

Risk-Guided Optimization of an Ethylcellulose-Hypromellose Coated Empagliflozin Tablet for Programmed Pulsatile Release

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Abstract: ***Objective:** To develop a 10-mg empagliflozin tablet with an approximately 6-h in-vitro lag period followed by rapid drug release. **Methods:** A 150-mg direct-compression core was screened, then seal-coated and covered with a Surelease® ethylcellulose/HPMC E5 functional film. HPMC E5 content and coating weight gain were screened using a risk-guided approach. **Results:** Core F9 showed hardness of 5.3 ± 0.2 kg/cm², friability of 0.49%, disintegration in 2.6 ± 0.2 min, and drug content of $98.73 \pm 0.52\%$. The selected C5 coat showed a reported lag time of 6.18 ± 0.11 h and $5.8 \pm 0.5\%$ release at 6 h. The final evaluation reached $98.1 \pm 0.8\%$ release at 12 h; the marketed immediate-release comparator released $87.6 \pm 1.6\%$ by 2 h. **Conclusion:** The coating produced a delayed, then accelerated, in-vitro release profile. These findings support formulation feasibility only and do not establish in-vivo timing or clinical benefit.*

Keywords: Empagliflozin, pulsatile drug delivery, ethylcellulose, hypromellose, Quality by Design, lag time

1. Introduction

Circadian organization influences glucose tolerance, insulin sensitivity, hormonal release and metabolic regulation. These variations motivate investigation of dosage forms in which the onset of drug release can be programmed independently of the time a conventional tablet is swallowed [1]. Empagliflozin is a sodium-glucose cotransporter 2 inhibitor that lowers glucose through renal glucose excretion. One crossover study compared morning and evening administration of a conventional 10-mg tablet, but found no statistically significant difference for the reported main pharmacodynamic comparison; therefore, a clinically optimal dosing time cannot be inferred from that study [2].

Pulsatile oral systems differ from sustained-release preparations by intentionally combining a low-release period with a later accelerated release event. In polymer-coated systems, membrane permeability, film thickness and changes in barrier structure can influence both the delay and the ensuing drug pulse [3]. Conventional immediate-release empagliflozin tablets cannot, by formulation alone, provide a prescribed multi-hour delay, whereas an engineered polymeric barrier may shift release onset while ultimately permitting near-complete dissolution.

The Quality by Design (QbD) framework relates intended performance to critical quality attributes (CQAs), material variables and manufacturing parameters, and encourages risk-based control rather than exclusive reliance on finished-product testing [4,5]. Failure mode and effects analysis (FMEA) offers a structured means of ranking influential variables [6]. In the present work, that approach was applied to a directly compressed empagliflozin core and an ethylcellulose-HPMC E5 functional coating. The specific objective was to obtain an approximately 6-h delay with limited premature release, followed by a rapid pulse, and to characterize the resulting in-vitro performance and preliminary stability.

2. Materials and Methods

2.1 Materials and formulation concept

The nominal 10-mg empagliflozin core contained mannitol SD 200, microcrystalline cellulose (MCC) PH 102, copovidone, crospovidone, colloidal silicon dioxide, and sodium stearyl fumarate. The multilayer design comprised the core, a Protectab®-HP1 seal coat, a Surelease®/hypromellose E5 (HPMC E5)/triethyl-citrate functional film, and a polyvinyl-alcohol-based outer coat. The materials and their intended functions are summarized in Table 1.

Table 1: Materials used in the empagliflozin tablet and their functions.

Component	Reported function
Empagliflozin (10 mg)	Active pharmaceutical ingredient
Mannitol SD 200; MCC PH 102	Diluent and compression aid
Copovidone; crospovidone	Binder; superdisintegrant
Colloidal silicon dioxide; sodium stearyl fumarate	Glidant; lubricant
Protectab®-HP1	Seal coat
Surelease® aqueous ethylcellulose dispersion	Hydrophobic time-controlling barrier
HPMC E5; triethyl citrate	Hydrophilic membrane modifier; plasticizer
PVA-based coating	Protective outer film

2.2 Preformulation and analytical characterization

Drug appearance, solvent solubility, and melting behavior were recorded. UV spectrophotometric quantification used the reported absorption maximum of 224 nm. A 1000 µg/mL stock and a 100 µg/mL working solution were prepared, and standards from 10 to 50 µg/mL were obtained by dilution. Standard absorbances were measured in triplicate. The calibration equation and regression statistics should be verified against the original analytical record before the method is treated as validated.

Drug–excipient compatibility was assessed by Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) using the pure drug and an optimized formulation mixture. Retention of characteristic absorption bands and the drug-associated endotherm were used as supporting indicators. Instrument models and complete acquisition settings should be reported from the laboratory records.

2.3 Risk-guided quality assessment

The target product profile specified a 10-mg oral pulsatile tablet, an approximately 6-h lag period, limited release during the lag phase, rapid post-lag release, acceptable assay and mechanical properties, and an intact coating. Potential material and process risks were organized using an Ishikawa diagram. Failure mode and effects analysis (FMEA) scores for severity, occurrence, and detectability were combined as $RPN = S \times O \times D$. HPMC E5 content and functional-coat weight gain were assigned the highest reported RPN (80) and were selected for screening. The study used sequential screening; it did not establish a statistical response-surface design space.

2.4 Core-tablet preparation and selection

Nine core formulations (F1–F9) were prepared by direct compression at a nominal tablet mass of 150 mg and empagliflozin dose of 10 mg. Binder, crospovidone, and lubricant levels were varied in three screening groups. Tablets were evaluated for appearance, mean mass, dimensions, hardness, friability, disintegration time, and drug content. F9 was selected based on its combined physical and disintegration profile. The quantitative batch compositions and compression settings should be confirmed from the original batch records for reproducibility.

F9 was advanced to the seal-coating and functional-coating stages.

2.5 Seal-coat and functional-coat preparation

A seal-coating solution was prepared from Protectab®-HP1 (20 g), isopropyl alcohol (152 mL), and methylene dichloride (228 mL). The solvents were combined in a closed vessel, the premix was added under stirring, and the mixture was deaerated and filtered. The solution was applied to inspected, dedusted F9 tablets to a target seal-coat weight gain of approximately 2% w/w.

For the functional coat, HPMC E5 was dispersed and hydrated in purified water. Triethyl citrate was added, followed by gradual addition of Surelease® under gentle agitation to limit foaming. Six coating conditions were prepared. C1–C3 varied HPMC E5 at 5, 10, and 15 reported parts while targeting 8% functional-coat weight gain. C4–C6 held HPMC E5 at 10 reported parts and varied weight gain at 6%, 10%, and 12%, respectively (Table 2). The basis for the reported parts should be confirmed from the coating-batch records.

Table 2: Functional-coating compositions and screening conditions (reported quantities)

Ingredient / Parameter	C1	C2	C3	C4	C5	C6
Screening variable	HPMC E5	HPMC E5	HPMC E5	Coating WG	Coating WG	Coating WG
Level	Low	Medium	High	Low	Medium	High
Surelease® (dispersion basis)	100	100	100	100	100	100
HPMC E5	5	10	15	10	10	10
Triethyl citrate	10	10	10	10	10	10
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Functional coating weight gain	8%	8%	8%	6%	10%	12%

Seal coating was performed at a pan speed of 8–12 rpm, spray rate of 2–4 mL/min, atomization pressure of 1.5–2.0 bar, inlet-air temperature of 30–40 °C, and product temperature of 25–30 °C. Functional coating used 8–12 rpm, 2–4 mL/min, 1.5–2.0 bar, inlet air at 40–50 °C, and product temperature at 30–35 °C. Weight gain was monitored by tablet weighing, followed by drying to consolidate the film.

A PVA-based protective coat was applied at approximately 2–3% w/w; the reported target was 2.5%. Weight gain was calculated as $[(\text{mass after coating} - \text{mass before coating}) / \text{mass before coating}] \times 100$. These are reported development ranges; batch-level set points should be checked against the manufacturing records.

2.6 Dissolution testing and release analysis

Dissolution testing used USP apparatus II (paddles), 900 mL of an aqueous medium, $37 \pm 0.5^\circ\text{C}$, 50 rpm, and a 12-h observation period. Samples were quantified at 224 nm. The available record does not identify the medium composition or pH, sampling and replacement details, filter validation, or the number of replicate tablets; these particulars are needed to reproduce and interpret the release results.

Lag time was defined as the onset of a distinct, sustained increase in release after the initial low-release phase. Cumulative release was summarized at the reported sampling times. Post-lag data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas relationships [7], [8]. The model fits are treated as exploratory descriptors and not as proof of a unique release mechanism.

2.7 Accelerated stability study

The optimized multilayer-coated tablets were stored for 3 months at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ relative humidity and evaluated at 0, 1, 2, and 3 months. Appearance, mass, dimensions, hardness, friability, assay, lag time, and dissolution were monitored. This was a preliminary accelerated study and does not establish shelf life or packaging suitability.

3. Results

3.1 Preformulation and drug–excipient characterization

Empagliflozin was described as a white-to-off-white crystalline powder. Reported solubility was 0.018 ± 0.002 mg/mL in purified water, 18.42 ± 0.31 mg/mL in methanol, 4.76 ± 0.18 mg/mL in ethanol, 1.21 ± 0.07 mg/mL in isopropanol, and 0.84 ± 0.05 mg/mL in acetonitrile ($n = 3$). The pure-drug DSC endotherm peaked at 152.3°C ; the optimized formulation mixture showed a reported drug-associated thermal event at 151.1°C . FTIR fingerprint features were broadly retained. Together, these observations show no major new thermal event in the reported traces, but do not exclude all possible interactions.

Representative FTIR spectra and DSC thermograms are shown in Figures 1 and 2, respectively.

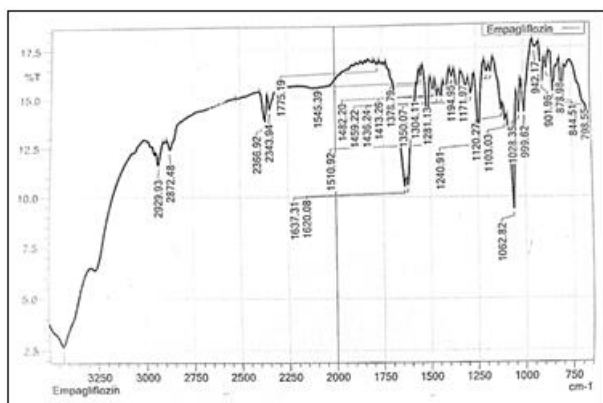


Figure 1(a): FTIR spectrum of pure empagliflozin.

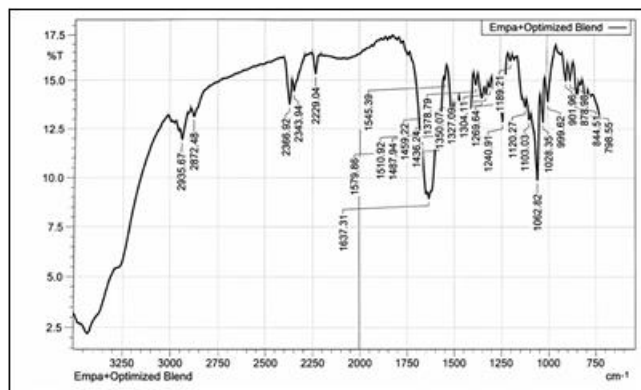


Figure 1(b): FTIR spectrum of the optimized F9–C5 formulation mixture.

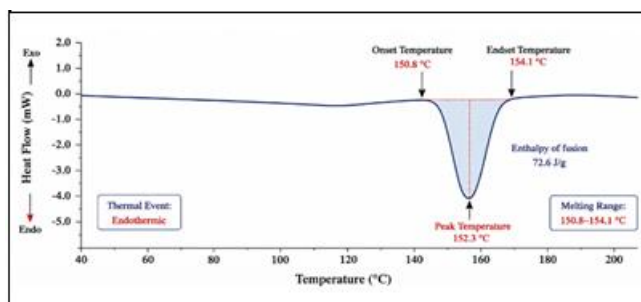


Figure 2(a): DSC thermogram of pure empagliflozin.

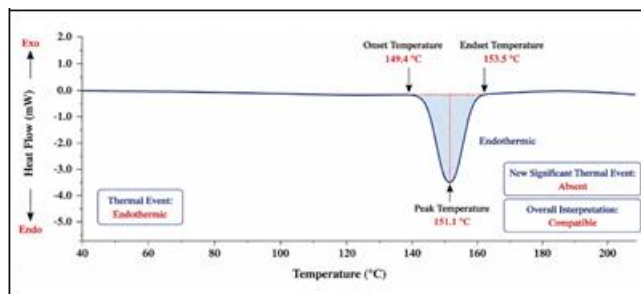


Figure 2(b): DSC thermogram of the optimized formulation.

3.2 Core-tablet screening and selection

The nine core formulations had mean masses of 149.3–150.4 mg, hardness values of 4.8–5.8 kg/cm², friability of 0.48–0.72%, and disintegration times of 1.9–5.1 min (Table 3). F9 combined a mean mass of 150.1 ± 0.9 mg, hardness of 5.3 ± 0.2 kg/cm², friability of 0.49%, disintegration in 2.6 ± 0.2 min, and drug content of $98.73 \pm 0.52\%$.

Table 3: Physical evaluation of core formulations F1–F9.

Batch	Weight (mg), Mean $\pm$ SD	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Disintegration time (min)	Drug content (%)
F1	149.3 $\pm$ 1.2	3.58 $\pm$ 0.03	4.8 $\pm$ 0.3	0.72	3.8 $\pm$ 0.2	97.21 $\pm$ 0.84
F2	150.1 $\pm$ 1.1	3.61 $\pm$ 0.03	5.2 $\pm$ 0.2	0.61	4.2 $\pm$ 0.2	98.06 $\pm$ 0.72
F3	150.4 $\pm$ 1.0	3.65 $\pm$ 0.04	5.8 $\pm$ 0.3	0.48	5.1 $\pm$ 0.3	98.42 $\pm$ 0.65
F4	149.7 $\pm$ 1.2	3.57 $\pm$ 0.03	5.0 $\pm$ 0.2	0.66	3.1 $\pm$ 0.2	97.68 $\pm$ 0.73
F5	150.0 $\pm$ 1.1	3.59 $\pm$ 0.03	5.2 $\pm$ 0.2	0.58	2.5 $\pm$ 0.2	98.34 $\pm$ 0.61
F6	150.2 $\pm$ 1.0	3.61 $\pm$ 0.03	5.3 $\pm$ 0.3	0.54	1.9 $\pm$ 0.1	98.61 $\pm$ 0.58
F7	149.6 $\pm$ 1.3	3.58 $\pm$ 0.03	5.1 $\pm$ 0.2	0.63	2.7 $\pm$ 0.2	98.12 $\pm$ 0.69
F8	149.9 $\pm$ 1.1	3.59 $\pm$ 0.03	5.2 $\pm$ 0.2	0.57	2.9 $\pm$ 0.2	98.47 $\pm$ 0.56
F9	150.1 $\pm$ 0.9	3.60 $\pm$ 0.02	5.3 $\pm$ 0.2	0.49	2.6 $\pm$ 0.2	98.73 $\pm$ 0.52

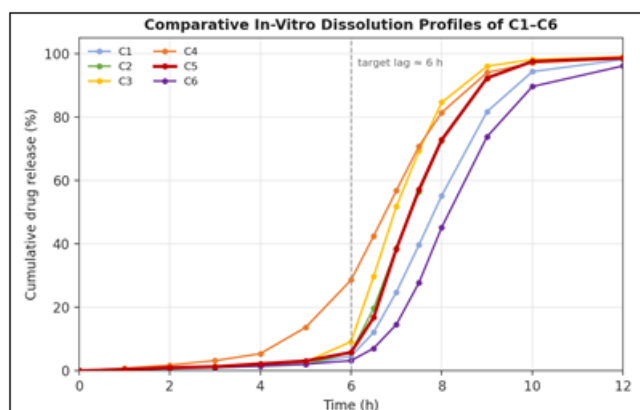
3.3 Functional-coating screening and selection

At a fixed 8% weight gain, increasing HPMC E5 from 5 to 15 reported parts reduced lag time from 6.72 ± 0.12 to 5.61 ± 0.13 h and increased release at 6 h from $4.6 \pm 0.5\%$ to $9.2 \pm 0.6\%$ (Table 4). At the intermediate HPMC E5 level,

increasing weight gain from 6% to 12% increased lag time from 4.82 ± 0.14 to 7.02 ± 0.13 h. C4 showed $28.6 \pm 1.4\%$ release at 6 h, whereas C6 showed $3.2 \pm 0.4\%$ release at 6 h and $96.1 \pm 1.0\%$ at 12 h. C5 was selected for the balance of lag-phase suppression and subsequent release. Figure 3 shows the reported comparative profiles.

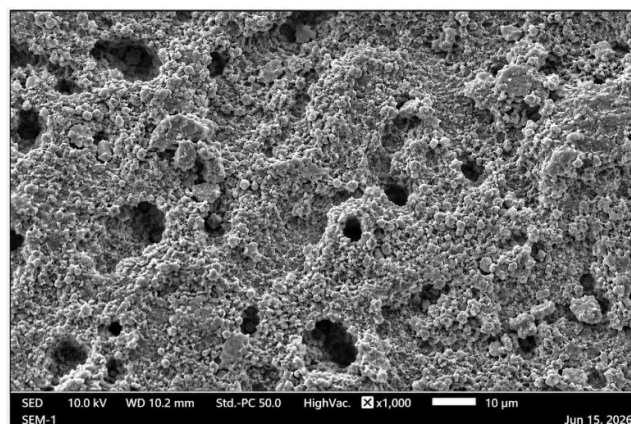
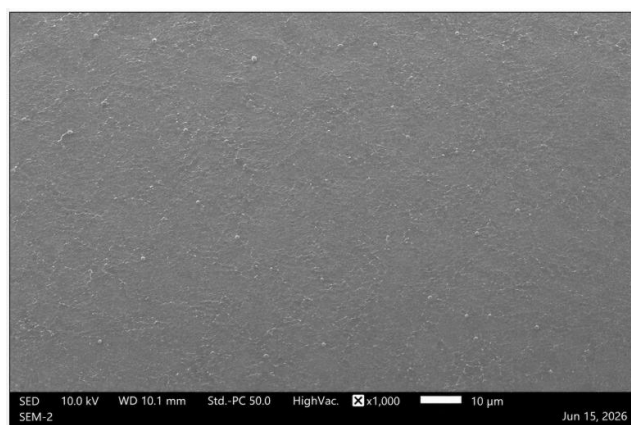
Table 4: Release endpoints for functional-coating screening conditions C1–C6.

Parameter	C1	C2	C3	C4	C5	C6
Lag time (h)	6.72 ± 0.12	6.18 ± 0.10	5.61 ± 0.13	4.82 ± 0.14	6.18 ± 0.11	7.02 ± 0.13
% release at 6 h	4.6 ± 0.5	5.8 ± 0.4	9.2 ± 0.6	28.6 ± 1.4	5.8 ± 0.5	3.2 ± 0.4
12-h release (%)	98.1 ± 0.8	98.8 ± 0.7	99.0 ± 0.6	98.4 ± 0.7	98.6 ± 0.7	96.1 ± 1.0

**Figure 3:** Comparative dissolution profiles for functional-coating conditions C1–C6.

3.4. Optimized tablet quality and morphology

The selected architecture comprised the F9 core, a 2% seal coat, the C5 functional barrier, and a protective overcoat. The final tablets had a mean mass of 172.71 ± 0.26 mg, thickness of 4.86 ± 0.06 mm, diameter of 8.03 ± 0.04 mm, hardness of 5.83 ± 0.11 kg/cm², friability of 0.25%, and drug content of $98.70 \pm 0.18\%$. Figure 4 compares the uncoated core surface with the coated tablet surface; the images suggest a smoother coated surface but do not establish defect-free coverage.

**Figure 4(a):** SEM micrograph of the uncoated F9 tablet core**Figure 4(b):** SEM micrograph of the F9–C5 coated tablet

3.5 Release profile and marketed-product comparison

The optimized tablet released $0.7 \pm 0.2\%$ at 1 h, $1.0 \pm 0.2\%$ at 2 h, $5.8 \pm 0.5\%$ at 6 h, $38.4 \pm 1.5\%$ at 7 h, $72.8 \pm 1.7\%$ at 8 h, $92.3 \pm 1.3\%$ at 9 h, and $98.1 \pm 0.8\%$ at 12 h. The reported lag time was 6.18 ± 0.11 h. The marketed

immediate-release tablet released $68.5 \pm 2.0\%$ at 1 h, $87.6 \pm 1.6\%$ at 2 h, $98.2 \pm 0.8\%$ at 6 h, and $99.4 \pm 0.5\%$ at 12 h (Figure 5 and Table 5). The main difference was the release timing rather than the 12-h extent.

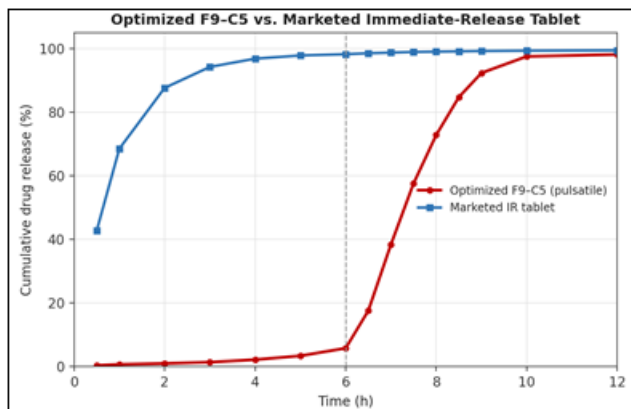


Figure 5: Release profiles of the optimized F9–C5 tablet and marketed immediate-release tablet

Table 5: Cumulative release from the optimized F9–C5 tablet and marketed immediate-release comparator.

Time (h)	Optimized F9–C5 (%)	Marketed immediate-release (%)
1	0.7 ± 0.2	68.5 ± 2.0
2	1.0 ± 0.2	87.6 ± 1.6
6	5.8 ± 0.5	98.2 ± 0.8
7	38.4 ± 1.5	—
8	72.8 ± 1.7	—
9	92.3 ± 1.3	—
12	98.1 ± 0.8	99.4 ± 0.5

3.6 Exploratory release-kinetic analysis

Exploratory fits to the reported post-lag data gave the highest R^2 for the first-order model (0.9667), followed by Korsmeyer–Peppas (0.9477), Higuchi (0.9385), and zero-order (0.9281) (Table 6). These empirical fits describe the selected data interval; they do not identify a unique transport mechanism. The fitting interval and replicate-level data should be checked before interpreting model rankings.

Table 6: Reported post-lag release-kinetic fit summaries.

Model	R^2	Rate constant / exponent	Rank
Zero-order	0.9281	$K_0 = 25.02 \text{ \%}/\text{h}$	4
First-order	0.9667	$K_1 = 0.932 \text{ h}^{-1}$	1
Higuchi	0.9385	$K_H = 52.74 \text{ \% h}^{-1/2}$	3
Korsmeyer–Peppas	0.9477	$K_p = 0.292 \text{ h}^{-n}$; $n = 1.006$	2

3.7 Accelerated stability

After 3 months of accelerated storage, appearance remained unchanged, assay decreased from $98.70 \pm 0.18\%$ to $98.34 \pm 0.25\%$, lag time changed from 6.18 ± 0.11 to 6.25 ± 0.13 h, release at 6 h changed from $5.8 \pm 0.5\%$ to $6.3 \pm 0.6\%$, and 12-h release decreased from $98.1 \pm 0.8\%$ to $97.4 \pm 0.9\%$ (Table 7 and Figure 6). Longer-term studies and a defined package are needed before making a shelf-life claim.

Table 7: Physical and release characteristics during preliminary accelerated storage

Parameter	0 Month	1 Month	2 Months	3 Months
Appearance	Good	Good	Good	Good
Weight (mg)	172.70 ± 0.27	172.78 ± 0.28	172.82 ± 0.30	172.89 ± 0.32
Thickness (mm)	4.86 ± 0.06	4.87 ± 0.06	4.88 ± 0.07	4.88 ± 0.07
Diameter (mm)	8.03 ± 0.04	8.03 ± 0.04	8.04 ± 0.05	8.04 ± 0.05
Hardness (kg/cm^2)	5.83 ± 0.11	5.79 ± 0.12	5.76 ± 0.13	5.74 ± 0.14
Friability (%)	0.25	0.26	0.27	0.28
Drug content (%)	98.70 ± 0.18	98.58 ± 0.21	98.46 ± 0.23	98.34 ± 0.25
Lag time (h)	6.18 ± 0.11	6.20 ± 0.12	6.23 ± 0.12	6.25 ± 0.13
Release at 6 h (%)	5.8 ± 0.5	5.9 ± 0.5	6.1 ± 0.6	6.3 ± 0.6
12-h release (%)	98.1 ± 0.8	97.9 ± 0.8	97.6 ± 0.9	97.4 ± 0.9

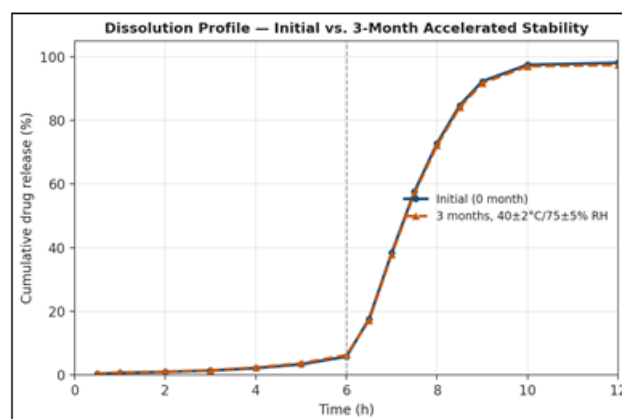


Figure 6: Release profiles at baseline and after 3 months of accelerated storage.

4. Discussion

The results support the in-vitro feasibility of a multilayer, time-programmed empagliflozin tablet. The rapidly disintegrating F9 core and the functional film served separate roles: the core provided the drug-containing substrate, while the outer barrier delayed release. This arrangement is consistent with polymer-barrier approaches to pulsatile delivery [3].

The screening results showed that both the hydrophilic-film modifier and barrier mass affected release timing. At fixed weight gain, higher HPMC E5 content was associated with a shorter lag and greater release at 6 h; at fixed HPMC E5, greater coating weight gain prolonged the lag. C5 was therefore selected as a practical balance within the six tested conditions. Because the work used sequential screening without a fitted response surface or formal interaction analysis, the results do not establish a validated design space [4]–[6].

The comparison with the marketed immediate-release tablet was intended to illustrate release timing, not to test bioequivalence. The optimized formulation released 5.8% by 6 h, while the marketed comparator released 98.2% by that time; both approached near-complete release by 12 h. This

in-vitro difference does not demonstrate a corresponding delay in systemic exposure or improved glycaemic outcomes. Gastric emptying, intestinal transit, absorption, and individual circadian phase could alter in-vivo timing [1], [2].

Mechanistic interpretation should remain conservative. The SEM images are consistent with surface coverage, while the FTIR and DSC traces show no major change in the evaluated signals. Direct measurements of film thickness, water ingress, permeability, and release-trigger formation would be needed to distinguish among possible release processes. The kinetic model fits are descriptive and do not prove a unique mechanism [7], [8].

This study is limited to in-vitro evidence and a preliminary 3-month accelerated assessment. In the available record, the dissolution-medium composition and pH, quantitative F1–F9 compositions, UV calibration equation, replicate count for dissolution, and detailed compression settings are not stated. These details are necessary for reproducibility. In addition, threshold-time descriptors should be recalculated from replicate-level dissolution data before they are reported. The formulation therefore remains a proof of concept and cannot support a clinical chronotherapy claim.

5. Conclusion

A risk-guided Surelease®/HPMC E5 coating converted a rapidly disintegrating 10-mg empagliflozin core into a multilayer tablet with a reported in-vitro lag of approximately 6 h followed by accelerated release. Among the tested conditions, C5 was selected for its balance of limited release at 6 h and subsequent dissolution. The final evaluation reached $98.1 \pm 0.8\%$ release at 12 h, with only modest changes reported after 3 months of accelerated storage. These findings establish formulation feasibility in vitro; complete method verification and in-vivo studies are needed before any claim about dosing-time performance or therapeutic benefit.

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