Scientific Evaluation and Validation of Hold-Time Stability in Empagliflozin Tablet Manufacturing: A Quality by Design Approach

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Abstract- Background: Ensuring the quality and stability of pharmaceutical intermediates and bulk materials during manufacturing interruptions is essential for regulatory compliance and patient safety. Hold-time studies provide evidence-based justification for permissible storage durations at each manufacturing stage, safeguarding critical quality attributes (CQAs) throughout the product lifecycle.

Objective: This study aimed to evaluate the effect of defined hold times on the physicochemical stability and quality of empagliflozin tablets at critical manufacturing stages, and to establish scientifically justified maximum allowable hold times in alignment with Quality by Design (QbD) principles and regulatory expectations.

Methods: Three commercial-scale batches of empagliflozin 25 mg tablets were manufactured under validated process conditions. Hold-time studies were conducted on post-blend, lubricated blend, core tablet, and film-coated tablet intermediates stored under ambient conditions (25±2°C, 40±5% RH). Physical, chemical, and performance parameters—including moisture content, assay, blend uniformity, hardness, friability, dissolution, and content uniformity—were evaluated at predetermined intervals using validated, stability-indicating analytical methods. Compression process robustness was additionally assessed through speed, hardness, and hopper fill challenges.

Results: Post-blend and lubricated blend samples remained compliant with all in-process specifications for up to 72 hours, with stable moisture content (LOD ≤1.40%), assay (98.3–98.8% LC), and blend uniformity (%RSD ≤2.8%). Core tablets retained acceptable physical and chemical quality for up to 30 days (dissolution ≥95.4% LC at 30 min), and film-coated tablets demonstrated stability for up to 45 days without clinically meaningful changes in assay, weight, or dissolution profiles. Compression robustness studies confirmed consistent tablet quality across variable operational parameters.

Conclusion: The validated hold times of 72 hours for blends and lubricated blends, 30 days for core tablets, and 45 days for film-coated tablets demonstrate adequate manufacturing flexibility without compromising empagliflozin tablet quality. These findings reinforce the robustness of the manufacturing process within a QbD framework and provide a sound scientific basis for regulatory submissions and lifecycle management.

Keywords: Empagliflozin, Hold-time study, Quality by Design, Process validation, Tablet stability, Solid oral dosage forms

I. INTRODUCTION

Pharmaceutical quality assurance encompasses not only end-product testing but also rigorous control of manufacturing processes to ensure consistent safety, efficacy, and performance throughout the product lifecycle [1,2]. Solid oral dosage forms, including tablets, involve multiple sequential unit operations—sifting, blending, granulation, drying, milling, compression, and coating—each susceptible to variability and unplanned interruptions that may compromise critical quality attributes (CQAs) if adequate safeguards are not in place [3,4].

Manufacturing interruptions arising from equipment maintenance, shift changes, line clearances, or quality investigations necessitate scientifically justified hold times for intermediate and bulk materials. Without validated hold-time data, such pauses present uncontrolled risks including moisture absorption, blend segregation, API degradation, and altered tablet performance [7,8]. Regulatory agencies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), increasingly require hold-time justification as part of process validation dossiers, reinforcing the need for product-specific empirical data [1–3].

Empagliflozin, a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor approved for the management of type 2 diabetes mellitus and heart failure, is manufactured as a solid oral tablet. Its physicochemical properties—including hygroscopicity, particle morphology, and sensitivity to mechanical stress—render its intermediate materials susceptible to quality changes during holding [6]. Despite the clinical importance of empagliflozin and growing regulatory scrutiny, specific hold-time data for its tablet manufacturing process remain underreported in the scientific literature.

Quality by Design (QbD) is an ICH Q8-endorsed systematic approach to pharmaceutical development that emphasizes enhanced process understanding, risk management, and robust manufacturing through the application of scientific principles [10,11]. Integration of QbD principles into hold-time validation provides a structured framework for identifying critical hold points, defining acceptable storage conditions, and interpreting stability data in the context of process performance [12].

This study addressed the existing knowledge gap by systematically evaluating the effect of defined hold times on the physicochemical stability and quality of empagliflozin tablets at four critical manufacturing stages: post-blend, lubricated blend, core tablet, and film-coated tablet. The study was designed to establish scientifically justified maximum allowable hold times, demonstrate process robustness across compression operational variables, and generate regulatory-compliant documentation consistent with ICH Q8/Q10 lifecycle management expectations.

II. MATERIALS AND METHODS

2.1 Materials

Empagliflozin active pharmaceutical ingredient (API; purity ≥99.5%) was sourced from a qualified supplier and characterized against in-house pharmacopoeial specifications prior to use. Pharmaceutical-grade excipients including microcrystalline cellulose (MCC; Avicel® PH-102), colloidal silicon dioxide (Aerosil® 200), magnesium stearate, purified water (USP), and Opadry® White YS-1-7040 film-coating system (Colorcon Inc., USA) were procured from approved vendors and subjected to incoming quality control testing prior to release for manufacturing.

2.2 Manufacturing Process

Three commercial-scale batches of empagliflozin 25 mg film-coated tablets were manufactured under validated process parameters at a GMP-compliant facility. The manufacturing sequence comprised: (i) sifting of API and excipients through a 40-mesh screen; (ii) dry mixing in a high-shear granulator; (iii) wet granulation with aqueous binder solution; (iv) fluid bed drying to target moisture (LOD: 1.0–3.0%); (v) milling and re-sifting; (vi) pre-lubrication blending; (vii) lubrication; (viii) compression on a 45-station rotary press (target weight: 200 mg); and (ix) film coating in a 24-inch pan to a target weight gain of 3±0.5%. Critical process parameters were documented and maintained within validated ranges throughout [13,14].

2.3 Hold-Time Study Design

Hold-time studies were conducted at four manufacturing stages, with sampling performed from three representative locations (top, middle, bottom) of the storage container at each time point to ensure representativeness. All intermediates were stored under ambient manufacturing conditions (25±2°C, 40±5% relative humidity) in primary containers replicating routine manufacturing practice. The time points evaluated were as follows:

- Post-blend powder: 0, 24, 48, and 72 hours
- Lubricated blend: 0, 24, 48, and 72 hours
- Core tablets (uncoated): 0, 7, 15, and 30 days
- Film-coated tablets: 0, 15, 30, and 45 days

A summary of the hold-time study design, including storage conditions and validated hold durations, is presented in Table 1.

Table 1: Summary of Hold-Time Study Design for Empagliflozin Tablet Manufacturing Stages

Intermediate/Bulk Material	Hold-Time Intervals	Storage Conditions	Max. Validated Hold Time
Post-blend powder	0, 24, 48, 72 h	Ambient (25±2°C, 40±5% RH)	72 hours
Lubricated blend	0, 24, 48, 72 h	Ambient (25±2°C, 40±5% RH)	72 hours
Core tablets (uncoated)	0, 7, 15, 30 d	Ambient (25±2°C, 40±5% RH)	30 days
Film-coated tablets	0, 15, 30, 45 d	Ambient (25±2°C, 40±5% RH)	45 days

2.4 Analytical Methods

All analytical testing was performed using validated, stability-indicating methods. Assay and degradation impurity profiling were conducted by reverse-phase high-performance liquid chromatography (RP-HPLC) using a C18 column with UV detection at 220 nm. Method specificity, linearity (50–150% of nominal concentration; R^2 ≥0.999), accuracy (98.5–102.0% recovery), precision (%RSD ≤1.5%), and robustness were confirmed per ICH Q2(R1) guidelines [22,23].

Physical characterization of blend samples included loss on drying (LOD; 105°C, Mettler Toledo halogen moisture analyzer), moisture content by Karl Fischer titration (coulometric), bulk and tapped density (USP ⟨616⟩), and blend uniformity by stratified sampling. Tablet testing comprised average weight, hardness (Dr. Schleuniger Pharmatron), friability (USP ⟨1216⟩), disintegration (USP ⟨701⟩), thickness, and dissolution using a USP Apparatus II (paddle, 50 rpm, 900 mL of 0.1 N HCl, 37±0.5°C, 30 min). Content uniformity was evaluated per USP ⟨905⟩ criteria [24,26].

2.5 Compression Process Robustness

Compression robustness was evaluated through systematic operational parameter challenges: compression speed (10, 20, and 25 rpm), hardness target (low, mid, and high), and hopper fill level (full, half, and quarter capacity). Each condition was assessed for its impact on assay, content uniformity, and dissolution, with results compared against finished product specifications.

2.6 Statistical Analysis

Data were expressed as mean values with standard deviations (SD). Analytical results at each hold-time interval were compared against initial baseline values (time zero) and evaluated against pre-defined in-process and finished product acceptance criteria derived from process validation data. Relative standard deviation (%RSD) was used to assess intra-batch variability. Where applicable, trends across time points were assessed for clinical and regulatory significance [32].

III. RESULTS

3.1 Process Validation Overview

All three commercial-scale batches consistently met in-process and finished product specifications across all manufacturing stages, confirming process reproducibility and control. Critical process parameters for sifting, granulation, drying, milling, lubrication, compression, and coating were maintained within validated ranges across all batches. Batch yield, particle size distribution, granule morphology, and coating weight gain were within acceptance criteria throughout, establishing a robust baseline for hold-time assessment.

3.2 Hold-Time Stability of Post-Blend Powders

Post-blend powder samples-maintained compliance with all in-process specifications over the 72-hour hold period. LOD values ranged from 1.31% to 1.40%, remaining well within the pharmacopoeial limit of ≤3.0%. Assay values were stable at 98.8% LC at

baseline, declining minimally to 98.5% LC at 72 hours, within the 98.0–102.0% LC specification. Blend uniformity (%RSD) ranged from 1.9% at baseline to 2.4% at 72 hours, consistently below the NMT 3.0% criterion. Bulk and tapped density remained unchanged, indicating no blend segregation during holding. Detailed results are presented in Table 2.

Table 2: Hold-Time Stability Results for Post-Blend Powder (n=3 batches, mean values)

Parameter	Acceptance Criterion	0 h	24 h	48 h	72 h
LOD (% w/w)	NMT 3.0%	1.31	1.34	1.37	1.40
Assay (% LC)	98.0–102.0%	98.8	98.7	98.6	98.5
Blend Uniformity (%RSD)	NMT 3.0%	1.9	2.1	2.3	2.4
Bulk Density (g/mL)	Report	0.42	0.43	0.43	0.43
Tapped Density (g/mL)	Report	0.58	0.58	0.59	0.59

3.3 Hold-Time Stability of Lubricated Blends

Lubricated blend samples demonstrated stable physical and chemical quality throughout the 72-hour evaluation period. Assay values ranged from 98.6% LC (0 h) to 98.3% LC (72 h), and blend uniformity (%RSD) remained ≤2.8% at all time points, indicating that extended lubrication holding did not adversely affect API distribution or homogeneity. Moisture content (Karl Fischer) was consistently approximately 3.3–3.5%, below the 5.0% specification limit, confirming absence of significant moisture uptake under ambient storage conditions.

3.4 Hold-Time Stability of Core Tablets (Uncoated)

Uncoated core tablets retained acceptable physical and chemical quality throughout the 30-day evaluation period. Hardness ranged from 65–95 N at baseline to 58–88 N at Day 30, remaining above the NLT 30 N specification. Friability was ≤0.42% at all time points, well within the NMT 1.0% limit. Assay values declined marginally from 98.7% LC to 98.2% LC over 30 days, remaining within specification. Dissolution at 30 minutes met the NLT 80% LC criterion at all time points, with values ranging from 96.5% LC (Day 0) to 95.4% LC (Day 30). Weight uniformity was within ±5% of the target at all intervals. Comprehensive results are presented in Table 3.

Table 3: Hold-Time Stability Results for Core Tablets (n=3 batches, mean values)

Parameter	Acceptance Criterion	Day 0	Day 7	Day 15	Day 30
Appearance	White, round, biconvex	Passes	Passes	Passes	Passes
Average Weight (mg)	±5% of target	Complies	Complies	Complies	Complies
Hardness (N)	NLT 30 N	65–95	62–92	60–90	58–88
Friability (%)	NMT 1.0%	0.30	0.34	0.38	0.42
Assay (% LC)	98.0–102.0%	98.7	98.6	98.4	98.2
Dissolution (% LC, 30 min)	NLT 80%	96.5	96.2	95.8	95.4
Content Uniformity (%RSD)	NMT 6.0%	2.1	2.3	2.5	2.7

3.5 Hold-Time Stability of Film-Coated Tablets

Film-coated tablets demonstrated consistent quality over the 45-day hold period. Appearance remained satisfactory with no visible discoloration, chipping, or coating defects. Average tablet weight was maintained within specification throughout. Assay values

remained within 98.0–102.0% LC at all time points (99.1% at Day 0; 98.6% at Day 45). Dissolution profiles met the NLT 80% LC criterion throughout (97.2% at Day 0; 96.3% at Day 45). Total impurities were well below the NMT 0.5% specification. Moisture content remained below 5.0% at all intervals. Results are summarized in Table 4.

Table 4: Hold-Time Stability Results for Film-Coated Tablets (n=3 batches, mean values)

Parameter	Acceptance Criterion	Day 0	Day 15	Day 30	Day 45
Appearance	White, film-coated	Passes	Passes	Passes	Passes
Average Weight (mg)	±3% of target	Complies	Complies	Complies	Complies
Assay (% LC)	98.0–102.0%	99.1	99.0	98.8	98.6
Dissolution (% LC, 30 min)	NLT 80%	97.2	97.0	96.7	96.3
Total Impurities (%)	NMT 0.5%	0.08	0.09	0.10	0.11
Moisture Content (% KF)	NMT 5.0%	3.3	3.4	3.4	3.5

3.6 Compression Process Robustness

Compression process robustness studies confirmed consistent tablet quality across a range of operational parameters. At compression speeds of 10 and 20 rpm, all quality attributes met acceptance criteria. At 25 rpm (high speed), content uniformity (%RSD: 3.1%) was within specification but classified as a marginal pass, suggesting increased variability at elevated throughput. Hardness variation from low (~40 N) to high (~90 N) targets did not significantly affect dissolution or assay. Hopper fill challenges at half and quarter capacity resulted in marginally increased content uniformity variability (%RSD: 3.4% and 4.1%, respectively), consistent with known feed system variability at reduced hopper levels, while remaining within the NMT 6.0% specification. Results are presented in Table 5.

Table 5: Compression Process Robustness Study Results (mean values, n=3 batches)

Challenge Variable	Level Tested	Assay (% LC)	Content Uniformity (%RSD)	Dissolution (% LC, 30 min)	Outcome
Compression Speed	10 RPM (Low)	98.9	2.4	96.8	Pass
	20 RPM (Mid)	98.7	2.6	96.5	Pass
	25 RPM (High)	98.5	3.1	96.2	Marginal Pass
Hardness Target	Low (~40 N)	98.8	2.5	97.1	Pass
	Mid (~65 N)	98.7	2.6	96.5	Pass
	High (~90 N)	98.6	2.8	95.8	Pass
Hopper Fill Level	Full	98.7	2.4	96.5	Pass
	Half	98.6	3.4	96.2	Marginal Pass
	Quarter	98.5	4.1	96.0	Marginal Pass

IV. DISCUSSION

This study provides comprehensive, empirical evidence supporting scientifically justified hold times in empagliflozin tablet manufacturing, addressing a substantive gap in the process validation literature for this therapeutic agent. The integrated QbD framework applied throughout the study facilitated systematic identification of critical hold points and structured evaluation of CQA behavior under defined storage

conditions, consistent with ICH Q8(R2) and Q10 principles [1,2,10].

The stability of post-blend and lubricated blend powders over 72 hours is consistent with prior investigations demonstrating that granule moisture content, blend homogeneity, and bulk physical properties are the most sensitive indicators of blend degradation during holding [7,8]. In the current study, LOD values remained below pharmacopoeial limits and blend uniformity %RSD values showed no statistically significant increase, indicating that moisture migration and blend segregation were effectively controlled under ambient conditions. The marginal increase in %RSD for lubricated blends at 72 hours, while compliant with specifications, suggests that extended lubrication holding warrants monitoring, as over-lubrication is known to reduce tablet tensile strength and impair dissolution through disruption of the hydrophilic matrix [17].

The 30-day stability of uncoated core tablets under ambient conditions is consistent with the literature demonstrating that mechanical integrity and dissolution are the primary quality risks for uncoated solid dosage forms during storage [8,18]. The modest decline in hardness observed over 30 days, attributed to stress relaxation within the tablet matrix following compression, did not compromise dissolution performance, as all values exceeded the NLT 80% criterion. This finding is important from a regulatory perspective as it demonstrates that compression-induced physical changes during holding do not translate to clinically meaningful performance differences [15].

The film-coating system demonstrated an effective barrier against moisture ingress and API degradation during the 45-day evaluation period, consistent with the established protective function of polymeric film coatings in solid oral dosage forms [13]. The consistently low total impurity levels (≤0.11%) throughout the hold period confirm the chemical stability of the empagliflozin molecule under ambient conditions and the absence of accelerated degradation attributable to the coating formulation or storage conditions. The observed dissolution profiles were within specification at all time points, supporting the absence of coating-related dissolution retardation during extended bulk holding.

Compression process robustness data confirmed adequate manufacturing flexibility across a range of operational parameters. The marginal content uniformity at high compression speeds (25 rpm) and reduced hopper fill levels reflects variability in powder feed dynamics that is inherent to rotary tablet compression and is widely documented in the literature [15,16]. These findings are clinically acceptable and consistent with the approved process validation performance standards; however, they suggest that operational parameters should remain within optimal ranges during routine manufacturing to minimize variability risk [10,11].

The integration of hold-time validation with QbD principles, as demonstrated in this study, provides a structured basis for defining the design space for manufacturing flexibility, reducing risks of batch rejection due to unplanned interruptions, and supporting lifecycle management documentation. From a regulatory perspective, the validated hold times established here provide explicit, data-driven justification for post-approval filings and provide a template for application to other novel solid oral dosage forms [31,32].

This study is subject to the limitation that hold-time data were generated under controlled ambient conditions only; extended environmental stress conditions (e.g., 40°2°C/75°5% RH) were not included in the current scope. Future investigations should consider real-time microbiological monitoring, process analytical technology (PAT)-guided in-situ quality assessment, and extrapolation of the QbD hold-time framework to other solid dosage forms.

V. CONCLUSION

The present study validated maximum hold times of 72 hours for post-blend and lubricated blend powders, 30 days for uncoated core tablets, and 45 days for film-coated tablets within the empagliflozin tablet manufacturing process. All evaluated CQAs, including moisture content, assay, blend uniformity, hardness, friability, dissolution, and content uniformity, remained compliant with predefined acceptance criteria at all hold-time intervals, confirming that manufacturing interruptions of these durations do not compromise product quality.

Compression process robustness studies demonstrated that consistent tablet quality is maintained across a range of operational parameters, with marginal variability at extreme conditions remaining within specification. The integration of QbD principles throughout the study ensured systematic, risk-based evaluation aligned with ICH Q8/Q10 regulatory frameworks.

These findings provide a robust scientific foundation for hold-time specifications in empagliflozin tablet manufacturing, supporting regulatory compliance, operational flexibility, and the continuous delivery of a high-quality pharmaceutical product to patients.

VI. FUTURE SCOPE

Future research directions may include: (i) integration of real-time process analytical technology (PAT) tools—such as near-infrared (NIR) spectroscopy and terahertz pulsed imaging—for continuous in-line monitoring of blend moisture and API homogeneity during holding periods; (ii) extension of hold-time evaluations to accelerated environmental conditions (40°C/75% RH) to further characterize stability margins; (iii) incorporation of microbiological quality assessments to address microbial risks in uncoated intermediates; and (iv) application of this validated QbD-based hold-time framework to other solid oral dosage forms to generalize and standardize hold-time validation methodologies across pharmaceutical manufacturing operations.

NOTE ON ETHICAL APPROVAL.

This study involved manufacturing process evaluation using commercially manufactured pharmaceutical batches and did not involve human subjects, animal experimentation, or patient data. Accordingly, formal ethical committee approval was not required. However, all manufacturing activities were conducted under Good Manufacturing Practice (GMP) guidelines in accordance with applicable regulatory requirements.

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CONFLICT OF INTEREST.

The authors declare no conflict of interest in relation to this work.

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