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Editorial

Routes of Antibody Drug Delivery and Challenges

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Antibody drugs have become the most rapidly growing marketed drug products within recent years. During January 1 to November 12, 2021, 11 antibody therapeutics were granted first approval in either the US or EU. And as of November 12, 2021, 18 investigational antibody therapeutics are in regulatory review in either the US or EU. More than 130 antibody drug products have been approved globally until today, of which most are in liquid solutions and ~27% are lyophilized powders. Antibody therapies are usually highly specific to their targets and with better safety profile comparing to traditional small-molecule drugs. However, antibody-based drugs usually have short pharmacokinetic properties (couple days to weeks), low tissue penetration, and stability issues during manufacturing, transport, storage, and formulation which limit their clinical use. The routes of administration are mainly subcutaneous or intravenous infusion with several intravenous bolus, intravitreal, and intramuscular in drug products so far. There are many opportunities in developing antibody formulations and delivery systems for better patient compliance, cost savings and lifecycle management.

Intravenous delivery

Due to its short half-lives and low tissue penetration, IV infusion is the most common route of administration for antibody-based drugs. Most of IV formulations are concentrate liquid formulations that require dilution into saline or another intravenous fluid prior to infusion. If a stable liquid formulation is not achievable within the development timeline, a lyophilized powder formulation can be pursued which require reconstitution upon usage. A typical stable liquid formulation consists of antibody, excipients to adjust tonicity or osmolality for solutions, lyoprotectants such as sucrose and trehalose, a buffer, and a surfactant. The pH range is usually 4.8 to 7.0. Screening and optimizing of pH, buffer species, sugars, ionic tonicity-adjusting excipients, and surfactants are critical to develop a successful liquid formulation with maximum long-term stability. Aggregation, fragmentation, oxidation, deamidation, isomerization, and particle formation etc. are common critical quality attributes to be monitored for formulation stability. Modifications of antibody itself has also been investigated to prolong the *in vivo* half-lives after IV infusion. Albumin fusions for antibody conjugation have been reported in several studies to increase the circulation time by HSA's binding capabilities to FcRn. PEGylation technology has also evolved recently to overcome the short half-life of antibody fragments in blood circulation, reduce the risk of immunogenicity and increase solubility. However, many PEGylation reagents must be used an excess stoichiometry, which requires tedious and expensive purification process.

Subcutaneous delivery

As an alternative routes to IV administration, subcutaneous delivery is thought to be a more desirable, and patient-centric route of administration, especially during the pandemic. However, due to the limited space, a typical injection volume is less than 2 ml. Therefore, a highly concentrated liquid formulation (usually > 150 mg/ml) is often needed to achieve targeted therapeutical concentration in the targeted tissue. The viscosity-lowering excipients such as sodium chloride and the amino acids arginine, glycine, proline, and lysine are most often needed to lower the viscosity to acceptable range at high concentrations. Recent advancements in using hyaluronidase with electronic devices to assist the large subcutaneous injection volume of 5-15 ml over 3 – 5 minutes have enhanced its applications.

Intravitreal delivery

Due to the significant success of anti-VEGF therapy in treating neovascular eye diseases, number of intravitreal injections of anti-VEGF antibodies, fusion proteins and antibody fragments have exponentially increased recently. The intravitreal route has been proved to be the most effective route to delivery antibody therapeutics to the posterior segment of the eye due to significant barriers present in the eye which limits bioavailability and tissue penetration of large macromolecules. However, repeated injections are required to maintain therapeutic dosage due to short ocular half-lives of antibody-based therapeutics. Extensive efforts have been made both from academia and industry to develop a long-acting release system or formulation for anti-VEGF. Recently, based on positive results from the phase III Archway study, Susvimo (previously called Port Delivery System) received FDA approval becoming a first-of-its-kind therapeutic approach for neovascular or wet age-related macular degeneration (nAMD). By continuously delivering anti-VEGF drug into the eye through a refillable implant, Susvimo can help people with nAMD maintain their vision with as few as two treatments per year. Other less invasive approaches using injectable degradable polymers, hydrogels or liposomes are under active research and development. However, one of the most significant barriers for these innovative long-acting release antibody formulation/delivery system is drug stability and CMC.

Oral delivery

Oral delivery of drugs provides a simple and non-invasive approach for drug delivery. However, it is generally well known that proteins and antibodies are prone to undergo enzymatic degradation and unfolding especially in the gastrointestinal tract. Thus, oral delivery systems for these biologically active macromolecules faces significant challenges to develop. Different research strategies have been explored to enable oral delivery of proteins and antibodies including inhibiting acid and enzymatic degradation using protease inhibitors, increasing contact time with the absorptive epithelium with mucoadhesive materials, using mucosal barrier permeability enhancers, loading antibodies into carriers with higher intestinal digestion and permeation etc. Recently collaborations between MIT engineers and scientists from Brigham and Women's Hospital and Novo Nordisk are seeking to develop a drug capsule technology that could allow the oral delivery of monoclonal antibodies, or other large protein-based drugs to treat cancer, rheumatoid arthritis, and Crohn's disease. The new technology is a type of self-injecting capsule, called a liquid-injecting self-orienting millimeter-scale applicator (L-SOMA), which is orally taken, and then effectively injects the liquid medication directly into the stomach wall. Although oral delivery is still in its early development stages, it has the potential to transform treatment regimens across a range of therapeutic areas.

In conclusion, antibody-based medicines continue to be one of the fastest growing drug products in pharmaceutical industry. With advancement in antibody engineering, modifications, formulation, better understanding of physiological barriers, *in vivo* stability, and evolution of technology, development of better antibody delivery technology will continue to evolve and transform the treatment regimen.

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