Recipharm

Overcoming fixed-dose combination development challenges for an investigational Amyotrophic Lateral Sclerosis (ALS) drug

Overcoming release rate challenges in fixed-dose development

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterised by the progressive degeneration and eventual death of nerve cells (neurons) in the brain, brain stem and spinal cord. Some 1.5 to 3 people per 100,000 are diagnosed with the condition every year in North America and Europe[1]. Currently, only two drugs have been demonstrated to be effective in ALS – Riluzole and Edaravone.

NeuroSense Therapeutics' therapy for ALS, Prime C, is a unique formulation of a fixed-dose combination drug comprising the active pharmaceutical ingredients (APIs) ciprofloxacin and celecoxib. The therapy aims to target multiple disease mechanisms, including microRNA dysregulation, iron accumulation and neuroinflammation.

NeuroSense Therapeutics approached Recipharm for support in creating a new extended-release fixed-dose combination tablet offering similar release rates for both APIs to ensure a similar level of *in vivo* exposure – a particular challenge for the two APIs being used.

Understanding ALS

ALS affects nerve cells responsible for controlling voluntary muscle movement – the upper and lower motor neurons gradually degenerate and die. Unable to function, the muscles degenerate in turn.

As a result, ALS is a progressive condition, with symptoms worsening over time. A patient's ability to control their own voluntary movements becomes affected, with individuals losing strength, the ability to speak, eat, move and breathe. Most patients with ALS die of respiratory failure within three to five years of the first symptoms appearing.

NeuroSense Therapeutics' Prime C aims to harness two drugs approved by the US Food and Drug Administration (FDA) – celecoxib and ciprofloxacin – to synergistically inhibit the progression of ALS symptoms.

With an effective formulation solution to allow them to work together in the human body, the two drugs have the potential to mitigate the degeneration and inflammation of affected motor neurons.

Formulation development challenges

To achieve a formulation with the target profile, the team at Recipharm's Bengaluru site considered the physicochemical and pharmacokinetic behaviour of both APIs.

Both drugs had opposing behaviour in terms of solubility and pharmacokinetic properties. Celecoxib belongs to Biopharmaceutics Classification System (BCS) class II (low solubility and high permeability), and ciprofloxacin to BCS class IV (low solubility and low permeability).

In practice, the latter is absorbed in the upper intestine with a half-life of approximately four hours, whereas the former is absorbed throughout the GI tract, with a half-life of approximately 11 hours. From this data, it was predicted that most of the ciprofloxacin would be released in the first four hours and celecoxib within approximately 10 hours.

The Recipharm team advised the development of a matrix-based conventional extended-release tablet using wet granulation and featuring hydrogel as the extended-release polymer. Optimising the level of the hydrogel was critical to the success of the project, ensuring the polymer offered the necessary targeted release profile. Since ciprofloxacin is known to have a very bitter flavour, it was decided to film coat the tablet for taste-masking.

1. Adriano Chio, Letizia Mazzini, Gabriele Mora. Disease-modifying therapies in amyotrophic lateral sclerosis

Table 1. Formulation of PrimeC tablet

Sl. No.	Material name	mg/tablet	% w/w
1	Ciprofloxacin Hydrochloride	xx	xx
2	Celecoxib	xx	xx
3	Diluent	Q. S.	Q. S.
4	Binder	Q. S.	Q. S.
5	Surfactant	Q. S.	Q. S.
6	Extended release polymer	Q. S.	Q. S.
7	Glidant	Q. S.	Q. S.
8	Lubricant	Q. S.	Q. S.
9	Opadry	Q. S.	Q. S.
10	Purified Water	Q. S.	Q. S.

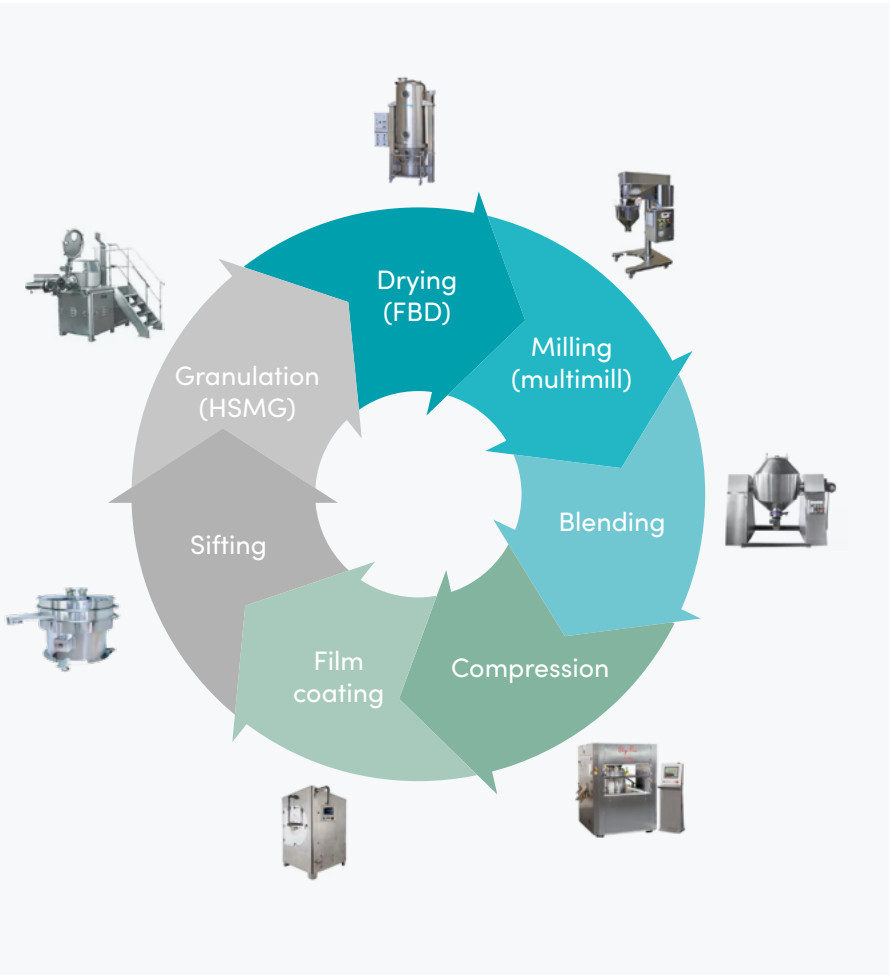


Figure 1. Manufacturing flow of the fixed-dose combination drug product

Developing an effective dissolution method

Based on the formulation type and the solubility of both drugs used in Prime C to achieve actual drug release in specific media, a two-stage dissolution method of discriminatory nature was established.

This two-stage dissolution method is more relevant to physiological pH. The two-stage dissolution method was developed by evaluating different concentrations of sodium lauryl sulfate (SLS) – an anionic surfactant under consideration for the formulation to enhance the solubility of both actives. Recipharm's experts evaluated different concentrations of SLS as well as a range of paddle revolutions per minute (RPM) – 50, 75, and 100xx.

Development results

The formulation developed showed that the release of the two APIs can successfully remain in balance throughout the formulation's target residence time.

This data indicated comparability and satisfactory results for both pilot and scale-up batches. Dissolution was also assessed for stability and found to be satisfactory.

As the two APIs had contrasting solubility profiles, a two-stage dissolution method was developed, starting with an acidic stage followed by a buffer stage with surfactant. A matrix tablet design was also utilized to control drug release.

The outcome

Recipharm's Bengaluru team successfully developed matrix tablets of a fixed-dose combination of celecoxib and ciprofloxacin using a controlled-release polymer that operates on both erosion and swelling mechanisms. This synchronises the release profiles of the two APIs – demonstrated in later in vivo studies carried out by NeuroSense Therapeutics.

As a result of the success of the formulation development process, both celecoxib and f ciprofloxacin successfully provide a synergistic effect in the treatment of ALS patients.

Prime C has received orphan drug status from the US FDA and the European Union's (EU) European Medicines Agency (EMA). The manufacture of clinical batches is planned for phase 3 studies, and registration batches for submission to regulators in Canada are in preparation.

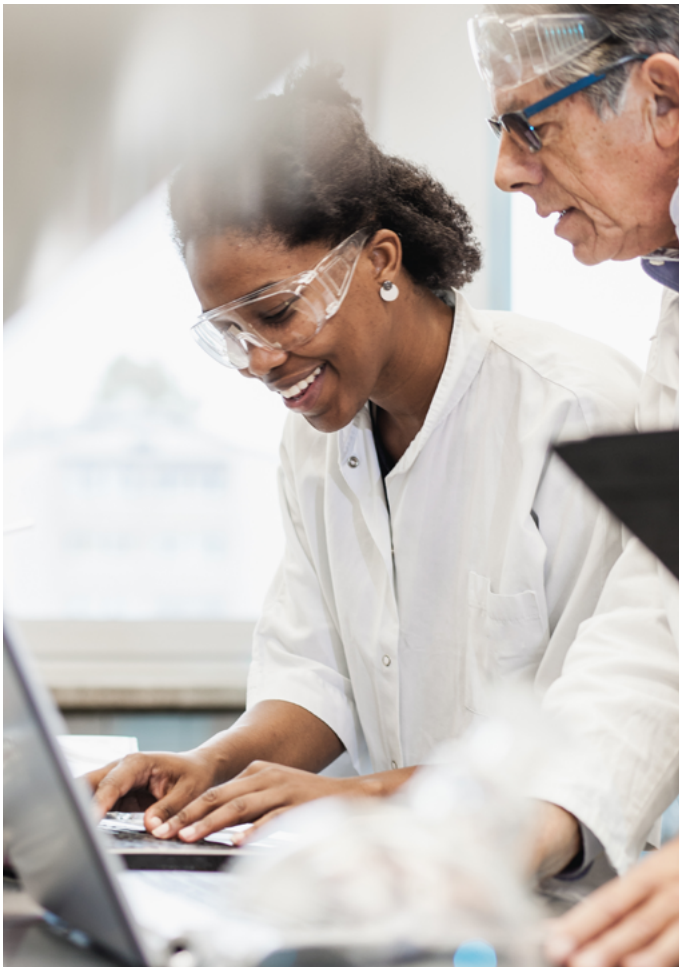
How Recipharm can help meet your complex formulation development needs

As a leading contract development and manufacturing organisation (CDMO), Recipharm is an experienced partner in the development of complex fixed-dose combination formulations. The company harnesses a range of analytical approaches to identify the ideal approach to deliver the target product profile (TPP), and has expertise spanning dosage form, manufacturing, formulation, analytics and method development.

Recipharm's analytical capabilities include:

- Method development
- Method validation
- Stability and forced degradation studies
- Impurity investigations
- Nitrosamines
- Extractables and leachables

Employing sophisticated techniques and methodologies, Recipharm can support not only in validating the integrity of pharmaceutical products but also in enabling companies to fine-tune formulations, optimise manufacturing processes and troubleshoot potential issues. With Recipharm's analytical expertise you can be confident in the product you are bringing to trial and to the market.



Work with experts to overcome challenging fixed-dose combination projects

Formulating drug products that harness multiple APIs can be a complex undertaking. When the APIs being explored for a new product have different solubility and bioavailability profiles, it can be difficult for pharmaceutical companies to identify an appropriate formulation solution to achieve their ideal TPP.

A matrix-based OSD formulation capable of interacting with changing pH levels as the drug product moves through the human body's GI tract is an effective method of balancing drug release rates for APIs with opposing solubility characteristics.

To benefit from the advantages of such approaches, it is vital to have an appropriate testing and validation method developed, and this requires specialist analytical expertise and infrastructure.

As a global CDMO with dedicated analytical method development experience, Recipharm has the capability, knowledge and capacity to support clients from around the world in developing the right testing methods for the needs of their products.

By working with a partner like Recipharm, companies can be confident they have the methods they need to identify an ideal formulation to deliver their desired therapeutic outcomes.

To find out more, contact Recipharm: www.recipharm.com/contact-us

About Recipharm

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden and the US and are continuing to grow and expand our offering for our customers. We are supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 30 years, we have partnered with our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. We conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do.

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