Recipharm

Overcoming tablet dissolution challenges with formulation expertise

During the technology transfer process for a well-established oral solid dose hypoglycaemia drug, it was found that the product's inconsistent dissolution rate was hindering performance. Recipharm harnessed its years of complex formulation development experience to optimise the drug formulation on behalf of the client, delivering a better experience for patients.

Hypoglycaemia (low blood sugar) is a condition that often presents in diabetes patients managing their disease with insulin. Although common in patients with diabetes (which affects 415 million people globally[1]), hypoglycaemia can present in those suffering from other underlying diseases such as insulinoma, or adrenal or pituitary insufficiency.

Without careful management of blood glucose levels, these patients can be at serious risk. Hypoglycaemia is predominantly associated with fast-onset symptoms such as headache, blurred vision, or palpitations, and, without prompt treatment, it can devolve into a true medical emergency.

Self-treatment to counteract low blood sugar will involve the ingestion of products to raise glucose levels, such as oral glucose tablets. As with most oral tablets and capsules, these tablets will typically have a dissolution specification as part of their formulation regardless of whether their release is immediate or extended. Drug absorption from an oral solid dosage form is in part dependent on the dissolution of the drug under physiological condition. Gaining an understanding of dissolution under in vitro conditions will help to predict in vivo performance and incorporating dissolution specifications into development will help to ensure lot-to-lot quality consistency.

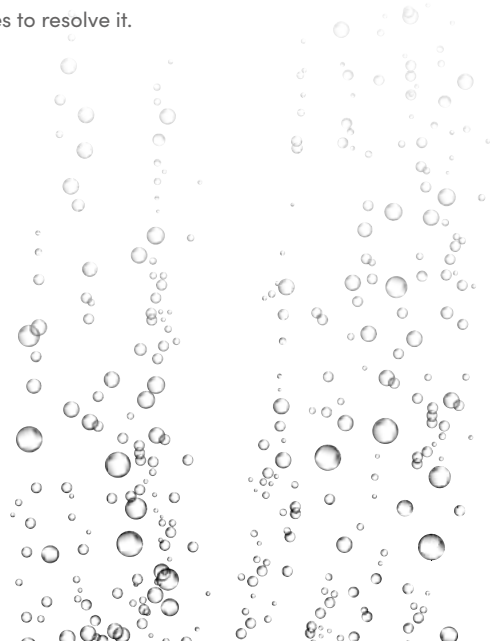
While supporting a leading drug developer with the manufacture of an immediate release hypoglycaemia tablet, it was identified that dissolution was not part of the originally approved specification prior to tech-transfer. When conducting the necessary dissolution studies, inconsistencies were found between batches. Without resolution, this could mean patients receiving inconsistent doses. Rising to the challenge, Recipharm investigated the root cause and proposed a new formulation that demonstrated consistent dissolution properties.

The challenge

Recipharm was responsible for transferring the manufacture of the commercial hypoglycaemia product to its multi-purpose development and manufacturing facility at Bengaluru, India. Upon review of the dossier submitted for approval for Bengaluru to be used as the new site for manufacturing, dissolution was noted to be absent from the originally approved specification. In line with other orally administered tablets, dissolution was suggested to be included.

However, when comparing the three validation batches supplied, the Bengaluru tech-transfer team quickly realised there was an inconsistency in dissolution between them, with one batch demonstrating much slower dissolution. Without evident reproducibility in validation batches, compliance with FDA regulations for the release of a finished drug product could not be demonstrated.

It was essential that Recipharm resolved the issue to ensure all batches were meeting the specified dissolution acceptance criteria to ensure consistent bioavailability and dosage. Achieving this within the stipulated time frame required extensive formulation expertise to identify the root cause of the problem and implement effective strategies to resolve it.



1. https://www.diabetes.co.uk/diabetes-prevalence

Understanding the cause of the dissolution inconsistencies

Determining the cause of the variation between the validation batches relied on an understanding of how the original formulation and manufacturing processes used could be impacting dissolution.

Considering the nature of the active pharmaceutical ingredient (API), the Bengaluru R&D team hypothesised that the use of starch paste as a binding agent (specifically its granulation) could be a key contributor to the inconsistent dissolution behaviour observed. This is because the disintegration properties of starch when gelatinised during preparation depend heavily on the operator's experience. Ensuring consistency when preparing the starch paste is challenging, and operation must almost be second nature to achieve this. As a result, validating this process is often extremely difficult.

The Bengaluru R&D team also identified a possible second contributor to the dissolution variation issue: the composition of the in-house sugar coating composition. Used to give a shine to the surface of the tablet, the coating contained waxes that could be further acting to slow the dissolution of the affected validation batch.

Proposal of a new formulation

With these hypotheses, Recipharm proposed a three-step strategy to solve the dissolution issues with a new formulation:

1) Rather than maize starch, pregelatinised starch would be used as a binder. As this project did not require activation starch to be used as a binder, the simpler process of adding pregelatinised starch into water could be used instead for binder preparation.
2) The multi-step sugar-coating processes would be replaced with a ready-to-use sugar-coating material (Opadry®).
3) Process optimisation of granulation and coating parameters of the new proposed composition would then take place.

The results

After implementing the formulation changes proposed, dissolution studies were conducted using two new development batches and a scale-up batch. After 60 minutes, the percentage of drug dissolution was comparable between the tested materials, all achieving ≥90%.

In comparison, when conducting the same test using the existing commercial product validation batches, two achieved between 50% and 60% drug dissolution, with the third batch only reaching 29%. The new proposed formulation therefore successfully reduced dissolution behaviour variations between batches while simultaneously improving achievable drug dissolution percentages.

With a satisfactory dissolution profile attained, this prototype formulation was used in process optimisation studies, along with analytical method development. Recipharm then completed the partial validation for the new proposed composition.

Looking ahead

Recipharm successfully overcame the dissolution inconsistencies observed in their client's product while navigating the challenges of tech-transfer, delivering the completed development project within the stipulated timeline.

To find out more about how Recipharm's experienced formulation teams could help overcome your formulation challenges, contact us today.

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 9,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 25 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.