

COMPACTION SIMULATION / INDUSTRIAL PRESS CORRELATION: TWO CASE STUDIES

In this article, Aline Moulin, PhD, Head of the New Product Introduction Department, and Lucile Kowalski, PhD, Pharmaceutical Development Project Manager, both of Skyepharma, examine two case studies comparing compaction simulation with industrial compression.

Compaction simulation has been of scientific interest since the 1970s, with a first compression simulator described in 1976.¹ The objective of compaction simulation is to be able to simulate industrial compression – that is, to be able to predict which parameters to apply on industrial equipment to obtain a tablet with the desired properties.

We have been involved in compaction simulation since 2016, with a STYL'One Evolution (Medelpharm, Beynost, France) compaction simulator. The choice of this equipment was driven by two key requirements. It had to be able to:

- Simulate industrial rotary presses
- Simulate complex compressions, such as multi-layer and tab-in-tab (also known as press coated tablets) which are the core Skyepharma development and industrialisation know-how.

Indeed, STYL'One Evolution has some characteristics that correspond well to our needs:

- It is equipped with two sensors on each punch thus allowing very accurate measurements of both tamping force and compression force in a very short time from 0 to 50 kN
- It simulates compression cycles of rotary industrial presses made possible by the fact that:

“ The objective of compaction simulation is to be able to simulate industrial compression – that is, to be able to predict which parameters to apply on industrial equipment to obtain a tablet with the desired properties.”

- You will use the same punches and dies as the ones you use on your industrial equipment
- The equipment mimics the kinetics of rotary presses, in terms of punches speed, penetration² and dwell time³
- It also takes into account symmetric and non-symmetric punch penetration on your industrial equipment (Table 1).
- And finally, Medelpharm designed a specific feeding system for the introduction and centring of the core tablet during tab-in-tab compression.

In the following paragraphs are two case studies of STYL'One / industrial equipment correlation established in our lab.

Press	Type	Compression Symmetry	Punch with Fixed Stroke
SVIAC PR51 CM3	Pilot multi-layer	Non-symmetrical	Upper punches
HATA HT AP LSU 3L	Industrial multi-layer	Non-symmetrical	Upper punches
FETTE P2100	Industrial multi-layer	Symmetrical or non-symmetrical	Upper punches in non-symmetrical mode
Kilian S 250 M	Industrial press coater	Non-symmetrical	Upper punches

Table 1: Different types of industrial presses of interest for our team.



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SVIAC

STYL'One

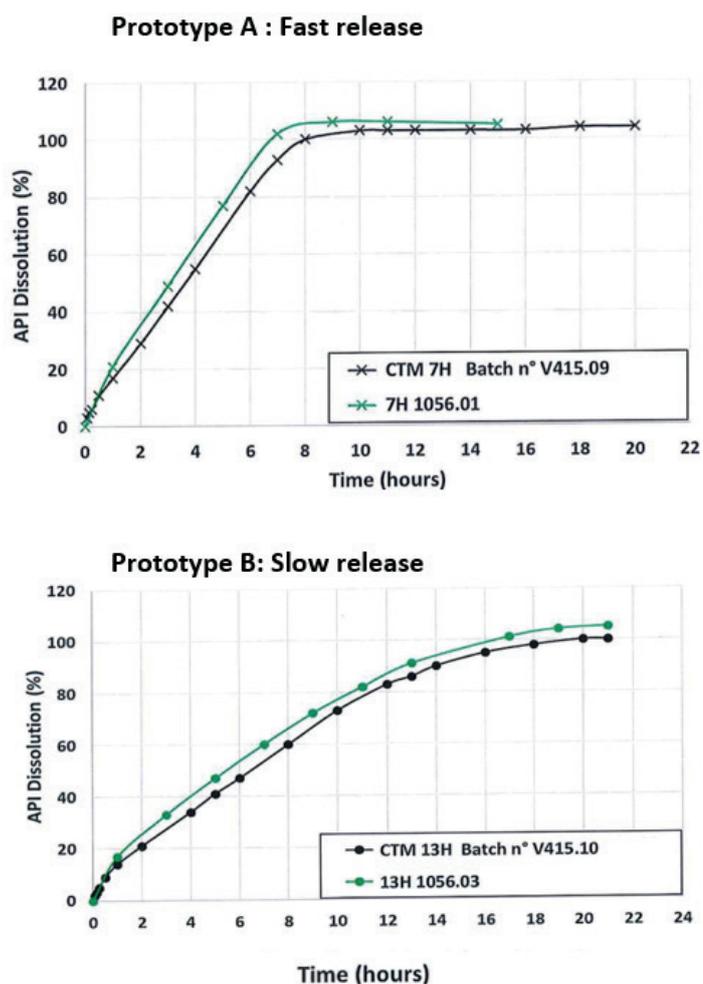


Figure 1: Dissolution profiles obtained for prototypes A and B manufactured with industrial equipment and with compaction simulator.

CASE STUDY 1: GEOMATRIX® MULTI-LAYER TABLET

Objective

The objective of this case study was to be able to replace the early-stage prototyping step we usually perform on industrial equipment (SVIAC PR51 CM3) by prototyping on the STYL'One Evolution.

Geomatrix® multi layer technology allows sustained release profiles to be achieved. Regulating and extending drug release is advantageous in many ways:^{4,5}

- Reduced fluctuations of the blood concentration of the active ingredient might result in decreased occurrence and severity of adverse effects
- Prolonging of the plasma concentration of drugs with short half-life also means reduced administration frequency, and improved patient compliance
- Benefits mentioned above are particularly important not only for patients themselves but also for clinicians and pharmaceutical scientists.

Methodology

The methodology was to demonstrate correlation between STYL'One and SVIAC PR51 CM3 on prototypes – to demonstrate that similar dissolution profile performance could be obtained for batches manufactured with SVIAC and with STYL'One equipment.

Results & Discussion

Two different prototypes were tested: prototype A (fast-release prototype) and prototype B (slow-release prototype). For each of them, the dissolution profiles are displayed below (Figure 1), with two dissolution profiles for each of them:

- In black, the dissolution profile of the batch manufactured with the SVIAC PR51 CM3 equipment
- In green, the dissolution profile of the batch manufactured with the STYL'One Evolution compaction simulator

We can observe that, for both prototypes, the black and green dissolution curves are similar ($F_2 > 50$),

“The most critical facet of a pulsatile release formulation is lag time, which can be engineered through different formulation strategies such as film coating or compression coating.”

thus demonstrating good correlation. Encouraged by these good results obtained on multi-layer tablets, we looked at even more complex oral solid dosage forms, i.e. press-coated tablets.

CASE STUDY 2: GEOCLOCK® TAB-IN-TAB/PRESS-COATED TABLET

Objective

This case study is about a tab-in-tab product, using Geoclock® technology, developed as a time-controlled pulsatile release formulation.^{6,7,8}

Chronological disorders exhibit diurnal variations in their amplitudes owing to the circadian rhythm of the body (the body clock). Various chronological disorders – such as bronchial asthma, rheumatoid arthritis, variant/Prinzmetal's angina and hypertension – exhibit peak disturbance in the early morning when patients are asleep. Conventionally, such early-morning attacks are treated with bedtime administration of medicines in the form of either immediate release or extended release formulations. In such cases, although effect is needed only in the early morning, the drug is continuously released throughout the night; entailing higher doses to extend its effect up to the next morning, with some risks of side effects.

One alternative approach is the pulsatile drug delivery system that can restrict the release for a predetermined period and subsequently provide burst drug release to exhibit peak effect in the early morning. The most critical facet of a pulsatile release formulation is the lag time which can be engineered through different formulation strategies such as film coating or compression coating.

Administration of the proposed formulation is made at bedtime and will release the drug only after midnight to provide the effect in the early morning.

The product of our case study presents a lag time, with a very narrow performance window:

- Sufficient lag time is needed to obtain the delayed release performance for middle-of-the-night delivery
- A too long lag time is to be avoided because of loss of bioavailability (API less absorbed in the colon).

Our objective was to demonstrate correlation between KILIAN S 250 M and STYL'One Evolution on this specific process.

Methodology

Figure 2 presents a high-level scheme of the process: manufacturing of the core tablet, of the upper-layer granulate and the lower-layer granulate, and final compression of the press-coated tablet. Given the very narrow performance window of this product, a press setting is performed to determine at which pressure the three intermediates will give the final product with the desired dissolution profile.

This setting is currently performed on an industrial KILIAN S 250 M press, and we wanted to see if it was possible to perform it on the STYL'One Evolution

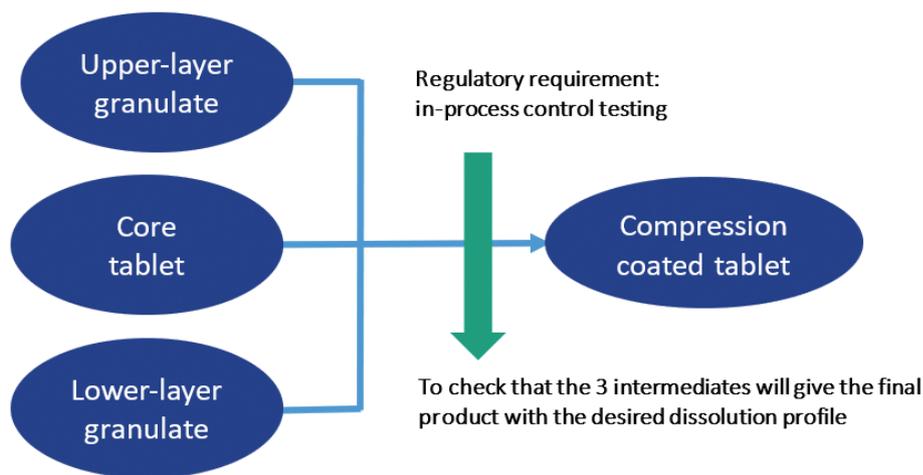


Figure 2: General scheme of the manufacturing process.

compression simulator. So a preliminary study was performed to compare lag-time dissolution performance between batches manufactured on both types of equipment.

Results & Discussion

The comparison was performed with three different independent batches. For each of them, the setting was performed with Kilian equipment and with STYL'One Evolution equipment. Three different compression forces were tested – A, B and C – to determine if the resulting lag time was compliant with specifications.

The setting performed on STYL'One Evolution gave the same results as the one performed with KILIAN (Figure 3). That means the setting performed on STYL'One Evolution allows selection of compression pressure that, once applied on Killian S250, will give drug product with compliant lag time. Based on correlation observed in this case study, definition of the press-coating compression force required for industrial tablet press could be carried out on the STYL'One with minimal waste of resources.

CONCLUSION

Good correlations were established between industrial equipment and the STYL'One compaction simulator, on two different examples: multi-layer tablet and compression-coated tablet. Based on these results, we can move forward by using the compaction simulator at different stages all along the pharma development of a new project – early stage, scale-up, quality by design with design-of-experiment matrices performed at small scales, and even in-process control during commercial manufacturing.

ABOUT THE COMPANY

Skyepharm provides solutions bringing value to its clients at any stage of a product development lifecycle, from early-stage development up to commercial manufacturing and packaging activities. Skyepharm's value proposition includes services tailored to clients' requirements, supporting them up to market for their solid dosage form projects.

	Mean Lag time vs compliance to specifications (dissolution on 6 vessels)			Selected Compression force to provide proper lagtime
	Compression Force A	Compression Force B	Compression Force C	
Batch 1 (Kilian S250M)	Not compliant	Compliant	Not compliant	Compression Force B
Batch 1' (Styl'One Evolution)	Not compliant	Compliant	Not compliant	Compression Force B
Batch 2 (Kilian S250M)	Not compliant	Not compliant	Compliant	Compression Force C
Batch 2' (Styl'One Evolution)	Not compliant	Not compliant	Compliant	Compression Force C
Batch 3 (Kilian S250M)	Not compliant	Not compliant	Compliant	Compression Force C
Batch 3' (Styl'One Evolution)	Not compliant	Not compliant	Compliant	Compression Force C

Figure 3: Comparison of the results obtained with Kilian and with STYL'One Evolution.

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ABOUT THE AUTHORS

Aline Moulin graduated from the National Graduate Chemistry School of Montpellier (France) and received her MSc in Biomolecular Chemistry from the University of Montpellier in 2004. She then achieved her PhD at the Institut des Biomolécules Max Mousseron in Montpellier. She was appointed Medicinal Chemistry Research Scientist in 2007 at Sanofi Research Center (Vitry sur Seine, France). She joined the Flamel Technologies (now Avadel Pharmaceuticals, Venissieux, France) R&D team in 2009 to work on the design, development and industrialisation of drug delivery systems. In 2018, she joined Skyepharma as Senior Project Manager and was appointed Head of the New Product Introduction Department in 2019.

Lucile Kowalski was awarded by the University of Pharmacy of Grenoble (France) in 2017 and received her MSc in Formulation and Industrial Chemistry from the University of Lyon (France) in 2017. Then she achieved her PharmD in 2019 on compaction simulation. During her years of study, she worked as an intern at Creathes (Hericourt, France) on micro-organism encapsulation and at Molecular Pharmacochimie Department (UMR 5063) on encapsulation for ophthalmic route. She joined Skyepharma in 2016 as an apprentice and was appointed Project Manager in 2017.

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