# Cutting-edge Formulation is Needed to Enable the Next Generation of Oral Biologics

**An Introduction to Oral Solid Dose**

**Traditionally, the pharmaceutical market has been dominated by oral drug delivery – whether oral solid dose (OSD) or liquid suspensions and solutions.**

**Oral drugs ease access by enabling patients to take medication at home with little discomfort or complexity. This differs from other dosage forms, such as parenteral, which often rely on healthcare professionals for their delivery. Additional OSD advantages include extended shelf-life, which eases transport and long-term storage.**

Despite OSD popularity, certain active pharmaceutical ingredients (APIs) are incompatible with traditional OSD formulation techniques, as is the case for biologics. This is due to a myriad of reasons that stem from biologic physicochemical properties, stability, absorption, and immunogenicity.

Many pharmaceutical industry research programmes are exploring new strategies and technologies to propel OSD biologic formulations. These novel approaches aim to overcome associated obstacles and include the use of prodrugs, nanoparticle-based delivery systems, and innovative methods to optimise absorption and stability.

In this article, Dr. Uwe Hanenberg, Head of Product Development in Oral Solid Dose at Recipharm, explores recent advances in formulation technologies for both OSD and oral liquid dosage forms designed to enable the creation of oral biologics.

**The Driving Force for Solid Dose Biologics**

By the end of 2022, biologic approvals had narrowly outpaced those of new small-molecule entities for the first time, setting a new precedent.[1] The biologic market is predicted to continue experiencing rapid growth with a compound annual growth rate of 4.1% between 2023 and 2028, reaching an estimated value of $415 billion by 2026.[2]

This rise in biologic approvals could contribute to the burden on the healthcare system, as biologics are often limited to parenteral administration, requiring healthcare professionals' (HCPs) involvement. The way the biopharma industry can help reduce the HCPs' load is by working towards self-administered therapeutics. Oral dosage forms seem an obvious alternative, but to make this delivery system viable, innovation is needed to improve biologic solubility, absorption, and stability. Patient centricity is also a priority for many pharmaceutical companies, and expanding the range of self-administered drugs increases patient access.

Many pharmaceutical companies are investing in OSD formulation research to find innovative solutions to current problems hindering oral biologic development. Overcoming these challenges requires a strong understanding of the issues that may arise during OSD biologic formulation.

**What are the main challenges associated with OSD biologics?**

The many difficulties developers and manufacturers face when taking on the challenges of formulating a biologic OSD include:

- **Instability:**
  As biopharmaceuticals are highly sensitive materials, they often degrade in acidic environments, such as in the stomach, as well as under the stress and harsh conditions of the intestinal tract. Upon degradation, the biologic is no longer medicinally beneficial due to loss of activity.
- **Physicochemical properties:**
  The inherently complex structures and properties of biologics, such as large molecular weight, high hydrophilicity, and sensitivity, make them difficult to formulate into oral drugs.
- **Absorption:**
  Larger molecules, such as biologic APIs, often struggle to be absorbed through the intestinal wall and into the bloodstream. This can further limit their bioavailability and effectiveness when taken orally.
- **Immune response:**
  Biopharmaceuticals may elicit an immune response in the body. The resulting formation of antibodies that specifically recognise and target the biologic API can reduce the drug's efficacy and increase the risk of adverse reactions.
- **Regulatory requirements:**
  The regulatory requirements for the development and approval of oral biologics are stringent, and the formulation must meet strict standards for quality, safety, and efficacy.

**How Excipients Can Help to Overcome Biologic OSD Challenges**

There are several approaches to overcoming the challenges surrounding biologic OSDs, and extensive research concentrates on developing strategies and techniques to enhance product stability and bioavailability.

Adding carefully selected excipients during product formulation – a common practice for small-molecule oral drugs – can beneficially alter the characteristics of the API to achieve the desired result, including bestowing attributes such as extended shelf-life or improved solubility. Biologic OSDs can utilise the same approach.

Strategies to achieve this include using coatings or capsules to protect biologics from harsh stomach and gastrointestinal tract conditions. These coverings act as a shield, protecting the product from degradation. They also allow the controlled release of the drug, increasing efficacy and safety for the patient by programming a predetermined release rate over a specified time period.[3]

Alternatively, using nanoparticle-based oral delivery, the biologic drug can be encapsulated within a nanoparticle, which also controls drug product release. The outer surface of the nanoparticle can be designed to target receptors within the intestinal barrier. This increases the bioavailability of the drug, helping it to be transported across the membrane.[3]

Although research is still ongoing, the following excipients have been explored for their impact on biologic properties:

- Permeation enhancers and absorption promoters to increase bioavailability. Examples of such excipients include

sodium caprate, chitosan, and bile salts.
- Surfactants, co-solvents, and complexing agents that can be used to improve solubility and enhance absorption. Examples include polysorbate 80, cyclodextrins, and polyethylene glycol (PEG).
- Stabilisers and antioxidants that can be added to the formulation to protect the drug from degradation. Examples of such excipients include trehalose, mannitol, and vitamin E.
- Immunomodulators and adjuvants that can be added to the formulation to reduce the immune response. Examples include aluminium hydroxide, MF59, and monophosphoryl lipid A.
- Mucoadhesive patches that can be placed in capsules to bind the intestinal mucus, prolonging residence time and localising biologics near the mucosal interface to enable unidirectional diffusion.
- pH-sensitive hydrogel patches for controlled release.

Formulated to form the final drug product, the excipient and API mixture must adhere to strict regulatory requirements, and the excipients used are carefully chosen to comply with regulations. For example, bulking agents, fillers, and binders, such as microcrystalline, cellulose, lactose, and magnesium stearate, can be added to the formulation to improve manufacturing and meet regulatory requirements.

**A Strategy for Determining Excipients**

Researching excipients to improve biologic OSD formulations is still in its early stages. Upon excipient addition, an in-depth analysis of product activity, stability, and bioavailability is essential to monitor the impact on the biologic formulation. A number of steps should be followed to ensure the appropriate excipient is selected for the required characteristic:

1. **Define the objective of the study:** Outline the desired characteristics that must be achieved with the chosen excipient, highlighting potential options.
2. **Select the appropriate excipient:** Quantify the effect of potential excipients on the stability, solubility, bioavailability, or pharmacokinetics of the biologic. Select an excipient that meets the intended application without altering biologic structure or function.
3. **Conduct a pre-formulation study:** Determine the physicochemical properties of the biologic and excipient. This includes particle size, morphology, surface area, and surface charge.
4. **Formulate the biologic with the excipient:** Use the appropriate techniques for product formulation, such as spray drying, freeze-drying, or hot melt extrusion.
5. **Conduct *in vitro* testing:** Analyse the impact of the excipient on the solubility, stability, and release of the biologic. This includes dissolution testing, stability testing, and particle size analysis.
6. **Conduct *in vivo* testing:** Determine the impact of the excipient on the pharmacokinetics and bioavailability of the biologic. This includes animal studies and clinical trials.
7. **Draw a conclusion:** Analyse and interpret data from in vitro and *in vivo* studies to determine the excipient's impact on the biologic. Compare it to a control group for statistical significance and, based on the results, draw a conclusion on what impact the excipient use has on the biologic.

Following the steps above is critical to ensure product efficacy and safety. However, extensive testing can be time consuming and lead to delays in bringing a desired biologic to market. To help ease this process, forming a communicative partnership with a contract development and manufacturing organisation (CDMO) with experience and expertise in biologic OSD formulation can be invaluable.

**How can a supportive partner help overcome these challenges?**

Access to an experienced partner can ease biologic OSD formulation, helping to overcome the challenges of bringing a product to market successfully.

CDMOs can irrevocably aid and accelerate drug production by providing expert sector knowledge, regulatory requirement insights, and scientific expertise. Forming a free-flowing partnership with a CDMO can ease OSD formulation, with access to high-end equipment, the latest technologies, continuously harnessing innovation to formulate a desired biologic OSD target.

**Looking to the Future**

Orally-taken biologic drugs offer a patient-centric approach to treating diseases. As our understanding of overcoming challenges associated with oral biologics grows, we can work to harness coatings, capsules, and excipients to drive oral biologic formulation from lab to market. Aided by a supportive CDMO partnership, innovative biologic OSD strategies can be used to accelerate development.

Biologic OSD development is expected to significantly impact the biopharma space in the coming years. As these new therapies become standard practice, we can anticipate increased patient compliance, improved biologic stability and efficacy, and enhanced drug solubility, leading to increased bioavailability and improved therapeutic outcomes. The market will likely also experience a shift as drugs only previously available via parenteral administration will now be available in OSD.

Biologic OSDs are now at the forefront of biologic development, helping manufacturers increase patient access by bringing vital medicines directly to patients.

**REFERENCES**


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