CASE STUDIES

Multiple Approaches to Address the Challenges of Oral Absorption of PROTAC Drugs

Introduction

A proteolysis targeting chimera (PROTAC) is a heterobifunctional molecule consisting of two covalently linked protein-binding domains: a target protein ligand and an E3 ubiquitin ligase ligand. After binding to the target protein, E3 ligase is first recruited for ubiquitination to form a stable ternary complex, and the target protein is then degraded by proteasome mediation. PROTACs put the protein of interest in close proximity to the E3 ligase to catalyze degradation. PROTACs have a catalytic mechanism, with the PROTAC itself being recycled after the target protein is degraded. Due to their catalytic mechanism, PROTACs can be administered at lower doses. As PROTACs need only to bind their targets with high selectivity (rather than inhibit the target protein's enzyme activity), there are currently many efforts to retool previously ineffective inhibitor molecules as PROTACs for next-generation drugs.

In recent years, PROTAC technology has been popular in the field of oncology drug development, and researchers have used this technology to develop a large number of PROTACs targeting oncoproteins. PROTAC technology is designed to induce the degradation of proteins, not to inhibit them like traditional inhibitors, providing a new pathway for targeting previously undruggable proteins and addressing the drug resistance problem. PROTACs offer many advantages compared to traditional therapeutics, such as:

1. Wide range of targets, high activity, and the ability to target previously "undruggable" proteins.
2. Improved selectivity, activity, and safety. Can be administered at lower doses due to their catalytic mechanism.
3. Overcoming drug resistance, degrading previously undruggable targets, etc.

However, as a new class of API molecule with large molecular weight and numerous functional groups, it does not comply with Lipinski's Rule of Five (Ro5), resulting in poor drug permeability, solubility, and oral bioavailability.

As a global CDMO serving global innovative pharmaceutical companies and research institutions, Porton has an extensive experience in research and manufacturing services, especially in the field of PROTAC drug development. Porton is committed to the development and production of PROTAC oral formulations and provides customers with comprehensive, reliable, fast, and compliant one-stop services, to meet customers' supply chain needs and facilitating the commercial success of their products from research and development to order fulfillment.

Project Background

An innovative pharmaceutical company has commissioned Porton with formulation development for a new PROTAC drug, aiming to progress the drug development from preclinical research (IND/Phase I) to the critical phase II clinical trials. To seize the market opportunity, the customer expects to complete the IND application within 5 months, and ultimately scale up the production to 40,000 tablets/batch to meet clinical research- and subsequent commercialization needs. The project faces multiple technical challenges:

1. The target PROTAC molecule has a complex structure, high molecular weight, and low solubility and permeability, which significantly restricts the bioavailability and effectiveness of the drug.
2. The tight timeline presents additional challenges for research and development, and IND filing preparation.

In order to address the technical challenges in a timely manner, the Porton team has developed a multiple-approach development strategy, simultaneously exploring various technologies such as nanoparticle delivery, lipid formulations, solid dispersions, etc. Based on the screening results, promising approaches will be selected to ensure the project meets milestones on time, laying a solid foundation for future clinical research and commercialization for the client.

Exploring Multiple Approaches to Address Oral Absorption Challenges

Multidimensional technology path parallel development

At the beginning of the project, the Porton team with rich experience in drug formulation development, quickly determined the development approaches of three major formulation technologies, nano formulations, lipid formulations, and solid dispersions, based on the characteristics of high molecular weight, low solubility, and poor permeability of PROTACs. The team conducted a systematic physicochemical property characterization, including solubility, lipophilicity, metabolic stability, permeability, etc. The team designed focused experiments for various technologies based on computer simulation and results from pilot experiments with both scientific soundness and efficiency in mind.

- Nanoformulations: Reduce the particle size of drug particles to the nanometer range by nanogrinding, high-pressure homogenization, and microfluidics. The exponential increase in specific surface area improves the dissolution rate and solubility of poorly soluble drugs and enhance their permeation and adhesion properties, thus improving bioavailability and absorption.
- Lipid based formulations: Utilizing the amphiphilicity of lipid excipients (such as phospholipids and fatty acids) to formulate delivery systems such as nanoemulsions and liposomes, which are compatible with drugs of various solubilities. Lipid formulations undergo digestion, forming mixed micelles with bile salts and phospholipids. These micelles facilitate drug diffusion across the intestinal membrane, improving absorption. Lipid formulations may promote the production of chylomicrons for lymphatic uptake, bypassing the hepatic first pass metabolism and improving overall drug availability. Some lipid excipients can increase permeability by altering the intestinal membrane's structure and function.
- Solid dispersion: Hot melt extrusion, spray drying and coprecipitation processes generate and maintain drug molecules in amorphous state. The carriers improve drug solubility and dissolution rate, and form a supersaturated system, thus significantly improve the bioavailability.

Innovative development model accelerates project progress

To meet the aggressive objective of the customer to complete IND declaration within 5 months, the Porton team adopted a combination strategy of "high-throughput screening + in vitro dynamic solubility research + parallel screening and optimization", significantly reducing the development time.

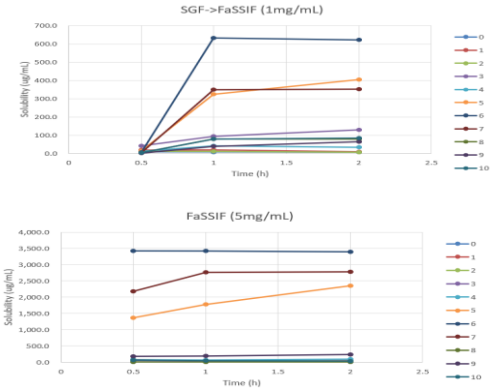
1. High Throughput Screening
   High-throughput screening offers several key advantages: it uses small amounts of samples, is highly efficient, sensitive, and accurate. For a new compound with little information available, a large set of experimental data are obtained through extensive testing from high-throughput screening to facilitate pattern recognition or formulation selection, and to identify a few more promising formulations for further development. This strategy is both fast and comprehensive.
   With a large set of high-throughput screening data already available for this project, ASD screening, drug load optimization, and preliminary stability studies were completed using only 5g of raw materials, significantly reducing raw material consumption and development time.
2. In vitro study: dynamic solubility
   The capacity of various solid dispersion formulations to enhance solubility and maintain supersaturation solubility was analyzed by dynamic solubility testing of solid dispersions in simulated intestinal and gastric fluids. Based on the in vitro dynamic solubility results, the solid dispersion formulation with high solubility and long maintenance time was selected for animal pharmacokinetic (PK) studies in beagles. The bioavailability was increased from 0.04% of API suspension to 32% of ASD, demonstrating the significant benefits of solid dispersion technology.

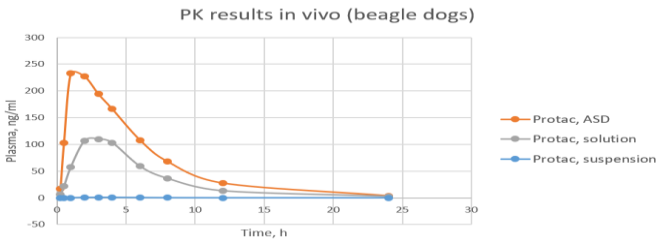
3.Parallel screening and optimization

Considering the need for timely IND filing and progressing to the clinical stage of the project, the lead formulations for the compound needed to be identified during screening. The Porton team immediately conducted parallel screening and optimization work on the project:

Parallel studies such as solubilizer screening, compound particle size optimization, permeability enhancer screening, lipid formulation screening, drug load optimization, animal PK studies (beagles and crab-eating macaques), and stability studies on the lead formulations were conducted to ensure that the candidate formulations are both efficacious and meeting the quality requirements for IND application.

As a result of the parallel studies of in vitro formulation research and in vivo studies, the bioavailability of this PROTAC compound was successfully increased by about 800 folds. The lab scale research, development work and phase I clinical trial material manufacturing were successfully completed within 5 months.





Efficient Resource Integration to Achieve Timely GMP Delivery

The project team seamlessly coordinated and integrated the R&D and production resources of two sites to ensure resources were pooled together to address technical challenges. With the excellent technology transfer and project management capabilities of Porton, the entire process from R&D formulation development to GMP production was seamless. The team completed the first phase of the project, from R&D to GMP production, within 5 months, and successfully delivered clinical trial material of 40,000 tablets per batch.

Summary

PROTAC drugs presents inherent challenges due to their high molecular weight, low solubility, and low permeability, limiting their oral bioavailability and clinical use. The Porton team adopted a "multi-approach in parallel" development strategy to address the above challenges with nano formulations, lipid formulations, and solid dispersions, making it possible to prepare PROTAC drugs into oral formulations.

As the CMC service provider for the PROTAC drugs, Porton provides comprehensive and customized end-to-end solutions for the development of PROTAC drug formulations. With efficient research on the physicochemical properties of active pharmaceutical ingredients, R&D formulation studies, animal PK studies, quality control studies, and supply chain support, the Porton team, in a flexible and collaborative approach, adjusted its CMC strategy to improve efficiency, reduce risk, and ensure product quality. Not only did the team successfully deliver the project from research and development to GMP production within 5 months, helping the customer complete IND registration in a timely manner, but they also made a breakthrough in bioavailability enhancement by increasing it by 800 folds, demonstrating Porton's technical strength in complex formulation development.

Today, Porton continues to provide professional technical support and additional resources to customers, deeply involved in progressing the clinical phase II development of the drug, demonstrating its leadership in service capabilities and long-term partnership potential in the field of PROTAC drugs.

Porton PROTAC Drug CDMO Service Platform

With 20 years of experience in traditional small molecule drug services, Porton is equipped to offer comprehensive services for PROTAC drugs, including synthesis building block development, API process development and production, formulation development and production, extensive quality studies, and CMC registration support. Leveraging a globally leading technology platform, Porton is dedicated to providing one-stop CDMO services to global pharmaceutical companies, covering intermediates, APIs, and formulations throughout all stages of drug development and commercialization, adhering to international standards.

Porton DP CDMO Service Platform

With rich experience in API development and crystallization research, we have established a leading formulation empowerment technology application platform. We have multiple research and development centers and GMP production facilities in Shanghai and Chongqing (China), and New Jersey (the United States). Our core facilities cover oral, injectable, and topical formulations, providing global pharmaceutical companies and new drug research and development institutions with integrated CDMO solutions from preclinical development to commercial launch, from small molecules to new modalities. Our services include: pre formulation research, formulation process development and optimization, IND, P1-P3 clinical trial material manufacturing, NDA/PPQ， pivotal batch manufacturing, Commercial production, CMC registration support, etc. Porton is committed to enabling the public's early access to good medicines.