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*Short communication*

# Quality by design based encapsulation of BCS Class IV API into hard gelatin capsules

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## Introduction

Active pharmaceutical ingredients (APIs) of the BCS Class IV are characterized by low solubility and low intestinal permeability. These limitations represent a significant challenge in conventional formulation strategies. As acknowledge, "Quality by design" (QbD) is a regulatory assigned systematic industrial contemporary approach for incorporating quality into pharmaceutical product, ensuring it consistently meet predefined quality standards (Yu et al., 2014). Additionally, Design of Experiments (DoE) methods enhance formulation robustness and reproducibility.

For hard gelatin capules formulation, the application of QbD begins with defining the target quality profile (QTPP) on therapeutic needs, target patient population, administration route, and drug release profile (Yu et al., 2014). Critical process parameters (CPPs) for hard gelatine capusles encapsulation typically include vacuum level for opening empty capsules, encapsulation machine speed and compression force. (Guila, 2022; Nair et al., 2004). However, large-scale production challenges persist. Overall, for BCS Class IV API hard gelatin capsules, the optimization of the encapsulation process is required in order to ensure product quality, stability, and an appropriate dissolution and absorption profile (Nair et al., 2004).

## Objective

The aim of this study is to improve and optimize the encapsulation process of BCS Class IV API hard gelatin capsules by applying a QbD approach and DoE methodology for identification and control of CPPs that influence the QTPP of the final product. To address the challenge of encapsulation process, the study focuses on monitoring process parameters such as vacuum level for capsule opening, encapsulation machine speed, and compression force. Additionally, the effective type of DoE methodology has been employed in optimization studies of encapsulation.

Within the experimental framework, the capsule mass should fall within specified limits (402.4 mg – 467.6 mg) while, the average fill weight should remain within 360 mg ± 10%.

## Materials

BCS Class IV API belongs to the nitrofuran group. The used excipients were: Microcrystalline cellulose (Avicel PH 101) – 6.870 kg, Starch (Maydis amylum) – 6.870 kg, Kollidon K-25 –

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1.957 kg, Aerosil 200 – 0.195 kg, Sodium lauryl sulfate – 0.195 kg and Magnesium stearate – 0.391 kg. Hard gelatin capsules (Capsugel, size #1) were used with an average empty capsule weight of 75 mg ± 10%. The granules flowability, monitored as an in-process parameter, was 38 s/100 g.

## Methods

A QbD approach was applied using a DoE framework and a Central Composite Design (CCD). (Yu et al., 2014). The manufacturing process of hard gelatin capsules included the following unit operations: wet granulation, homogenization and encapsulation. The following encapsulation CPPs were monitored: vacuum level for opening empty capsules (inHg), encapsulation machine speed (90 000 – 110 000 cps/h) and compression force (N). The quality of the final product was evaluated through: capsule fill weight (mg), mass variation analysis and physical characteristics. Encapsulation was performed on fully automated equipment MG2 G140 (equipped with a complete mass control system, including automatic rejection of capsules outside specification limits).

## Results and discussion

Industrial application of the QbD approach identifies CPPs, for dug encapsulation, and their optimal ranges: vacuum for capsule opening: 15–45 inHg, encapsulation speed: 90,000–110,000 capsules per hour (cps/h) and compression force: 1–5 N. However, it was revealed that vacuum levels of 40–45 inHg resulted in capsules with physical defects such as cracking and deformation. Therefore, the optimal results were achieved at 15–20 inHg. The vacuum parameter proved particularly critical for preventing physical defects in filled capsules and is therefore equally important as other CPPs. The optimal encapsulation speed, yielding capsules with minimal mass variation, was 100,000 cps/h. Increasing the speed to 110,000 cps/h again resulted in capsule defects such as deformation and rupture of the capsule body. The compression force used for capsule body filling was 5 N and it was confirmed as optimal, especially for size #1 capsules. The obtained results also confirmed that the selection and concentration of excipients, as well as process parameters, significantly influence granule flowability (critical for capsule filling) and capsule fill uniformity.

Three validation batches of capsules were evaluated to access fill weight consistency. The mean fill weight was 360,20 mg for Batch 1, 360,48 mg for Batch 2 and 360,23 mg for Batch 3. The standard deviation remained low across all batches (0,89 mg, 0,88 mg and 0,49mg, respectively), indicating low variability and good process reproducibility. The minimum fill weights ranged from 358,14 mg to 359,21 mg, while the maximum values ranged from 361,33 mg to 363,28 mg. Based on the obtained results, it is shown that the average mass of a capsule filling is within the specification limits (360 mg ± 10%.), while the application of CCD empowered the determination of the optimal values for the CPPs monitored during the encapsulation process.

## Conclusion

The application of QbD and DoE methodologies enables efficient optimization and enhanced control of the encapsulation process for BCS Class IV APIs. This approach contributes to: reduced variability, improved product quality and enhanced robustness and reproducibility of the manufacturing process.

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