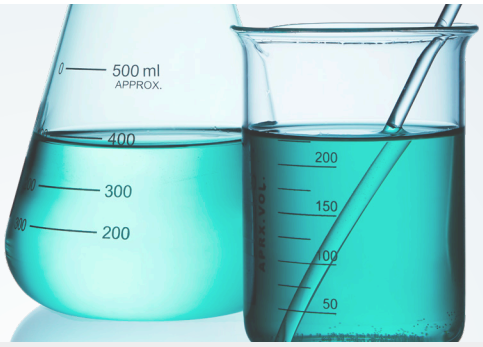
Recipharm
Analytical Solutions™



CASE STUDY: DEVELOPING A STABILITY INDICATING METHOD FOR THE ANALYSIS OF A COMPLEX COMBINATION DRUG PRODUCT

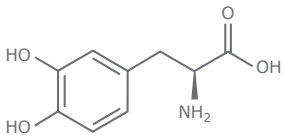
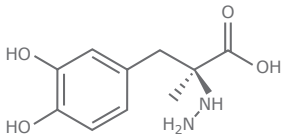
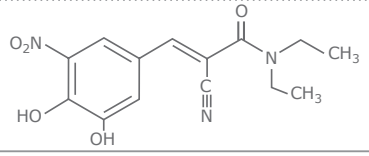
Swedish speciality pharmaceutical company, Lobsor Pharmaceutical AB, recently gained approval for its advanced Parkinson's disease (PD) treatment, Lecigon® intestinal gel. A combination drug product containing three active pharmaceutical ingredients (APIs) in a viscous gel, the treatment is continually administered directly to the small intestine via a small portable pump enabling a dosage within the narrowing therapeutic window in advanced PD.

Recipharm's experience of developing complex drug products, including analytical chemical control methods, scale-up of manufacturing processes and tech transfer to commercial manufacturing, led Lobsor to select the company to perform all formulation development work. This included establishing the necessary analytical methods and providing module 3 of the Marketing Authorisation Application (MAA). The complexity of the product meant that developing a suitable analysis method was highly challenging due to the combination of an unstable/reactive API and the liquid (gel) formulation.

LECIGON® INTESTINAL GEL

Lecigon® intestinal gel contains the active ingredients levodopa (20mg/ml), carbidopa monohydrate (5mg/ml) and entacapone (20mg/ml). The APIs are suspended in an aqueous vehicle containing a polymeric thickener to obtain a defined viscosity for maximum physical stability. The structures and chemical properties for the three APIs are presented in *Table 1*.

Table 1 – Chemical properties of the APIs

NAME	STRUCTURE	LIPOPHILICITY	AQUEOUS SOLUBILITY
Levodopa		Low	Slightly soluble in water Soluble in dilute mineral acids
Carbidopa		Low/medium	Slightly soluble in water Soluble in dilute mineral acids
Entacapone		High	Practically insoluble in water

The Lecigon treatment circumvents many of the troubles seen in the advance stage, gastrointestinal dysfunction with erratic gastric emptying, the short half-life of levodopa and the narrowing of the therapeutic window, all this with a reduced levodopa dose.

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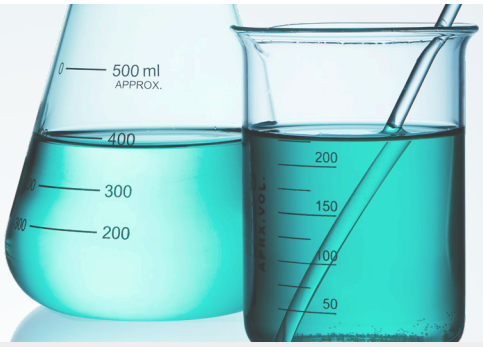


Challenges in analysis

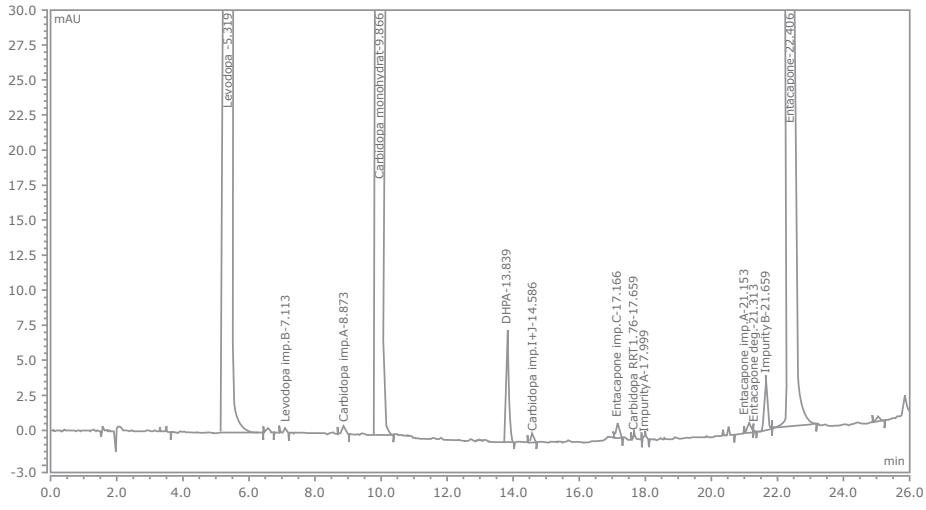
High performance liquid chromatography (HPLC) is usually used to determine the concentration of APIs, their impurities and degradation products. The complexity of developing a reliable stability indicating analysis method for a product depends on several factors, including the number of APIs and potential degradation products that need to be separated, the properties of the inactive excipients in the formulation, and the stability and chemical properties of the analytes. Here, several challenges needed to be overcome to develop a stability indicating method for the product. These included:

- The widely varying lipophilicity and aqueous solubility of the APIs (as seen in *Table 1*).
- A low concentration of carbidopa compared to the other APIs in the product.
- The potential of the polymeric thickener to cause HPLC column blockage if not sufficiently removed during sample work-up.
- The poor chemical stability and high reactivity of carbidopa, which results in formation of degradation products as well as combination products with one of the other APIs.

Developing a single method of analysis for assay and impurities

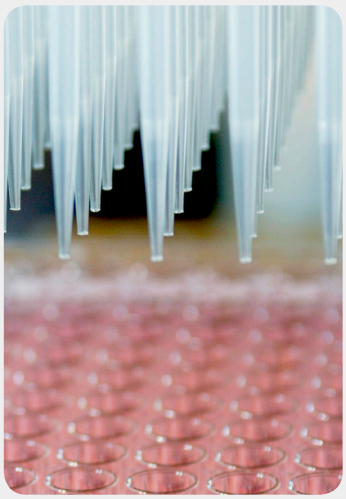
Due to the APIs widely varying lipophilicity and adequate UV properties, a reversed phase gradient method with UV detection was developed. The method was successfully validated according to The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. In 30 minutes, the HPLC method separates all APIs, their synthesis related impurities, and degradation products. Samples are prepared in a step-wise procedure using both 0.1 M HCl and an organic solvent. Analysis of assay and related substances is done in separate injections (with different injection volumes). Obtaining the required ICH reporting limits for all degradation products requires the use of different sample preparation procedures, including different sample concentrations, % organic modifier and dilutions. Analysis of the APIs and the majority of the related substances is done at 280nm, but some of the related substances require detection at 220nm. A chromatogram at 280 nm of a typical degraded stability study sample is shown in *Figure 1.*

Figure 1 - Chromatogram at 280 nm of a typical degraded stability study sample



The collaboration with Recipharm has been crucial for Lobsor! Recipharm has shown a great flexibility, openness and expertise which has significantly contributed to the success of Lecigon

- Roger Bolsöy,
Co-founder of Lobsor Pharmaceuticals



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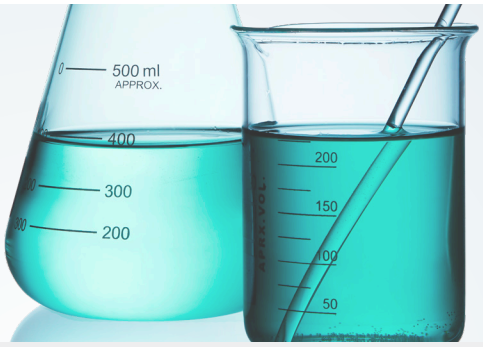

Resolving issues

The poor chemical stability of carbidopa and one of the drug product impurities required specific sample preparation procedures to avoid degradation, including the use of refrigerated conditions and limited preparation times. HPLC column blockage was seen when the polymeric thickener was not sufficiently removed during sample preparation. This was overcome by changing to an organic solvent that precipitated most of the polymer. Performing centrifugation at refrigerated conditions also resulted in clear sample solutions being obtained and all problems with column blockage were eliminated.

Entacapone has poor aqueous solubility that requires the use of a certain amount of organic solvent in sample and standard diluents to prevent precipitation in refrigerated conditions. This however, resulted in problems with peak shape distortions for the early eluting very hydrophilic levodopa and some of its impurities during injection. This is a common problem seen in reversed phase HPLC methods when attempting to inject standard and sample solutions containing a much higher percentage organic solvent than that which is present during the gradient starting conditions. Issues were overcome by careful optimisation of injection volumes, percentage organic solvent in the diluent and by using trifluoro acetic acid (TFA) in the mobile phase to increase retention of early eluting hydrophilic compounds.

In the early stability studies a large unknown peak was sometimes seen. Investigations identified this to be an artefact peak from an unwanted reaction between one of the APIs and a very low level (ppm), uncontrolled contaminant in one of the solvents used for sample preparation. To manage the problem, a specific pre-test of the solvent was developed, which should be applied whenever a new batch is needed.

Transfer to QC lab

Transfer of the analytical method to two of Recipharm's other analytical labs verified that, despite its complexity, the method is robust. The method development devised by Recipharm's team identified the problems and established suitable solutions to allow the method to be successfully used for routine analysis in a QC lab environment. Furthermore, the on-site, hands-on, support (provided by the analytical expert who developed the method) before the formal transfer activities greatly facilitated the technology transfer process to the receiving QC-labs.

Project results

The result of this project was that one single chromatographic method could be used for all the active ingredients which of course is advantageous in terms of efficiency and cost. Careful planning, thorough method development and validation work, as well close collaboration with the QC lab during tech transfer, made it possible to launch this product without the cost increase that two or three methods would have caused. It was also important that the analytical method was robust, which is increasingly difficult as the complexity of a method increases.

Recipharm's approach to provide customer tailored development and support, adapted to the specific demands of this complex drug product, were key factors to the successful outcome of this project.

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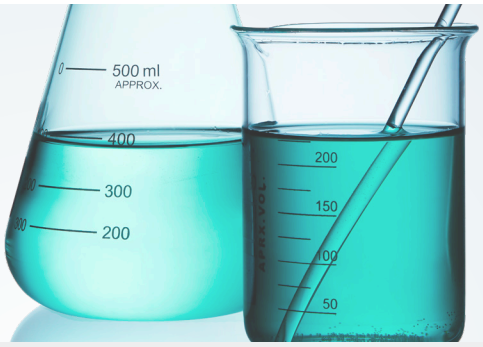

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ABOUT LOBSOR PHARMACEUTICALS

Lobsor Pharmaceuticals is a Swedish specialty pharmaceutical company focusing on innovative, proprietary technologies and drug formulations. The Lobsor team has substantial experiences from pharma and the treatment of Advance stage Parkinson's disease treatment.

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, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 6,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 20 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, 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. That's the Recipharm way.

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