauroxil; prodrug; sorbitan monolaurate; polysorbate 20; ionizable lipids; SM-102; MC3; ALC-0159; lipid nanoparticles (LNPs); RNA delivery; HPβCD; cyclodextrin.

INTRODUCTION

A durable misconception in formulation science is that excipients are merely passive carriers. In practice, many important products reach the market only when an excipient or excipient system is selected, designed, or even invented to solve a specific pharmaceuticals problem. Those problems may be chemical, as in hydrolysis, oxidation or self-reaction of an unstable active ingredient; physical, as in low solubility, or crystal settling, caking, or poor syringeability of a suspension; or biological, as in the need to package and deliver large nucleic acids into cells with efficiency and potency not afforded to the large nucleic acid payload. In each case, the excipient is not peripheral to the product. It is part of the enabling technology to make a medicine.

This review reflects on excipient innovation organized around three case studies drawn from product development experience: carbapenem stabilization with bicarbonate, surfactant engineering in the long-acting injectable antipsychotic ARISTADA, and ionizable lipid systems for RNA medicines (Table 1). These examples were selected because they span distinct eras of pharmaceutical innovation while illustrating the same underlying idea: The value statement asserting that molecules become medicines through materials[1].

The purpose of this review is not to provide exhaustive product histories, but rather to distill mechanistic lessons from the authors’ experience that are broadly useful for excipient research. The cases show that productive, successful excipient selection is chemistry-driven, context-specific, and inseparable from manufacturability, product profile and clinical use. They also show how the field has evolved from

adapting existing materials to inventing new excipients whose function can define an entire therapeutic modality.

Bicarbonate as a stabilizing excipient: from meropenem to ertapenem

Why carbapenems posed an excipient problem

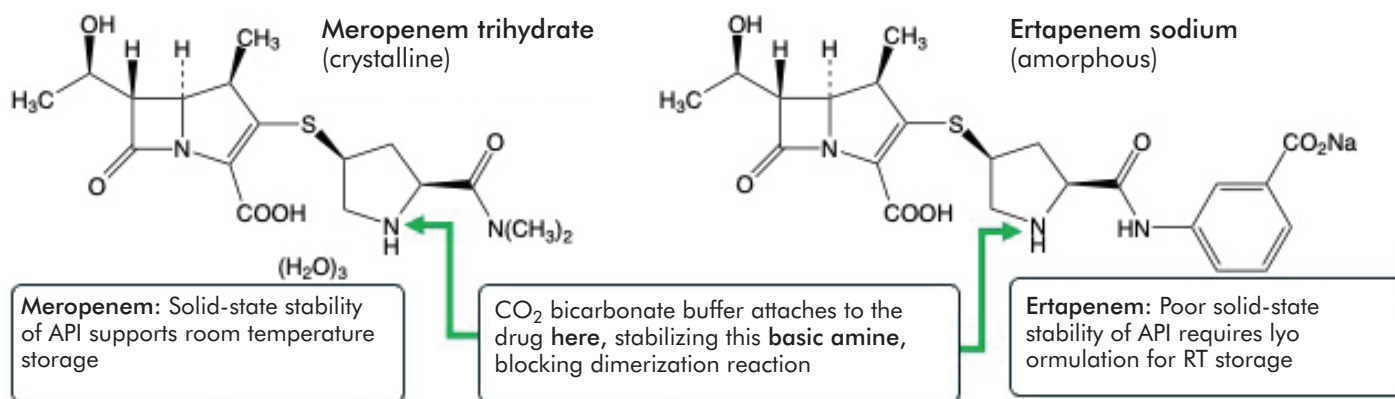
Carbapenem antibiotics are among the clearest examples of an active ingredient whose value depends on taming intrinsic chemical instability. The beta-lactam system is highly strained and vulnerable to degradation in solution. In addition, carbapenems that contain a basic amine can undergo intermolecular reactions that produce dimers or related degradation products. The practical consequence is severe formulation risk: the drug may be potent pharmacologically, yet unusable commercially if it cannot survive manufacturing, storage, and clinical preparation and hold times.

A key mechanistic advance was the recognition that meropenem exists in equilibrium with a carbon dioxide adduct in bicarbonate solution [2]. That observation reframed bicarbonate from a conventional buffer into a functional excipient participating in a reversible chemical interaction with the drug substance. Rather than simply adjusting pH, bicarbonate generated carbon dioxide species that temporarily masked the reactivity of the amine. The chemistry was elegant because the CO₂ adduct was stabilizing during formulation yet reversible under physiological conditions. In the case of meropenem, the MERREM® IV product contained crystalline drug (as trihydrate, see Figure 1) with a solid sodium carbonate excipient. It is unclear whether the developer intended for a chemical reaction to occur or the selection was done based on the need for pH adjustment and

Table 1. Product-enabling functions illustrated by the three case studies

Case	Excipient(s)	Mechanistic contribution	Product impact
Carbapenem antibiotics meropenem/ertapenem	Bicarbonate / carbon dioxide, buffer	Reversible CO2 adduct formation suppresses API self-reaction and improves product chemical stability	Enabled practical injectable carbapenem products
ARISTADA (aripiprazole lauroxil)	Sorbitan monolaurate + polysorbate 20	Interfacial control improved redispersion and syringe performance in a crystalline suspension	Enabled a ready-to-use, easy to use, long-acting injectable product
siRNA / mRNA / RNA lipid nanoparticles (LNPs)	Ionizable lipids with helper lipids and PEG-lipids	pH-responsive RNA complexation, self-assembly, colloidal stabilization, intracellular transfer, endosomal escape, leading to efficacy	Enabled siRNA therapeutics and mRNA vaccines; created a platform modality

Figure 1. Chemical structures of meropenem and ertapenem sodium. CO₂ from sodium carbonate (meropenem) and bicarbonate (ertapenem) functions as a product-enabling excipient by transiently suppressing a self-reaction — dimerization, with resulting loss of potency and safety — while providing bioreversibility under physiological conditions. The stability-improving impact of the reversible reaction on solutions of these beta-lactams is substantial and is essential for the lyophilization process for and resulting stability profile of INVANZ® (ertapenem sodium for IV/IM injection).



pharmaceutical stability.[3] Regardless, the solution speciation of chemicals in the sterile injectable is characterized by presence of a reversible CO₂ adduct of the drug.

Why the meropenem observation mattered for ertapenem

The significance of this chemistry extends beyond meropenem. It helped establish a generalizable way of thinking about pyrrolidinyl-containing carbapenem stabilization, including for ertapenem, where formulation success required control of both hydrolysis and self-reaction pathways. Unlike meropenem, which has a stable crystalline API with a long-term room temperature storage option, ertapenem sodium is an amorphous drug substance with poor storage stability insufficient for a product. Patent work from Merck documents stabilized carbapenem compositions and processing strategies for carbon dioxide adduct-based formulations [4,5]. In product terms, the bicarbonate strategy converted a highly labile molecule into a realistic injectable dosage form rather than leaving the API trapped at the stage of attractive but impractical medicinal chemistry. Fortunately, the excipient-drug chemistry employing the CO₂ adduct of ertapenem enabled lyophilization without loss of potency en route to the dry, room-temperature stable product we now know as INVANZ®.

The scientific lesson is broader than carbapenems. Formulators often describe stability in terms of pH-rate profiles, antioxidants, chelators, or moisture control. Those tools remain important, but the carbapenem example shows that an excipient can succeed by participating directly in a favorable reversible equilibrium. This is a different category

of excipient function, involving transient chemical partnership for stabilization of the drug, and while unusual it illustrates well the central role of chemistry in understanding formulation options and strategies.

Product impact

For ertapenem, bicarbonate-mediated stabilization is best viewed as product-enabling chemistry. Without a suitable excipient strategy, the active ingredient would have remained a liability and formulation would have required cold-chain storage. The unfavorable storage profile was considered a critical barrier to commercialization. With the adduct involved, it became possible to develop and prove a robust lyophilized product with clinically workable handling characteristics and the critical room-temperature storage label. The transition from unstable drug candidate to INVANZ was therefore not merely an API story; it was an excipient story rooted in chemical mechanism and engineering.

Suspension engineering in ARISTADA: surfactants as performance enablers

The formulation challenge in long-acting injectable aripiprazole lauroxil

Long-acting injectable (LAI) therapies have evolved from early oil-based depots designed simply to extend dosing intervals into sophisticated parenteral systems engineered to deliver predictable, months-long drug exposures while improving adherence and clinical outcomes across chronic diseases. Depots have been particularly impactful in manag-

ing symptoms and relapses in serious mental illness such as schizophrenia, and the long-acting atypical (LAI) antipsychotics are a prominent category in this therapeutic area. These depots are increasingly in the form of concentrated intramuscular suspensions, where formulation design must balance syringeability, physical stability, and dose uniformity while relying on controlled crystal dissolution at the injection site. ARISTADA, a line of suspension depot products, use a two-stage prodrug aripiprazole lauroxil (Figure 2). The initiating step in biotransformation to active aripiprazole is injection into muscle, deltoid or gluteal, where the crystals delivered begin to slowly dissolve and undergo release of the active from the injection site. Delivering such a depot plug of solid drug creates both formulation challenges—such as managing particle size, rheology, and injection-site tolerability—as well as opportunities to use novel excipient systems to fine-tune depot performance, optimize clinical handling, and support broader adoption of LAI therapy. Within this landscape, aripiprazole lauroxil products represent a distinct subfamily of crystalline aqueous depot formulations that leverage functional excipients to enable stable, ready-to-use suspensions supplied in prefilled syringes and other user-friendly presentations. Aripiprazole lauroxil microcrystalline suspension was deliberately designed using a prodrug for ultra-slow release after intramuscular administration,

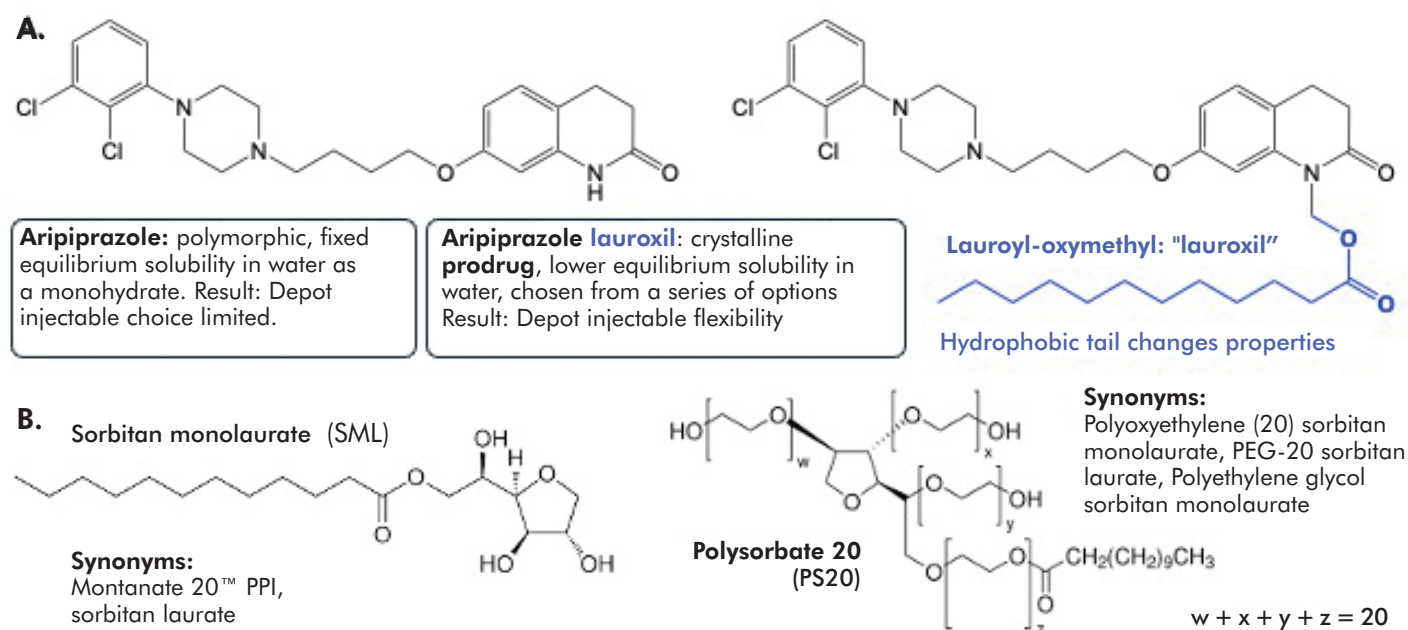
but the very hydrophobicity of the prodrug made formulation as an aqueous crystalline suspension challenging. Settling, compaction, resuspension energy, and syringeability all mattered because they affect dose uniformity and clinical acceptability.

Surfactant synergy rather than single-excipient optimization

The ARISTADA formulation history highlights the value of interfacial design. Patents from Alkermes, Inc., describe pharmaceutical compositions of suspensions containing sorbitan esters and later compositions with improved storage stability for hydrolytically labile antipsychotic agents [6,7]. In practical terms, the formulation path converged on a combination of sorbitan monolaurate and polysorbate 20. That pairing is notable because it suggests that the winning solution did not come from maximizing the amount of a single stabilizer, but from balancing complementary interfacial effects in a suspension system.

The resulting excipient system improved resuspendability and administration characteristics while avoiding a more cumbersome polymer-heavy approach. While polymer delivery has had success in RISPERDAL CONSTA[®], the loading of drug in the dosage form is reduced by the polymer matrix, while prodrug products like INVEGA SUSTENNA[®] and ARISTADA[®] rely on the crystal form of the pure drug

Figure 2. ARISTADA components, actives and two key surfactants. A. Actives: Chemical structures of aripiprazole and the prodrug aripiprazole lauroxil, with the lauroxil promoiety highlighted. B. Surfactant excipients in ARISTADA[®]: Chemical structures of sorbitan monolaurate (SML) and polysorbate 20 (PS20).



In the administration-focused paper on ARISTADA by Farwick and co-workers, the product is described in terms of formulation properties that translate directly into use instructions, including the need for proper tapping and shaking prior to injection [8]. This is an important bridge between formulation science and real-world performance. The product is not only physically engineered, with optimal resuspendability in a pre-filled syringe prior to handling at the time of administration; it is also behaviorally engineered through human factors research for reliable and safe administration.

A broader lesson from ARISTADA

The broader lesson is that excipients in injectable suspensions should be evaluated for more than the traditional metrics such as particle size, viscosity, or sedimentation rate: The full chain of product performance, including storage and transportation stability, ease of redispersion, needle gauge, injectability, and robustness to user handling, need early integration into design. The surfactants in ARISTADA did not function as generic wetting agents. They were part of a carefully tuned microenvironment that allowed an otherwise difficult suspension to become a commercially viable product with successful use over almost a decade.

Prodrugs as chemical solutions to delivery problems

Taken together, the ertapenem and aripiprazole lauroxil stories also underscore the utility of prodrugs as delivery-enabling chemical entities. In the classical sense, a prodrug is a bioreversible derivative introduced to improve formulation properties, pharmacokinetics, targeting, or route of administration [19,20]. The bicarbonate-derived carbapenem carbon dioxide adduct, is not a purpose-synthesized pro-moiety, but it is reminiscent of a prodrug acting as a stabilizing species: a transient, reversible covalent modification that suppresses a key degradation pathway while remaining biologically labile [2,19].

ARISTADA, by contrast, contains an engineered prodrug tailored for depot delivery. Aripiprazole lauroxil was deliberately designed to lower aqueous solubility, with very slow liberation of active aripiprazole after intramuscular administration, thereby enabling prolonged systemic exposure from a practical injectable suspension [8,21]. These examples sit at different points on the same conceptual spectrum. One uses reversible adduct formation generated in the formulation environment; the other uses intentional covalent derivatization of the drug substance itself. Both illustrate how chemical modification can be central to solving delivery problems rather than peripheral to them.

Ionizable lipids: excipients that define a therapeutic modality

The shift from adapted excipients to invented excipients

RNA therapeutics brought a new scale of excipient challenges. Naked RNAs are large, polyanionic, chemically fragile, and rapidly cleared or degraded *in vivo*. The delivery problem is not solved by a conventional stabilizer or solubilizer. It requires an integrated delivery system that can bind RNA during manufacture, promote nanoparticle self-assembly, protect the cargo in biological fluids, facilitate cell entry, and assist endosomal escape while remaining tolerable and manufacturable. Ionizable lipids emerged because this demanding specification could not be met with legacy excipient sets.

The historical lineage commonly traced in the field begins with potent siRNA delivery lipids such as MC3 (Figure 3), which emerged from rational design efforts to optimize ionization behavior and delivery performance [10]. Later work on biodegradable lipids refined this logic by linking potency with faster post-dose clearance and improved tolerability considerations [11]. These developments established key design principles for the modern LNP era: tune apparent pKa (an ionization property of the particle, not the pure component ionizable lipids), exploit pH-responsive protonation, and embed biodegradable motifs that improve the fate of the lipid after delivery.

SM-102, ALC lipids and the vaccine-era maturation of excipient science

In mRNA systems, the same design principles were extended and adapted to the requirements of larger nucleic acid cargos and vaccine administration. The SM-102 series of modified lipids was part of that transition (Figure 3). Sabnis and co-workers reported a novel amino lipid series for mRNA delivery with improved endosomal escape and sustained *in vivo* performance, including non-human primate data [12]. Hassett and co-workers subsequently described optimization of LNPs for intramuscular administration of mRNA vaccines, capturing the point at which ionizable lipid selection, helper lipid choice, and route-specific performance were being engineered as a coordinated system rather than as isolated variables [13].

By the time COVID-19 vaccines were developed at pandemic speed, much of the decisive excipient science had already been done. The appearance of SM-102 in authorized Spikevax formulations therefore should not be interpreted as a single late-stage selection event, but as the visible endpoint of years of medicinal chemistry, nanoparticle

screening, mRNA vaccine R&D, process development, and excipient manufacturing scale-up [14,16]. It is worth noting that excipient innovation was one essential layer within a broader technological ecosystem that also included microfluidic manufacturing methods, nucleoside modification chemistry to reduce innate immune responses to mRNA, cold-chain logistics, and regulatory frameworks capable of moving at pandemic speed; the excipient story told here is deliberately focused on the materials dimension.

MC3, ALC-315, SM-102 and ALC-0159 as predecessors in the LNP excipient space

It is important to reflect on the histories of MC3 and the first clinically proven ionizable lipids. MC3 anchors the earlier clinically successful siRNA generation and represents a conceptual predecessor for later ionizable lipid design [10,11]. ALC-0159, by contrast, is not an amino lipid but a PEG-lipid conjugate used in ONPATRO® and the Comirnaty® mRNA vaccine LNP system; its importance lies in showing that clinical success depends on a complete lipid ensemble rather than on the ionizable lipid alone. In the Comirnaty assessment record, ALC-0315 and ALC-0159 are identified as novel excipients [17].

This distinction matters. Discussions of ionizable lipids can become overly centered on the protonatable lipid head-group, yet the clinically validated LNP is a multicomponent assembly whose behavior depends on structural lipids, cholesterol, and surface-active PEG-lipids as well. ALC-0159 contributes colloidal behavior and surface presentation in a different way than SM-102 or ALC-0315, but it belongs to the same product-level story: excipient innovation in LNPs is system design[15]. An alternative PEG lipid is PEG2k-DMG, SUNBRIGHT® GM-020 (NOF Corporation), which is used to stabilize LNP colloidal structure in Moderna vaccine products.

The ionizable lipids in Figure 3 get the most attention, given their disproportionate impact on the delivery profile of large RNAs. This situation is likely to change, as formulation design efforts for large nucleic acid payloads will depend on co-optimizing all functions of the LNP systems, such as the surface lipids (PEG alternatives and phospholipid replacements), sterol alternatives (beta-sitosterol augmented LNPs boosting delivery relative to cholesterol-containing LNPs) [22], for example. The multi-component nature of LNPs offers a vast canvas for design and development of RNA and DNA non-viral formulation systems of the future.

Figure 3. Schematic of a lipid nanoparticle (LNP) loaded with a nucleic acid (RNA, DNA) with chemical structures of lipids including ionizable lipids. While ionizable lipids drive the potency of delivery substantially, overall LNP product performance emerges from a complete excipient ensemble and process rather than from the ionizable lipid alone. PEG lipids provide colloidal stability of LNPs in product prior to administration.

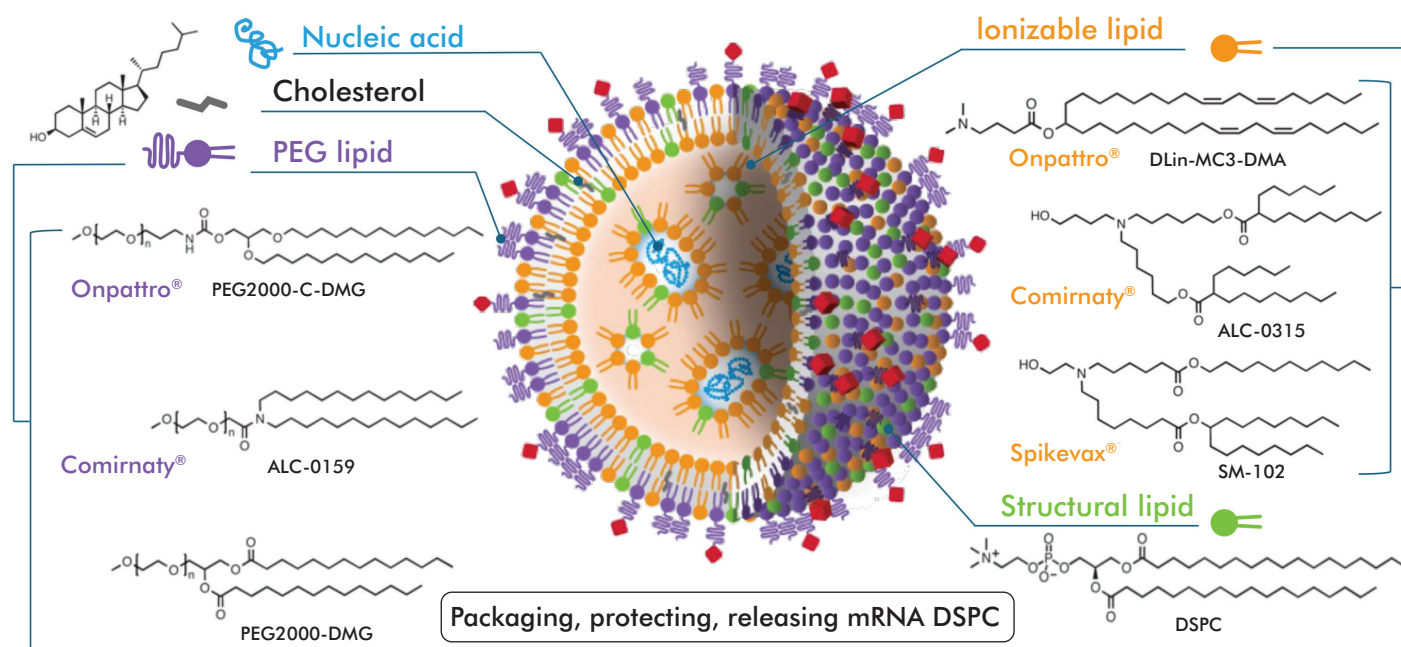
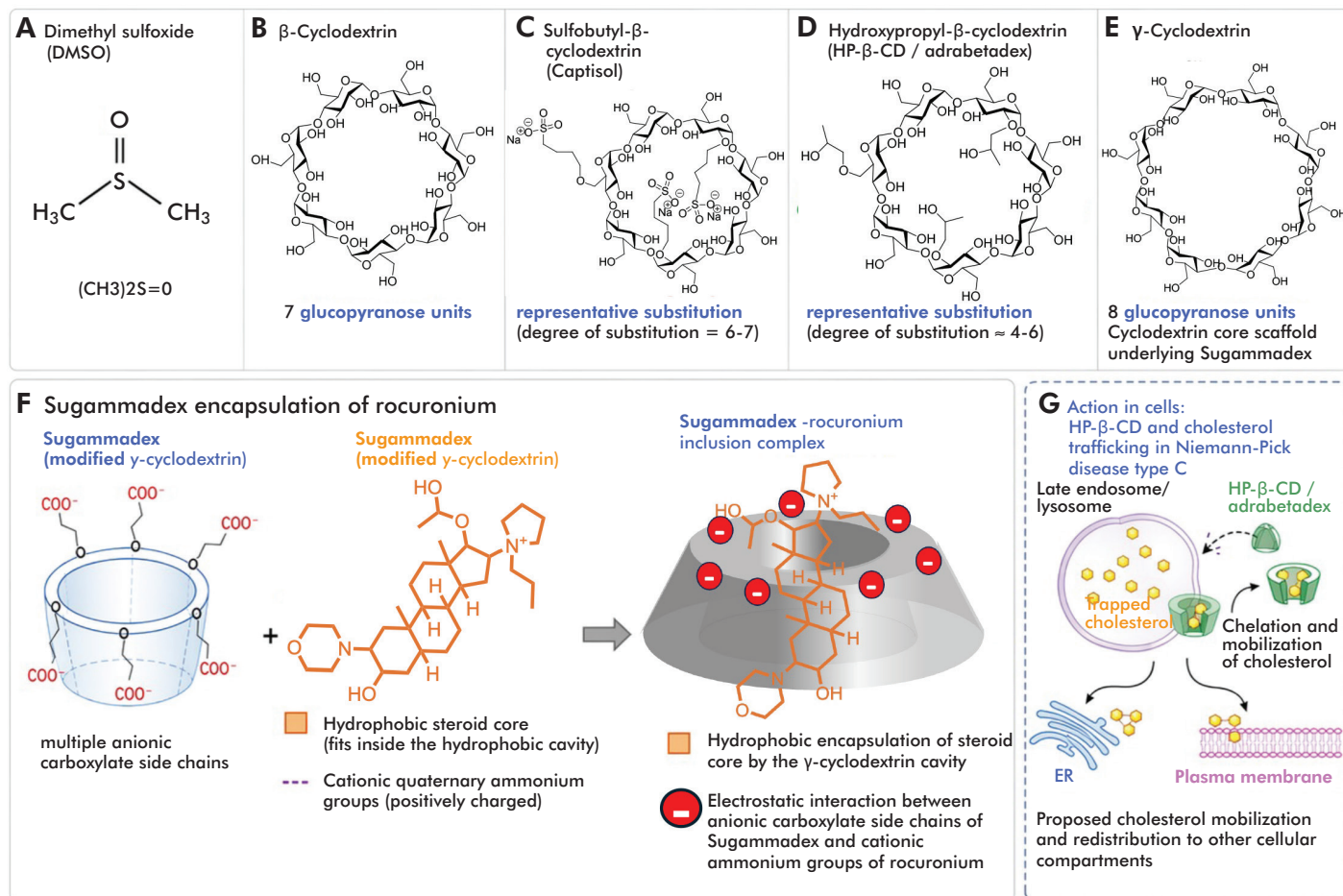


Figure 4. Chemical structures of dimethyl sulfoxide (A), beta-cyclodextrin (B), sulfobutyl-beta-cyclodextrin (C), hydroxypropyl-beta-cyclodextrin (D), and gamma-cyclodextrin (E) in Sugammadex. (F) Host-guest complex schematic showing a neuro-muscular blocker complexed in the gCD. (G) Linking hydroxypropyl-beta-cyclodextrin to cholesterol trafficking in Niemann-Pick disease type C.



The rise of excipients as platforms

Ionizable lipid systems differ from the earlier case studies in one important respect. Bicarbonate enabled a product. The surfactant system in ARISTADA enabled a product class within a formulation type. Ionizable lipids, however, can enable an entire modality. Once the excipient platform is validated, it can support multiple cargos, indications, and administration strategies. That is a major reason why LNP excipients now sit at the center of contemporary therapeutic innovation rather than at the periphery of formulation development[18].

Cross-cutting design principles for excipient research

■ **Mechanism first.** The most productive excipient programs begin by mapping the dominant failure mode. In carbapenems the problem was reactive instability; in ARISTADA it was particulate behavior during storage and administration; in mRNA systems it was coordinated delivery,

release, and tolerability. The mechanistic diagnosis points to the correct material strategy.

■ **Fit-for-product rather than fit-for-class.** There is no universal ranking of excipients independent of dosage form and use scenario. A material that is excellent in a tablet or solution may be irrelevant in an intramuscular suspension or an LNP. Product development therefore depends on contextual fit rather than excipient reputation.

■ **Multifunctionality.** Modern excipients often do more than one job. Bicarbonate acts as buffer and reactive stabilizer. Sorbitan monolaurate and polysorbate 20 affect wetting, interfacial behavior, redispersion, and usability. Ionizable lipids influence encapsulation, self-assembly, systemic and cellular interactions, endosomal escape, potency, and safety.

■ **Manufacturability is part of function.** An excipient that performs well in a benchtop experiment but cannot be synthesized reproducibly, purified adequately, or scaled eco-

nominally has not fully solved the pharmaceutical problem. This point is especially evident in the LNP field, where excipient supply and process chemistry were among many prerequisites for vaccine deployment.

■ **Clinical handling should be designed, not left to chance.** The distinction between formulation performance and user performance is false. ARISTADA demonstrates that administration behavior is part of the formulation outcome, and reconstitution or preparation constraints in injectable products similarly belong within the excipient design.

When excipients have direct drug action

DMSO in RIMSO-50

Dimethyl sulfoxide (Figure 4) provides a classic example of a material widely used as a solvent and process aid that also has direct pharmacologic activity. In RIMSO-50, DMSO is the

active intravesical ingredient indicated for symptomatic relief of interstitial cystitis, not merely a formulation vehicle [23]. Its long-recognized solubilization, membrane transport, anti-inflammatory, analgesic, and radical-modulating effects help explain why DMSO has occupied a distinctive place at the boundary between excipient and drug for decades [24].

Cyclodextrins as both excipients and drugs

Cyclodextrins (Figure 4) comprise a group of homologous cyclic sugar analogs that have had a role in drug delivery for decades due to interesting complexation properties: As excipients, they are well-known host-guest materials used to improve solubility, reduce local irritation, and stabilize difficult molecules in parenteral and other formulations [25][26]. Cyclodextrins provide a particularly instructive example of how a material originally developed as a formulation excipient

Table 2. High priority cyclodextrin clinical programs: status signals and evidence notes

Program / asset	Cyclodextrin type	Key trial(s)	Current status signal
Trappsol Cyclo in NPC1	Intravenous HPβCD	NCT04860960	Phase 3 / registration. NPC fully enrolled; active/in progress but not accepting new participants.
Trappsol Cyclo in early Alzheimer's disease	Intravenous HPβCD	NCT05607615	Phase 2/2b; recruiting in workbook and public trial listings.
VTS-270 in infantile-onset NPC	Intravenous and intrathecal HPβCD	NCT02534844 and legacy/EAP data	Legacy trials are completed/terminated/not recruiting; NDA accepted for review in 2025.
Allopregnanolone + Dexolve/SBECD in PTSD	SBECD / Dexolve formulation	NCT07079761; NCT04468360	Phase 2 PTSD studies listed as recruiting or active-recruiting in public sources.
OCS-01 in DME and aract inflammation/pain	Gamma-CD nanoparticle formulation lineage	NCT05066997; NCT06172257; NCT05147233	DIAMOND Phase 3 DME last patient visits cat-complete; top-line expected June 2026; OPTIMIZE-1 completed.
SFX-01	Alpha-CD stabilized sulforaphane complex	NCT01948362; NCT02055716; NCT02970682; NCT02614742; EudraCT 2020-003486-19	Phase 1/2 clinical precedent; no active recruitment in workbook; STAR-COVID/CAP discontinued.
Captisol/SBECD formulation portfolio	SBECD / Captisol	Examples: NCT01660633; NCT01401647; NCT01128959; NCT04431453	Mostly completed, approved, approval-enabling, withdrawn or PK/safety-focused programs.
Cyclodextrin-polymer oncology platforms	Cyclodextrin-containing polymer systems	NCT00689065; NCT02769962; NCT04669002 and related CRLX101/NLG207 studies	Mostly completed. No active recruitment

can be engineered into a therapeutic agent. A notable example of a cyclodextrin crossing into drug territory is sugammadex, a modified gamma-cyclodextrin with a therapeutic action that is a supramolecular binding event:⁹ encapsulation of rocuronium or vecuronium to reverse neuromuscular blockade [27][28].

Cyclodextrins in clinical-trial and sponsor/public-source data are surprisingly common: An April 2026 survey identified 81 cyclodextrin-related clinical records across U.S. and rest-of-world registries, as summarized in Table 2. The scope was intentionally selective for cyclodextrin as an active therapeutic exposure, stabilizing complex, named formulation or delivery technology, or prespecified pharmacokinetic/safety endpoint; routine approved-drug studies where cyclodextrin was only an inactive excipient were not exhaustively enumerated. As shown in Table 2, Trappsol Cyclo is in late-stage NPC1 development, with the NPC fully enrolled and active, but not-recruiting, and is also in an early Alzheimer's Phase 2/2b study listed as recruiting [29]. VTS-270 provides a separate HP β CD precedent with multiple legacy NPC trials listed as completed, terminated, withdrawn or not recruiting.

Aside from HP β CD, the landscape is primarily formulation- or platform-enabled rather than cyclodextrin acting as the disease-modifying mechanism. Alpha-CD records are dominated by SFX-01, a stabilized sulforaphane/alpha-CD complex with Phase 1/2 studies and completed nutrition/mechanistic alpha-CD trials. SBECD/Captisol/Dexolve are mostly formulation-enabling programs, with active PTSD neurosteroid studies using allopregnanolone/Dexolve and historical approved or approval-enabling Captisol formulations such as EVOMELA and IV carbamazepine. Gamma-CD/modified gamma-CD records include approved sugammadex.

Polymeric cyclodextrin platforms have produced substantial oncology clinical experience but limited current active recruitment in the workbook. The CRLX101/NLG207/EP0057 camptothecin-polymer lineage and CALAA-01 siRNA nanoparticle program collectively demonstrate clinical translation of cyclodextrin-based delivery architectures, but most listed studies are completed, terminated or withdrawn.

Outlook

Excipients are continually evolving from support roles toward more explicit recognition as innovation drivers. This shift has several implications for the field. First, the discovery and qualification of novel excipients will increasingly resemble medicinal chemistry, pharmaceutical science and materials engineering rather than simple selection from a compendial menu. Second, regulatory science will need to continue to adapt so that unfamiliar but well-characterized excipients can be assessed in a way that rewards mechanism knowledge, quality of components, and clinical benefit without creating unnecessary barriers. Third, platform technologies such as LNPs are likely to deepen the strategic value of excipient intellectual property, because the material itself may be the key determinant of which medicines can be made.

For researchers, the practical takeaway is straightforward: excipient science and product definition should begin early in development. Too many programs still treat formulation as downstream optimization after API discovery or sequence design. The case studies reviewed here argue for the opposite model. Chemistry, materials, dosage form design, and product strategy should be integrated from the outset[1].

CONCLUSION

Across carbapenem antibiotics, long-acting crystalline injectable suspensions, lipid nanoparticles for RNA delivery, and the emerging examples of DMSO and cyclodextrins as direct therapeutic agents, the same principle holds: the right excipient is often what transforms a promising molecule into a viable medicine. Excipients are not peripheral or incidental to product preparation and performance. They are often the decisive material technologies through which drug stability, injectability, release, targeting, and sometimes desirable pharmacology is achieved.

REFERENCES

- 1 Gardner CR, Walsh CT, Almarsson Ö. Drugs as materials: valuing physical form in drug discovery. *Nat Rev Drug Discov.* 2004 Nov;3(11):926-934. doi:10.1038/nrd1550. PMID:15520815.
- 2 Almarsson Ö, Kaufman MJ, Stong JD, Wu Y, Mayr SM, Petrich MA, Williams JM. Meropenem exists in equilibrium with a carbon dioxide adduct in bicarbonate solution. *J Pharm Sci.* 1998;87(5):663-666. doi:10.1021/js970370u.
- 3 Tomasello C, Leggieri A, Cavalli R, Di Perri G, D'Avolio A. In vitro stability evaluation of different pharmaceutical products containing meropenem. *Hosp Pharm.* 2015;50(4):296–303. doi:10.1310/hpj5004-296. PMID:26448659.
- 4 Zimmerman DE, Williams JM, and colleagues. Carbapenem antibiotic, composition and method of preparation. US Patent 5,952,323. September 14, 1999.
- 5 Merck & Co., Inc. Process for formulation of carbapenem antibiotic compositions. EP1244444B1. December 29, 2004.
- 6 Perry JM, Deaver DR, Hickey MB, Remenar JF, Vandiver J. Pharmaceutical compositions comprising sorbitan esters. US Patent 9,034,867 B2. May 19, 2015.
- 7 Perry JM, Deaver DR, Hickey MB, Remenar JF, Vandiver J, Palmieri MJ Jr, Pan Z. Pharmaceutical compositions having improved storage stability. US Patent 11,097,006 B2. August 24, 2021.
- 8 Farwick S, Hickey MB, Jacobs G, Faldu SP, Vandiver J, Weiden PJ. Best practices for aripiprazole lauroxil administration: from formulation development to injection technique. *J Psychiatr Pract.* 2019;25(2):82-90. doi:10.1097/PRA.0000000000000376.
- 9 Citrome L. Aripiprazole long-acting injectable formulations for schizophrenia: aripiprazole monohydrate and aripiprazole lauroxil. *Expert Rev Clin Pharmacol.* 2016;9(2):169–186. doi:10.1586/17512433.2016.1121809.
- 10 Semple SC, Akinc A, Chen J, et al. Rational design of cationic lipids for siRNA delivery. *Nat Biotechnol.* 2010;28(2):172-176. doi:10.1038/nbt.1602.
- 11 Maier MA, Jayaraman M, Matsuda S, et al. Biodegradable lipids enabling rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics. *Mol Ther.* 2013;21(8):1570-1578. doi:10.1038/mt.2013.124.
- 12 Sabnis S, Kumarasinghe ES, Salerno T, et al. A novel amino lipid series for mRNA delivery: improved endosomal escape and sustained pharmacology and safety in non-human primates. *Mol Ther.* 2018;26(6):1509-1519. doi:10.1016/j.ymthe.2018.03.010.
- 13 Hassett KJ, Benenato KE, Jacquinet E, et al. Optimization of lipid nanoparticles for intramuscular administration of mRNA vaccines. *Mol Ther Nucleic Acids.* 2019;15:1-11. doi:10.1016/j.omtn.2019.01.013.
- 14 Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. *Nat Rev Mater.* 2021;6(12):1078-1094. doi:10.1038/s41578-021-00358-0.
- 15 Vasileva O, Zaborova O, Shmykov B, Ivanov R, Reshetnikov V. Composition of lipid nanoparticles for targeted delivery: application to mRNA therapeutics. *Front Pharmacol.* 2024;15:1466337. doi:10.3389/fphar.2024.1466337.
- 16 European Medicines Agency. Spikevax: EPAR product information. Updated 2026. Available from the European Medicines Agency.
- 17 European Medicines Agency. Comirnaty: EPAR public assessment report. 2020; and current product information identifying ALC-0315 and ALC-0159 as novel excipients.
- 18 Li B, et al. Artificial intelligence-driven rational design of ionizable lipids for mRNA delivery. *Nat Commun.* 2024;15:10804. doi:10.1038/s41467-024-55072-6.
- 19 Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Oh D, Järvinen T, Savolainen J. Prodrugs: design and clinical applications. *Nat Rev Drug Discov.* 2008;7(3):255-270.
- 20 Huttunen KM, Raunio H, Rautio J. Prodrugs--from serendipity to rational design. *Pharmacol Rev.* 2011;63(3):750-771. doi:10.1124/pr.110.003459.

- 21 Citrome L, Correll CU, Cutler AJ, Dunbar M, Hoberg AR, Hopkinson C, Mattingly GW, McGrory JA, Rege B, Weiden PJ, McDonnell D. Aripiprazole lauroxil: development and evidence-based review of a long-acting injectable atypical antipsychotic for the treatment of schizophrenia. *Neuropsychiatr Dis Treat*. 2025;21:575-596. doi:10.2147/NDT.S499367.
- 22 Sahay G, Patel S, Robinson E, Brown A, Almarsson Ö, Benenato KE, Sabnis S, Narayana AK. US11969506B2. Current Assignee: Oregon State University; ModernaTx, Inc.
- 23 DailyMed. RIMSO-50 (dimethyl sulfoxide) irrigation, prescribing information. U.S. National Library of Medicine. Current label accessed 2026.
- 24 The Pharmaceutical Applications of Dimethyl Sulfoxide. Editors: Nigel Langley, Örn Almarsson, David W. Osborne. AAPS Advances in the Pharmaceutical Sciences Series ,Springer, 2026 ”
- 25 Loftsson T. Cyclodextrins in parenteral formulations. *J Pharm Sci*. 2021;110(2):654-664. doi:10.1016/j.xphs.2020.10.026.
- 26 Kali G, Haddadzadegan S, Bernkop-Schnürch A. Cyclodextrins and derivatives in drug delivery: New developments, relevant clinical trials, and advanced products. *Carbohydr Polym*. 2024;324:121500. doi:10.1016/j.carbpol.2023.121500. PMID:37985088.
- 27 DailyMed. BRIDION (sugammadex) injection, prescribing information. U.S. National Library of Medicine. Current label accessed 2026.
- 28 Pirvu AS, Varut RM, Trasca DM, Stoica GA, Radivojevic K, Carmen S, Arsenie CC, Popescu C. Cyclodextrins as Active Therapeutic Agents: Beyond Their Role as Excipients. *Pharmaceutics*. 2025;18(10):1592. doi:10.3390/ph18101592. PMC12567201.
- 29 Beren Therapeutics. FDA acceptance of the new drug application for adrabetadex in infantile-onset Niemann-Pick disease type C. *Business Wire*. February 23, 2026.