CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208658Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 208658
Review #1
Review Date (see last page)

Drug Name/Dosage Form	empagliflozin and metformin hydrochloride extended release tablet
Strength	5/1000, 10/1000, 12.5/1000, and 25/1000 mg/mg empagliflozin/metformin hydrochloride
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Boehringer Ingelheim

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	2/10/2016
0004	5/27/2016
0006	7/28/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Adequate (see page 1 of Drug Product review)

B. Other Documents:

DOCUMENT	APPLICATION	DESCRIPTION
NDA	21748	GLUMETZA (metformin HCl) extended release tablet Authorized reference from applicant (Salix)
NDA	204629	JARDIANCE (empagliflozin) tablet Same applicant
NDA	206111	SYNJARDY (empagliflozin/metformin HCl) tablet Same applicant
NDA	201281	JENTADUETO (linagliptin/metformin HCl) tablet Same applicant

2. CONSULTS: not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the Overall Manufacturing Inspection Recommendation) is for **APPROVAL**.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(1) application but not for an New Molecular Entity. Both active ingredients have several approved NDAs. Reference is made to the applicant's approved NDAs 204629 and 206111 for CMC information on the empagliflozin component. In addition, the applicant has full right of reference to the approved NDA 21748 for the metformin HCl extended release component.

Two pivotal BE studies (1276.15 and 1276.28) were conducted to compare the 10/1000 (batch B141002025) and 25/1000 (batch B141002762) strengths to the concomitant administration of Jardiance and Glumetza products. The biobatches had the commercial formulation, manufactured at commercial scale and site. A biowaiver is granted for the additional 5/1000 and 12.5/1000 strengths based on the following: 1) the strength of metformin is the same for all four combinations and there are 2 sets of proportionally similar strengths within the empagliflozin strengths; 2) in vivo BE studies were conducted with the highest strength 25/1000 and middle strength 10/1000, bracketing the 12.5/1000 strength; and 3) similar dissolution profiles were obtained with all 4 strengths, including the lowest 5/1000 strength. Note: both active ingredients are highly soluble (BCS III).

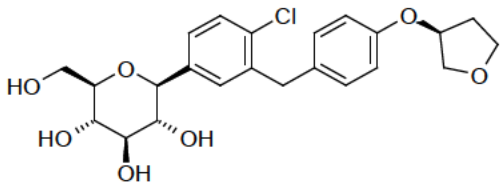
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	not applicable

B. Quality Assessment Overview

Drug Substance

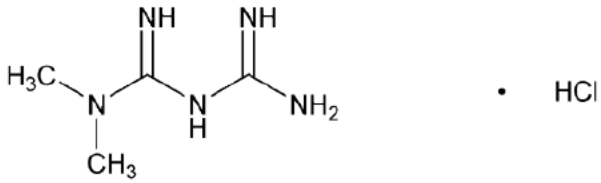
Chemical Name or IUPAC Name/Structure:

Empagliflozin
D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S)
Molecular formula: $C_{23}H_{27}ClO_7$
Molecular weight: 450.91



Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Metformin hydrochloride
(*N,N*-dimethylimidodicarbonimidic diamide hydrochloride)
Molecular formula: $C_4H_{11}N_5$•HCl
Molecular weight: 165.63



Metformin hydrochloride is a white to off-white crystalline compound, freely soluble in water and practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

NDA 204629 Jardiance (empagliflozin) tablets, by the same applicant, is referenced for all CMC information on the drug substance empagliflozin. The NDA is currently approved.

DMF [redacted] (b) (4) is referenced for all CMC information on the drug substance metformin HCl. The DMF is currently adequate.

Drug Product

The product consists of an extended-release metformin core tablet that is [redacted] (b) (4) coated [redacted] (b) (4) including the immediate-release empagliflozin [redacted] (b) (4). The metformin extended release core development is based on that of the approved Glumetza tablets of NDA 21748 (applicant of NDA 21748 provides a letter of authorization for this reference): [redacted] (b) (4) (polyethylene oxide, [redacted] (b) (4)

(b) (4)

- 5 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets are olive green, oval-shaped, film-coated tablets printed on one side in black ink with the Boehringer Ingelheim company logo and "S5" on the top line and "1000 M" on the bottom line.
- 10 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets are orange, oval-shaped, film-coated tablets printed on one side in black ink with the Boehringer Ingelheim company logo and "S10" on the top line and "1000 M" on the bottom line.
- 12.5 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets are blue, oval-shaped, film-coated tablets printed on one side in black ink with the Boehringer Ingelheim company logo and "S12" on the top line and "1000 M" on the bottom line.
- 25 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets are light green, oval-shaped, film-coated tablets printed on one side in black ink with the Boehringer Ingelheim company logo and "S25" on the top line and "1000 M" on the bottom line.

(b) (4)

Tablet Core: polyethylene oxide, hypromellose, and magnesium stearate (b) (4). Film Coatings and Printing Ink: hypromellose, titanium dioxide, polydextrose, polyethylene glycol, talc, carnauba wax, purified water, ferrosoferric oxide, propylene glycol, isopropyl alcohol, ferric oxide yellow (5 mg/1000 mg, 10 mg/1000 mg, 25 mg/1000 mg), ferric oxide red (10 mg/1000 mg), FD&C blue#2/indigo carmine aluminum lake (12.5 mg/1000 mg, 25 mg/1000 mg).

The product manufacturing process consists (b) (4)

(b) (4)

Container Closure: HDPE bottles [redacted] (b) (4).

Expiration Date & Storage Conditions: 24 months at room temperature (excursions permitted to 15-30 C).

Stability data include three batches of each strength packaged in all the commercial container closure systems, manufactured at the commercial sites and scale. The NDA includes data from 12 months at 25 °C/60% RH and 6 months at 40 °C/75% RH. A bracket design was used: three bulk final product batches were packaged in the smallest bottle size/fill count and largest bottle size/fill count, and one bulk final product batch was packaged in the intermediate bottle size/fill count. The two biobatches and stability batches have the same formulation with the only exception of printing ink (the biobatches did not have printing).

C. **Special Product Quality Labeling Recommendation**: not applicable
D. **Life Cycle Knowledge Information/ Final Risk Assessment:** page 10 of API/drug substance review, page 27 of Drug Product review, page 56 of Process review

Application Technical Lead Signature:

Suong (Su) Tran, Ph.D.
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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 208658

Drug Product Name / Strength: Synjardy® XR, empagliflozin and metformin, 5mg / 1000mg, 10mg / 1000mg, 12.5mg / 1000mg, and 25mg / 1000mg Tablets

Route of Administration: Oral

Formulation: Extended release tablets

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Review Summary:

The proposed drug product, empagliflozin/metformin hydrochloride extended release (ER) coated tablets combine immediate release of empagliflozin with extended release of metformin hydrochloride and thus simplifies the antidiabetic therapy by decreasing the frequency tablets have to be taken by the patient. The proposed dose strengths for empagliflozin and metformin HCl extended release fixed dose combination (FDC) tablets are 5mg / 1000mg, 10mg / 1000mg, 12.5mg / 1000mg, and 25mg / 1000mg, for once-daily use in patients with type 2 diabetes mellitus. This is a 505b (1) submission, with reference drugs as Glumetza® (metformin extended-release tablets) tablets, and Jardiance® (empagliflozin). The composition of different strengths of the proposed drug products is shown in Table 1.

Table 1. Qualitative and quantitative composition of empagliflozin/metformin HCl ER coated tablets

Ingredient	5 mg / 1000 mg	10 mg / 1000 mg	12.5 mg / 1000 mg	25 mg / 1000 mg	Function	Reference to Standards
	[mg / tablet]					
Tablet Core						
Metformin HCl[1]	1000.0	1000.0	1000.0	1000.0	Drug substance	USP
Polyethylene Oxide	(b) (4)					NF[2]
Hypromellose	(b) (4)					USP
Magnesium Stearate	(b) (4)					NF
						USP
Film-Coat						
	(b) (4)					Company Standard
Purified Water						USP
Film-Coat						
Empagliflozin	(b) (4)				Drug substance	Company Standard
						Company Standard
Polyethylene Glycol	(b) (4)					NF
Talc						USP
Purified Water						USP

Ingredient	5 mg / 1000 mg	10 mg / 1000 mg	12.5 mg / 1000 mg	25 mg / 1000 mg	Function	Reference to Standards
	[mg / tablet]					
(b) (4) Film-Coat						
(b) (4) Green (b) (4)					(b) (4)	Company Standard
(b) (4) Orange (b) (4)						Company Standard
(b) (4) Blue (b) (4)						Company Standard
(b) (4) Green (b) (4)						Company Standard
Purified Water						USP/Ph.Eur.
(b) (4)						
(b) (4) Clear (b) (4)					(b) (4)	Company Standard
Carnauba Wax						NF
Purified Water						USP
(b) (4)						
(b) (4) Black (b) (4)					(b) (4)	Company Standard
Isopropyl Alcohol						USP
Total mass	1606.9	1611.9	1614.4	1626.9		
1 (b) (4)						
2						
3						
*						
-						

BCS Designation

Reviewer's Assessment:

The applicant mentioned in their pharmaceutical development report that both empagliflozin and metformin HCl could be classified as Biopharmaceutics Classification System (BCS) class III compounds (high solubility and low permeability).

Solubility: The solubility of crystalline empagliflozin is pH independent (approximate 0.4 mg / mL at 37 °C in different media (Table 2A)). The solubility of metformin HCl shows high solubility (>10 mg/mL) in aqueous media over the entire pH range of 1-8 (Table 2B). And metformin HCl can be characterized as highly soluble" (the highest dose of 1000 mg metformin hydrochloride is soluble in 250 mL medium in the pH range of 1 - 8) according to BCS.

Table 2A. Solubility of Empagliflozin at different pH values at 37°C

Medium	pH after 2 hours	Solubility after 2 hours (mg/mL)	Solubility (mg/900 mL)
water	6.3	0.5	450
0.1 N HCl, pH 1	1.2	0.5	450
McIlvaine buffer, pH 3.0	3.0	0.5	450
acetate buffer 0.1 M, pH 4.5	4.5	0.5	450
phosphate buffer 0.1 M, pH 6.8	6.8	0.4	360
phosphate buffer 0.1 M, pH 7.5	7.5	0.4	360

Table 2B. Solubility of Metformin HCl at different pH values at 37°C

Medium	pH-Value	Solubility (mg/mL)	Solubility (mg/900 mL)
0.1 N HCl	1	> 10	> 9000
acetate buffer 50 mM	3.0 – 5.0	> 10	> 9000
phosphate buffer 50 mM	6.0 – 8.0	> 10	> 9000
water	7.2	> 200	> 180000

Permeability: For the permeability of empagliflozin and metformin HCl, the Applicant refers to permeability studies conducted in the submission of NDA 206111 (synjardy, empagliflozin/metformin hydrochloride immediate release tablets), which suggests that both empagliflozin and metformin are low permeability compounds. Therefore, permeability rather than solubility is the rate limit step for the bioavailability of empagliflozin and metformin HCl.

Dissolution: Refer to Figure 1 and Figure 2.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

1. Dissolution method

The proposed dissolution method for both components in proposed FDC tablets is shown in Table 3:

Table 3: Dissolution method and proposed dissolution acceptance criteria

Dissolution parameters	Settings
USP Apparatus	USP 1 (basket)

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Dissolution medium	**900 mL 50 mM phosphate buffer at pH 6.8**
Agitation speed	**100 rpm**
Dissolution specifications	**Empagliflozin: Q= (b)(4)% in 45 min** **Metformin HCl: 2hr: (b)(4)%** **4hr: (b)(4)7%** **12 hr.: NLT (b)(4)%**

Compared to the approved dissolution method for Glumetza (metformin) 500 mg extended release tablets, the proposed dissolution method used a different dissolution medium. Table 4 shows the approved dissolution method for Glumetza. Table 5 shows the approved dissolution method for empagliflozin in empagliflozin tablets or empagliflozin/linagliptin FDC tablets. As Table 4 shows, the proposed dissolution medium, pH 6.8 buffer, for metformin HCl in the proposed FDC is different as the approved dissolution method for Glumetza, in which SFG without enzymes was used.

Table 4. Glumetza® 500 mg *In-vitro* Dissolution Testing

Parameter	Condition
Apparatus	USP Apparatus I (rotating baskets)
Agitation	100 rpm
Medium	Simulated Gastric Fluid (SGF) without enzymes
Medium Volume	900 mL
Temperature	37°C ± 0.5°C
Sampling Times	2, 4, and 12 hours

Table 5. Approved dissolution methods for drug products containing empagliflozin (OGD dissolution database)

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Empagliflozin	Tablet	II (Paddle)	75	0.05 M Phosphate Buffer, pH 6.8	900	5, 10, 15, 20 and 30	05/28/2015
Empagliflozin/Linagliptin	Tablet	II (Paddle)	50	pH 6.8 Phosphate Buffer	900	10, 15, 20, 30 and 45	12/24/2015

1.1 Effect of dissolution medium pH on dissolution of metformin HCl from FDC tablets

Figure 1 shows the comparative dissolution testing of metformin HCl in three different media pH (1.2, 4.5, and 6.8) using the proposed dissolution method for four different strengths of proposed FDC tablets. The batches in this study include batches used in clinical BE studies (126.15 and 1276.28). As Figure 1 shows, the dissolution profiles of metformin HCl in dissolution media of different pH are similar; and thus the dissolution of metformin HCl is independent of pH.

Figure 1A. Metformin HCl Dissolution Profile from Empagliflozin/Metformin HCl ER Coated Tablets 5 mg/1000 mg, Batch 3122757R in dissolution Media of Different pH

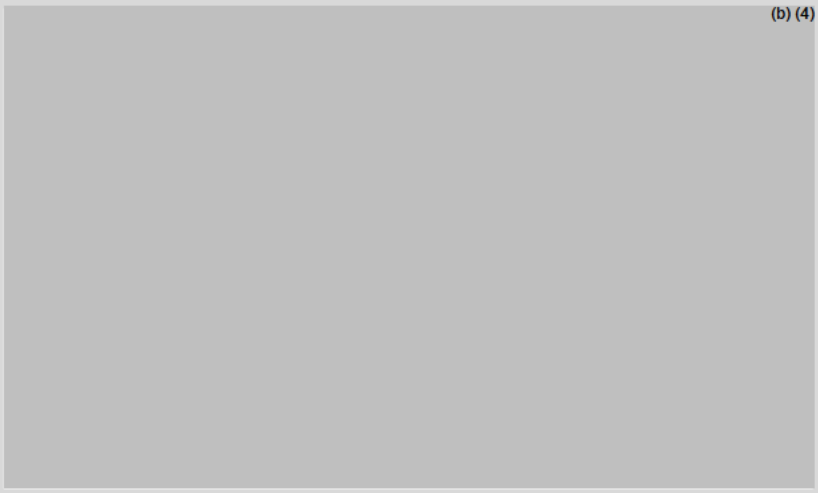


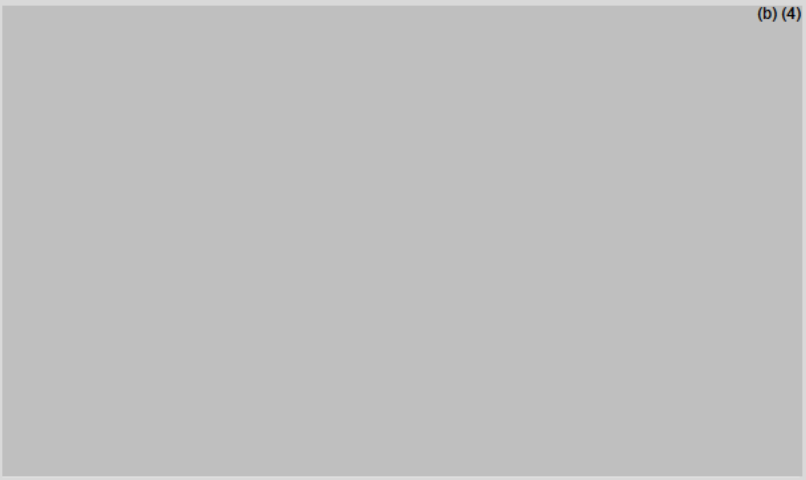
Figure 1B. Metformin HCl Dissolution Profile from Empagliflozin/Metformin HCl ER Coated Tablets, 10 mg/1000 mg, Batch 3122750R, in dissolution Media of Different pH

Figure 1C. Metformin HCl Dissolution Profile from Empagliflozin/Metformin HCl ER Coated Tablets, 12.5 mg/1000 mg, Batch 3122760R, in dissolution Media of Different pH

(b) (4)

Figure 1D. Metformin HCl Dissolution Profile from Empagliflozin/Metformin HCl ER Coated Tablets, 25 mg/1000 mg, Batch 3122745R, in dissolution Media of Different pH

(b) (4)



As the dissolution characteristics of metformin HCl ER core tablets in the proposed drug product and Glumetza 500 mg (metformin) are pH independent, the (b) (4)

1.2 Selection of apparatus, rotation speed, and dissolution medium for empagliflozin

(b) (4)

(b) (4)

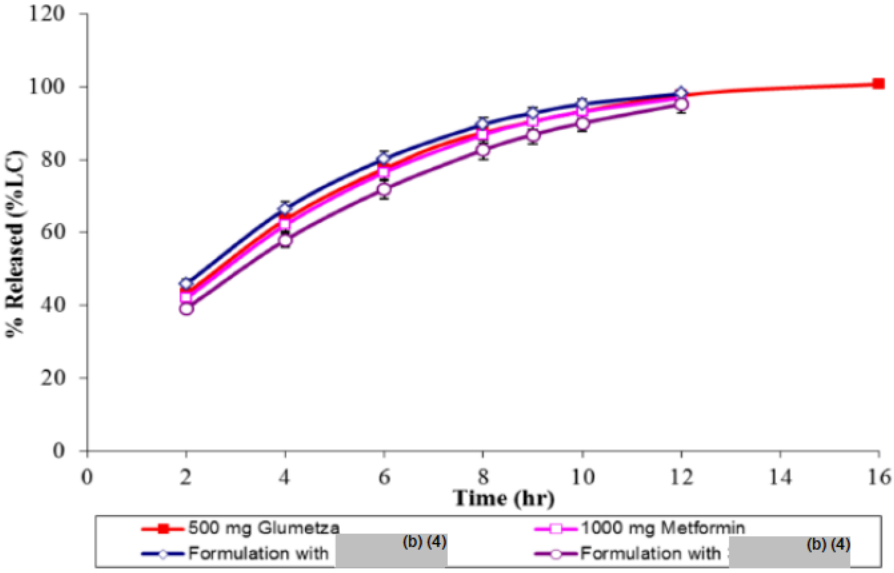
Based on above evaluations, the final dissolution method for proposed FDC tablets is determined to be USP Apparatus 1 and pH 6.8 buffer as the dissolution medium. The proposed dissolution method is acceptable.

1.3 Discriminatory ability

Influence of the percentage of (b) (4) in the metformin HCl ER tablet cores on metformin HCl dissolution behavior

The metformin HCl ER tablets core in proposed FDC tablets applied the same (b) (4) used in approved Glumetza 500 mg metformin HCl formulation. During the pharmaceutical development, the Applicant found that it was necessary to decrease the overall percentage of (b) (4) while increasing the molecular weight of the (b) (4) to maintain the drug release and swelling characteristics. Due to the pH independent dissolution of metformin HCl (Figure 2), the Applicant evaluated the influence of different percentage of (b) (4) in the metformin HCl ER tablet cores on metformin HCl dissolution profiles by using the dissolution method of Glumetza, in which a dissolution medium of SGF without enzyme was used (Figure 4). As , the dissolution profiles of metformin HCl in formulations with (b) (4)% (b) (4) are slightly different, but based on f2 calculation (f2 (b) (4)), they are similar.

Figure 4. Comparative Dissolution for Results of Glumetza® 500 mg versus Metformin HCl ER tablets, 1000 mg, with (b) (4) (selected formulation) and (b) (4) in SGF without enzymes (reference: (b) (4) Report 2011003-FD 15Mar12).


120
100
80
60
40
20
0
% Released (%LC)
0
2
4
6
8
10
12
14
16
Time (hr)
500 mg Glumetza
1000 mg Metformin
Formulation with (b) (4)
Formulation with (b) (4)

(b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

1.3.3 Influence of storage conditions on dissolution behavior

Dissolution data of one batch of each strength FDC tablets are presented for up to 12 months at 25°C/60% RH, and are compared to the data storage at 40°C /75% RH (Figure 7). Although there are some variability in the dissolution profiles of empagliflozin under different storage periods at 25 °C /60 % RH, no change in either the empagliflozin or metformin HCl dissolution profiles are observed for drug product stored in the commercial packaging materials. Figure 7 only shows the dissolution profiles of 5 mg / 1000 mg FDC tablets, and the dissolution profiles of other strengths are similar as 5 mg / 1000 mg FDC tablets (results not shown).

Figure 7A. Empagliflozin Dissolution of Batch 3123039 (5 mg/1000 mg, bottles of 60 tablets) on Stability stored at25°C/60% RH

Figure 7B. Empagliflozin Dissolution of Batch 3123039 (5 mg/1000 mg, bottles of 60 tablets) on Stability stored at 40°C /75% RH

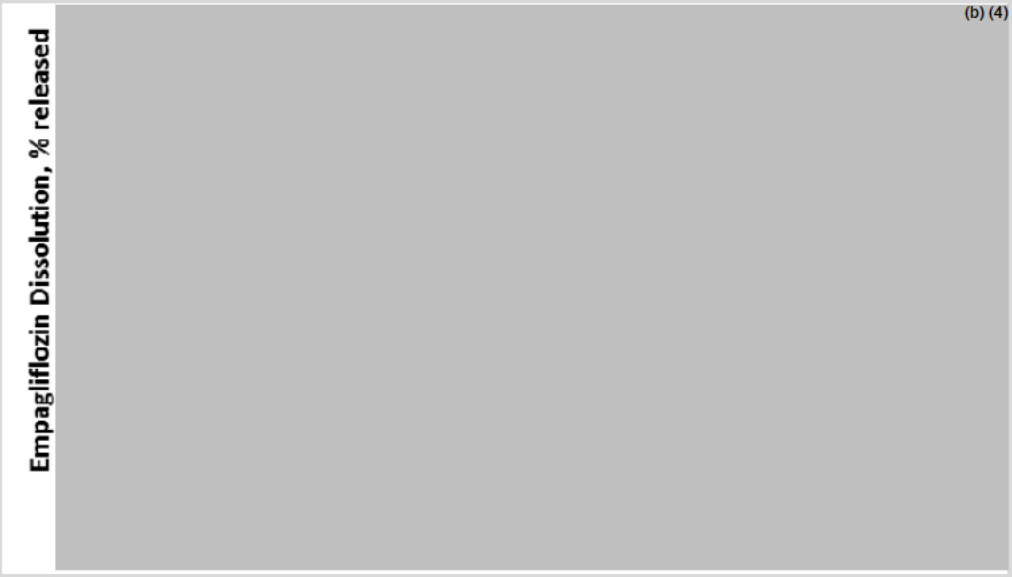


Figure 7C. Metformin HCl Dissolution of Batch 3123039 (5 mg/1000 mg, bottles of 60 tablets) on Stability stored at 25°C/60% RH

Figure 7D. Metformin HCl Dissolution of Batch 3123039 (5 mg/1000 mg, bottles of 60 tablets) on Stability stored at 40°C/75% RH

Influence of the particle size of both drug substances on in vitro drug dissolution is not observed, because of the fast release and high solubility for both drug components.

With current dissolution method, it can distinguish the different dissolution profiles of empagliflozin in FDC tablets between batches that with (b) (4) hardness values (b) (4) of the metformin HCl cores and (b) (4) lower limit of hardness (b) (4)

As shown in Figure 2, the dissolution profiles of empagliflozin in proposed FDC tablets and mono-component drug product Jardiance are different. The Applicant conducted two clinical BE studies, which demonstrated bioequivalence to bridge 10 mg / 1000 mg and 25 mg/1000 mg empagliflozin/metformin FDC tablets to respective free combination of mono drug products, Jardiance and Glumetza. Therefore, the difference in dissolution of empagliflozin and demonstrated BE between the empagliflozin in FDC tablets and Jardiance in free combination, suggests that the proposed dissolution method over-discriminated the dissolution of empagliflozin.

2. Comparative dissolution profiles of different strengths of FDC tablets

Figure 8A shows the dissolution profile of empagliflozin and the listed drug Jardiance in the current proposed dissolution method. As shown in Figure 8A below, the drug release of empagliflozin in the listed drug Jardiance is (b) (4) than that in the proposed drug product, but all reach complete release after (b) (4) min. Figure 8B-C show the dissolution profile of empagliflozin in other different dissolution media. Similarly, the listed drug has a (b) (4) release of empagliflozin in all pH of media compared to the empagliflozin component in the proposed drug product. The difference in the dissolution rate of empagliflozin between the proposed drug product and the listed drug might be explained by the different formulation principles used. Jardiance® is designed as an immediate release disintegrating tablet, whereas in empagliflozin/metformin HCl ER coated tablets. (b) (4)

Figure 8A. Empagliflozin Dissolution Profiles in Phosphate Buffer, pH 6.8

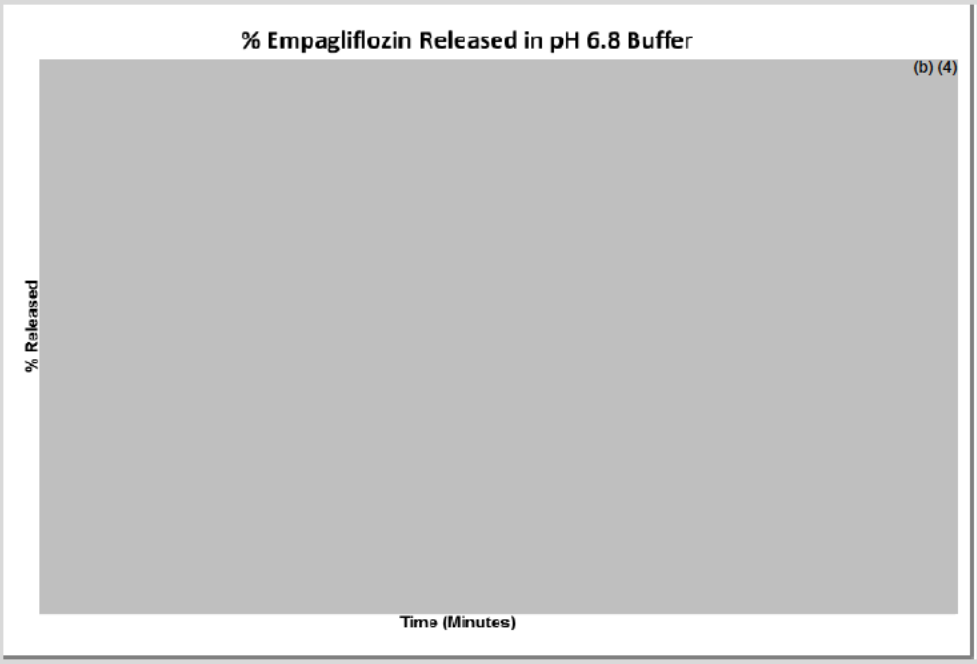


Figure 8B. Empagliflozin Dissolution Profiles in Phosphate Buffer, pH 4.5

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(b) (4)

[redacted]

3. Dissolution acceptance criteria

The proposed dissolution acceptance criteria for the immediate release of empagliflozin and extended release of metformin HCl in FDC tablets are shown in Table 7.

Table 7. Dissolution Specifications for Empagliflozin/Metformin HCl ER Coated Tablets

Drug Substance	Time point	Acceptance Criteria
Empagliflozin	45 minutes	Not less than (b) (4)% (Q)
Metformin HCl	2 hours	(b) (4) [redacted]
	4 hours	
	12 hours	Not less than (b) (4) %

Figure 10 shows the dissolution profiles of empagliflozin and metformin in different strengths of FDC tablets. Batch 3122750R empagliflozin / metformin 10 mg /1000 mg tablets and batch 3122745R empagliflozin / metformin 25 mg /1000 mg are clinical batches.

Figure 10A. Dissolution profiles of empagliflozin in different strengths of FDC tablets (red dashline represents the proposed dissolution acceptance criterion NLT (b) (4) % in 45 min)

Figure 10B. Dissolution profiles of metformin in in different strengths of FDC tablets (red dashline represents the proposed dissolution acceptance criteria)

As shown in Figure 10, the dissolution profiles supported the proposed dissolution acceptance criteria for both empagliflozin and metformin components in FDC tablets.

Figure 11 shows the release data generated during the stability test. As shown in Figure 11A below, although the release of empagliflozin in some tested units were less than (b) (4)%, they will all meet the Stage 2 test. For the release of metformin tested in stability test up to 12 months, they all met the proposed dissolution acceptance criteria.

Figure 11A. Release data (presented in mean, minimum (min), maximum (max) release of all units tested) of empagliflozin in different strengths of FDC under stability test at 25°C/60% RH up to 12 months (line represents the proposed dissolution acceptance criterion for empagliflozin NLT (b) (4)% in 45 min)

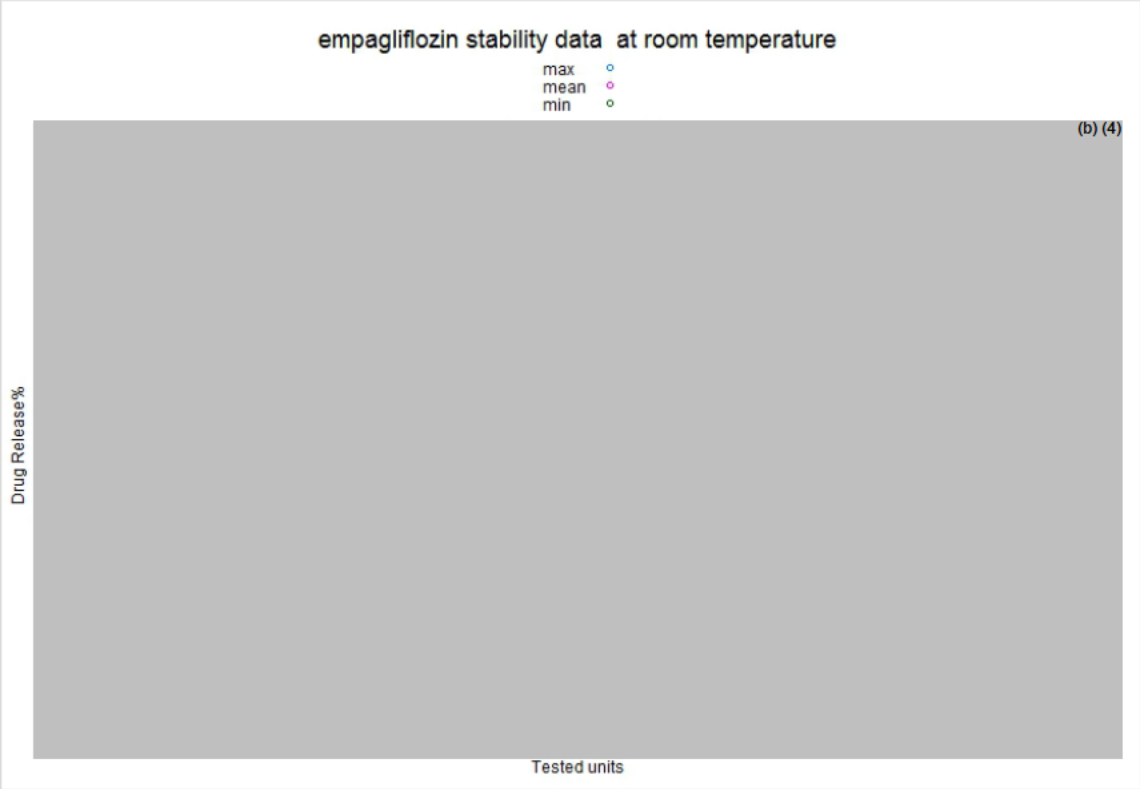
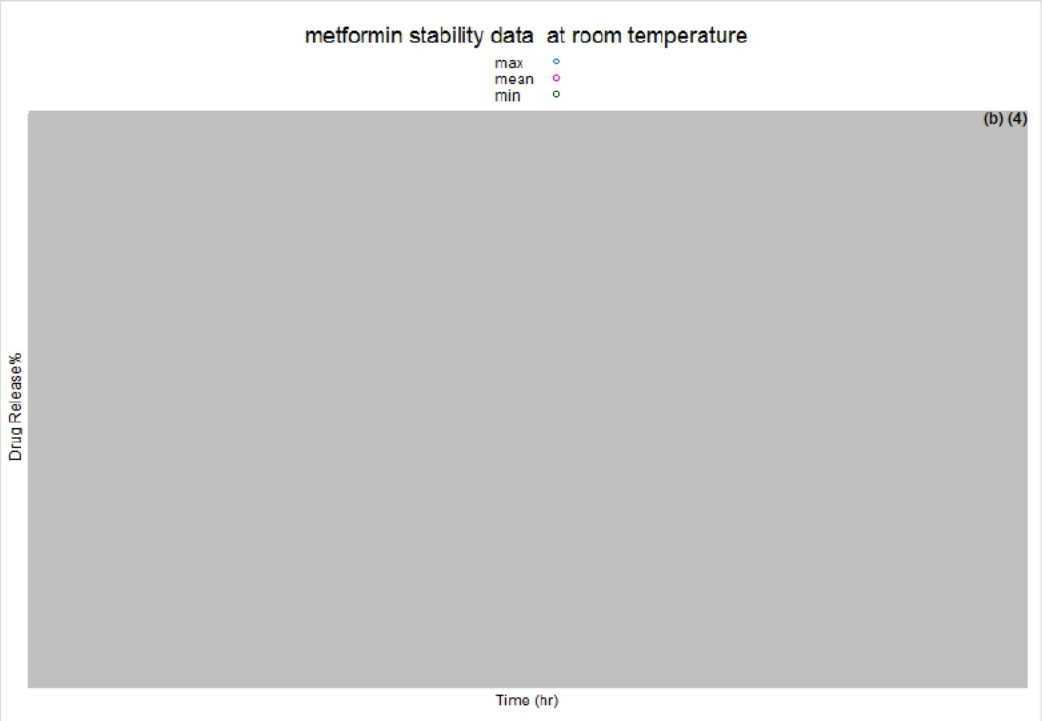


Figure 11B. Release data of metformin HCl in different strengths of FDC under stability test at 25°C/60% RH up to 12 months (line represents the proposed dissolution acceptance criterion for metformin: 2hr (b) (4)%, 4hr (b) (4)%, and 12 hr NLT (b) (4)%)



Based on the dissolution data and release data generated from long-term stability test, the proposed dissolution acceptance criteria for empagliflozin and metformin are acceptable.

4. Validation report for analytical method for dissolution

Table 8 shows the validation summary for analytical method for dissolution. The applicant evaluated the linearity, accuracy, precision (repeatability and reproducibility), specificity, and robustness of the procedure, stability of analytical solution, and filter study in accordance with ICH-Guideline Q2 (R1) "Validation of Analytical Procedures: Text and Methodology". The Applicant also conducted system suitability test (SST), which includes control of precision of injection, acceptability of the response of the standard preparations, system drift and peak shape. Overall, the validation report for dissolution analytical method is acceptable.

Table 8. Validation summary

Validation Parameter	Method of Determination	Results		
Linearity – empagliflozin	Performed at 6 concentrations from approx.10% up to 120% of empagliflozin potency	Correlation coefficient: 1.000 5 mg, 10 mg: Y-intercept of 3.160 mAU*s (0.2 %, 10 mg) Slope of 130.8 mAU*s/(µg/mL) 12.5 mg, 25 mg: Y-intercept of -4.110 mAU*s (0.1 %, 25 mg) Slope of 135.5 mAU*s/(µg/mL) Linear range from 0.5453 - 33.41 µg/mL, corresponding to 10 % for 5 mg to 120 % for 25 mg of empagliflozin potency		
Linearity – metformin HCl	Performed at 6 concentrations from approx.10% up to 100% (750 mg) or 120% (1000 mg) of metformin HCl potency	Correlation coefficient: 1.000 Y-intercept of 24.17 mAU*s (0.3 %) Slope of 8.424 mAU*s/(µg/mL) Linear range from 83.34 - 1333 µg/mL, corresponding to 10 % for 750 mg to 120 % for 1000 mg of metformin HCl potency		
Accuracy – empagliflozin	Performed by analysing spiked placebo sample solutions in triplicate at approx. 20%, 100% and 120% of the nominal sample solution concentration of empagliflozin	Average recovery results ranging from 101 % to 102 % per strength and overall RSD of 1 %		
		20%	5 mg strength	Individual recovery results 101%
		100%	5 mg, 10 mg, 12.5 mg and 25 mg strengths	Individual recovery results 101% to 102%
		120%	25 mg strength	Individual recovery results ranging from 101% to 102%
Accuracy – metformin HCl	Performed by analysing spiked placebo sample solutions in triplicate at approx. 30%, 80%, 100 % and 140% of the nominal sample solution concentration of metformin HCl	Average recovery results ranging from 99 % to 101 % per strength and overall RSD of 1 %		
		30%	750 mg strength	Individual recovery results ranging from 99% to 100%
		80%	750 mg strength	Individual recovery results ranging from 99% to 100%
		100%	750 mg, 1000 mg strengths	Individual recovery results ranging from 100% to 102%
		140%	1000 mg strength	Individual recovery results ranging from 100% to 102%
Precision (repeatability) – empagliflozin	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD of the percent recoveries (n=12) should not be more than 6.0 % at 45 minutes. Results: 5 mg/750 mg: 3.6 % 5 mg/1000 mg: 3.8 % 25 mg/1000 mg: 5.3 %		

Validation Parameter	Method of Determination	Results
Precision (repeatability) – metformin HCl	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD of the percent recoveries (n=12) should not be more than 6.0 % at 2, 4, and 12 hours. Results: 2 hours / 4 hours / 12 hours 5 mg/750 mg: 1.8 % / 1.1 % / 0.8 % 5 mg/1000 mg: 2.0 % / 1.5 % / 0.6 % 25 mg/1000 mg: 1.7 % / 1.5 % / 1.4 %
Precision (reproducibility) – empagliflozin	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD (n=12) should not be more than 6.0 % at 45 minutes for each analyst and the overall RSD for all analysts (n=36) should not be more than 6.0 % at 45 minutes. Analyst 1: 5 mg/ 750 mg: RSD = 3.6 %; 5 mg/1000 mg: RSD = 3.8 %; 25 mg/1000 mg: RSD = 5.3 % Analyst 2: 5 mg/ 750 mg: RSD = 3.5 %; 5 mg/1000 mg: RSD = 2.9 %; 25 mg/1000 mg: RSD = 4.7 % Analyst 3: 5 mg/ 750 mg: RSD = 3.6 %; 5 mg/1000 mg: RSD = 4.1 %; 25 mg/1000 mg: RSD = 2.0 % Overall: 5 mg/ 750 mg: RSD = 3.5 %; 5 mg/1000 mg: RSD = 3.6 %; 25 mg/1000 mg: RSD = 5.0 %
Precision (reproducibility) – metformin HCl	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD (n=12) should not be more than 6.0 % at 2 hours, 4 hours and 12 hours for each analyst and the overall RSD for all analysts (n=36) should not be more than 6.0 % at 2 hours, 4 hours, 12 hours. Analyst 1: 5 mg/750 mg: 1.8 % / 1.1 % / 0.8 %; 5 mg/1000 mg: 2.0 % / 1.5 % / 0.6 %; 25 mg/1000 mg: 1.7 % / 1.5 % / 1.4 % Analyst 2: 5 mg/750 mg: 1.2 % / 0.8 % / 0.8 %; 5 mg/1000 mg: 1.7 % / 1.0 % / 1.0 %; 25 mg/1000 mg: 1.3 % / 1.0 % / 1.0 % Analyst 3: 5 mg/750 mg: 1.3 % / 1.0 % / 0.9 %; 5 mg/1000 mg: 1.5 % / 1.1 % / 1.3 %; 25 mg/1000 mg: 1.9 % / 1.7 % / 1.2 % Overall: 5 mg/750 mg: 2.3 % / 1.9 % / 1.2 %; 5 mg/1000 mg: 2.2 % / 1.9 % / 1.3 %; 25 mg/1000 mg: 2.3 % / 2.3 % / 1.4 %

Validation Parameter	Method of Determination	Results	
Range	Concentration span where both linearity and accuracy have been determined	Based on the linearity and accuracy data, the range of the empagliflozin dissolution method was established from 20 % for 5 mg empagliflozin strength (1.1 µg/mL) to 120 % for 25 mg empagliflozin strength (33.4 µg/mL) and the range of the metformin dissolution method was established from 30 % for 750 mg metformin HCl strength (250 µg/mL) to 120 % for 1000 metformin HCl strength (1333 µg/mL).	
Specificity	Evaluation if degradants or other relevant peaks are separated from empagliflozin and metformin HCl (dissolution media & placebo sample solutions for both the empagliflozin and metformin HCl methods)	In the chromatograms of the dissolution media and placebo sample solutions, there were no significant interfering peaks present in the retention time window of empagliflozin or metformin HCl.	
Robustness (HPLC conditions)	One chromatographic method parameter was varied at a time. Different column batches were also used during the repeatability & reproducibility studies.	Empagliflozin and metformin HCL percent of target value are evaluated with variations in 50 mM Ammonium Phosphate pH (mobile phase), mobile phase composition, detector wavelength and column temperature. If significant performance deviations are noted then a precautionary statement is in the method. Results: No significant shifts in performance were observed as a result of varying the HPLC parameters.	
Robustness (sampling mode and dissolution medium pH)	Three tablets were analyzed by the proposed method and sampled at 45 minutes for empagliflozin and 2 hours, 4 hours and 12 hours for metformin HCl.	The absolute difference in the mean percent release values from results obtained at 45 minutes for empagliflozin and 2 hours, 4 hours and 12 hours for metformin HCl between robustness and target dissolution conditions should be ≤5%.	
		5 mg/750 mg (empagliflozin)	Sampling (auto vs manual): 0 % pH 6.9: 1% pH 6.7: 1%
		25 mg/1000 mg (empagliflozin)	Sampling (auto vs manual): 0 % pH 6.9: 1% pH 6.7: 3%
		5 mg/750 mg (metformin HCl)	Sampling (auto vs manual): 0%, 0%, 1% pH 6.9: 0%, 1%, 2% pH 6.7: 1%, 1%, 0%
		25 mg/1000 mg (metformin HCl)	Sampling (auto vs manual): 1%, 1%, 3% pH 6.9: 0%, 0%, 1% pH 6.7: 0%, 0%, 1%

Validation Parameter	Method of Determination	Results
Robustness (stability of analytical solutions) – *continued*		sample solutions are shared between the empagliflozin and metformin analysis. The standard solution stored in volumetric flask are stable up to 14 days. The standard solution stored in HPLC vials is stable up to 39 days for metformin analysis when stored under ambient laboratory conditions; however, for ease of the analyst, the method specifies an earlier time point (29 days) based on the stability of the empagliflozin standard solution as these solutions are often used in parallel. The standard solution in HPLC vials is stable up to 8 days under refrigerated conditions.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment:

The metformin component in FDC is in extended release formulation. As a result, the Applicant needs to evaluate the alcohol dose dumping of metformin in FDC in the presence of various concentrations of alcohol. The Applicant conducted in vitro alcohol dose dumping study on primary stability batches of empagliflozin/metformin HCl ER coated tablets, 5 mg/ 1000 mg and 25 mg/ 1000 mg (Figure 12), which is the lowest and the highest strength for the proposed drug product, respectively. Since as described above, the dissolution of metformin is independent of pH, the Applicant applied simulated gastric fluid (SGF) with pH 1.2 as the dissolution medium in the in vitro alcohol dose dumping study rather than applying QC dissolution method. This dissolution method is the same dissolution method as the one approved for Glumetza 500 (metformin ER) (Table 4).

Figure 12A. Metformin HCl Dissolution from empagliflozin metformin HCl ER coated tablets, 5 mg / 1000 mg in the presence of different concentrations of alcohol

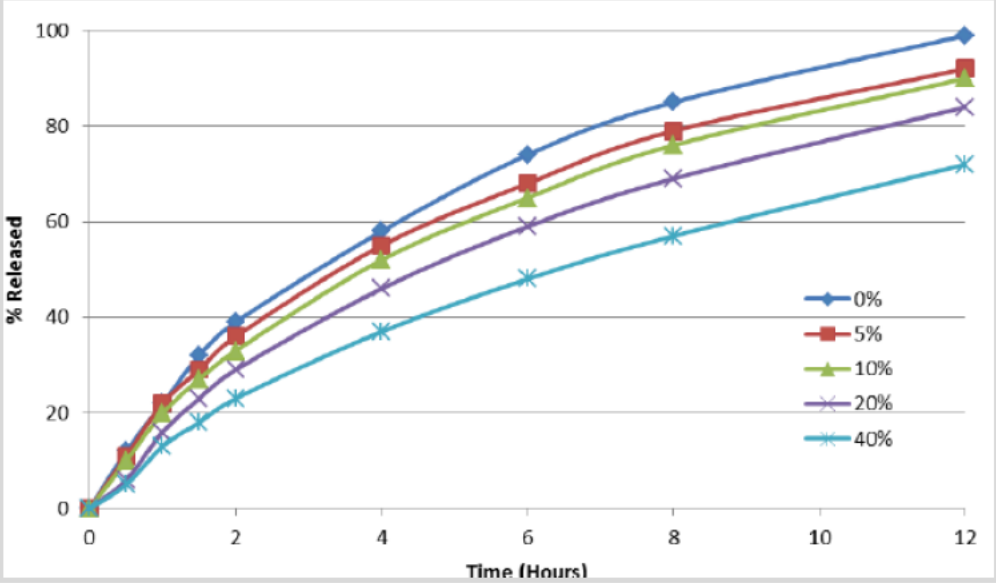
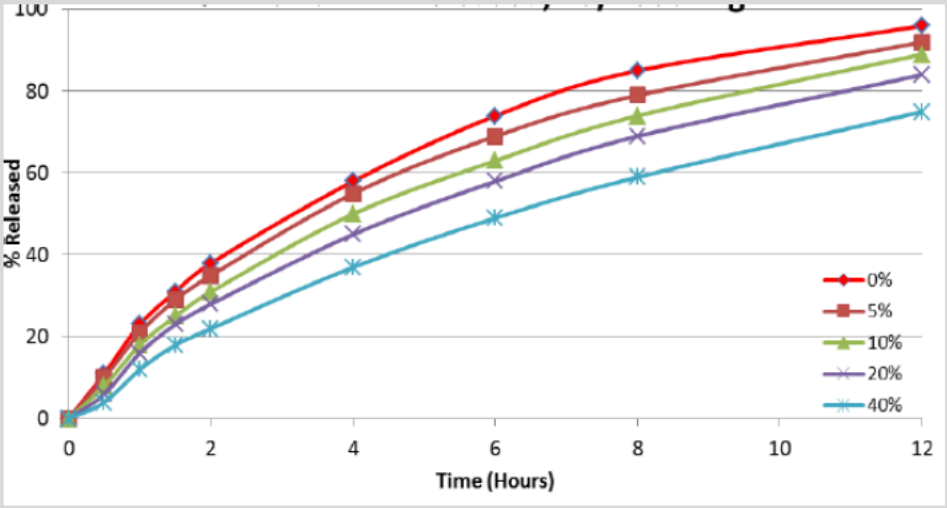


Figure 12B. Metformin HCl Dissolution from empagliflozin metformin HCl ER coated tablets, 25 mg / 1000 mg in the presence of different concentrations of alcohol



The Applicant evaluated the in vitro alcohol dose dumping in SGF dissolution medium, rather than pH 6.8 buffer used in the proposed dissolution medium. However, since the dissolution of metformin is pH independent, it is expected that the dissolution behavior of metformin in the presence of alcohol up to 40% by using SGF dissolution medium, will be similar to that by using pH 6.8 buffer as the dissolution medium.

As shown in Figure 12, for both strengths, the release of metformin in absence of alcohol is faster compared to the one in the presence of alcohol up to 40%. As shown in Table 8, the dissolution similarity demonstrated by the calculation of f2 indicate that the dissolution profiles of metformin in both strengths of the FDC tablets were different compared to those in the presence of 20% or higher of alcohol. The f2 calculations from the Applicant are consistent with the reviewer's own calculation. However, since the dissolution of metformin is decreasing rather than increasing in the presence of alcohol, the safety concern as a result of dose dumping is unlikely. Furthermore as stated in the label of the proposed FDC product as well as the listed drug Glumetza, patients were suggested to be cautious against excessive alcohol intake when taking Glumetza because alcohol potentiates the effects of metformin on lactate metabolism. Overall, the in vitro alcohol dose dumping study is acceptable, and the safety concern for the metformin in FDC tablets as a result of alcohol dose dumping might be minimal.

The results of the alcohol dose dumping study were conveyed to the reviewer in Office of Clinical Pharmacology, and they will determine whether in vivo alcohol dose dumping study is needed (please refer to clinical pharmacology review for additional details).

Table 8. *f*2 Calculation between the Samples in the Presence of 0% Ethanol and Various Ethanol Concentrations

Tablet Strength	Dissolution Media Ethanol Concentration (v/v)				
	0%	5 %	10 %	20 %	40%
5 mg/1000 mg	NA*	67.7	58.8	46.4	35.1
25 mg/1000 mg	NA*	71.3	55.5	46.8	36.5
References	Table 4 Table 5	Table 6 Table 7	Table 8 Table 9	Table 10 Table 11	Table 12 Table 13

*Not applicable; reference: CIN-AD-R-4492

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment:

The proposed drug product is a combination of immediate release component of empagliflozin and extended release component of metformin HCl.

Based on **21 CFR 320.25** ***(f) Extended release formulations.*** *(1) The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if all of the following conditions are met:*

(i) The drug product meets the extended release claims made for it.

(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

(iii) The drug product's steady-state performance is equivalent to a currently marketed nonextended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

Two BE studies 1276.15 and 1276.28 were conducted to compare 25 mg /1000 mg and 10 mg /1000 mg strengths of proposed FDC products, respectively to the free combination of the individual reference drug products Jardiance 25 mg empagliflozin IR and Glumetz XR metformin 500 mg (which is an extended release formulation). Both BE studies met the BE acceptance criteria, and the empagliflozin and metformin in FDC showed similar PK as respective individual components. In single- and multiple-dose studies of the reference drug Glumetza XR (metformin) 500 mg ER tablets in healthy subjects, once daily 1000 mg (2x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher Cmax, of metformin relative to the immediate release given as 500 mg twice daily. The

Applicant also conducted alcohol dose dumping study on metformin component of the FDC tablets, and as Figure 10 shows, there is no risk of alcohol dose dumping.

Overall, the metformin component of the FDC tablets qualifies the extended release claim.

Biowaiver Request

Reviewer's Assessment:

The proposed FDC tablets have four tablet strengths, including 5 mg/1000 mg, 10 mg/1000 mg, 12.5 mg/1000 mg, and 25 mg/1000 mg. Two BE studies 1276.15 and 1276.28 were conducted to compare 25 mg /1000 mg and 10 mg /1000 mg strengths of proposed FDC products, respectively to the free combination of the individual reference drug products Jardiance 25 mg empagliflozin IR and Glumetz XR metformin 500 mg. Both BE studies met the BE acceptance criteria, and the empagliflozin and metformin in FDC showed similar PK as respective individual components. A biowaiver request was submitted for the lower strengths 5 mg/ 1000 mg, and 12.5 mg / 1000 mg empagliflozin / metformin combination tablets.

Based on ***Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations***, an in vivo BE demonstration of one or more lower strengths can be waived if:

1) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BA or BE testing has been conducted.

2) An in vivo BE study was conducted on the highest strength

3) Similarity in dissolution profiles from the different strengths of the product

As shown in Table 1, the composition of the different strengths of FDC tablets only varies on the amount of the active ingredient (empagliflozin), while the amount of another active ingredient (metformin) is the same. Therefore, the different strengths of the proposed drug product are not proportionally similar. However, as shown in Table 1 and Figure 13, the formulation of the proposed drug product, metformin component is only contained in the tablet core, whereas another active component empagliflozin is in the coat layer outside the metformin core tablet. Therefore, based on the formulation design, empagliflozin component could be considered as an immediate release product, which will be released immediately before the extended release of metformin core tablet. Within empagliflozin coat layer, different strengths are proportionally similar.

Figure 13. Schematic of the Cross Section of an Empagliflozin/Metformin HCl ER Coated Tablet

(b) (4)

The Applicant conducted comparative dissolution studies to determine the similarity of dissolution profiles from different strengths in various dissolution media including pH 1.2 SGF without enzyme, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. As dissolution profiles from different strengths shown in Figure 8 and f2 calculations shown in Table 6 and Table 9 (reviewer's calculations are consistent with the Applicant's calculations), the dissolution profiles of different strengths are similar.

Table 9. *f*2 Values for Empagliflozin and Metformin Hydrochloride from Empagliflozin/Metformin HCl ER Coated Tablets with reference to additional strengths

Test Product	5 mg/1000 mg Batch 3122757R	12.5 mg/1000 mg Batch 3122760R
Reference Product	10 mg/1000 mg Batch 3122750R	25 mg/1000 mg Batch 3122745R
Dissolution Media	**Similarity factor f_2 (Empagliflozin / Metformin)**	
Phosphate Buffer, pH 6.8	66 / 86	78 / 90
Acetate Buffer, pH 4.5	43 (n =12, original data) / 84 71 (n=24, retest data) / n.a. 60 (n=36*, combined data) / n.a.	94 / 84
SGF without enzymes, pH 1.2	86 / 96	55 / 83

* Relative standard deviation of first sampling time point (15 min.) of batch 3122750R is slightly above 20 % (21.2 %); Reference CIN-AD-R-4491

Since BE studies 1276.15 and 1276.28 have established the bioequivalence of 25 mg /1000 mg and 10 mg /1000 mg strengths of proposed FDC products, the biowaiver request for the strength 12.5 mg/1000 mg empagliflozin/ metformin tablets could be granted based on bracketing approach (12.5 mg is bracketed by 25 mg/1000 mg and 10 mg / 1000 mg).

The dissolution profiles from different strengths are similar as shown in Table 6 and Table 9. The possible interaction between the empagliflozin layer and metformin core, which might be different across different strengths seems unlikely based on in vitro dissolution similarity among different strengths as well as PK

similarity based on the bioequivalence from BA/BE studies conducted on highest strength 25 mg /1000 mg and medium strength 10 mg /1000 mg. Therefore, the biowaiver request for 5 mg /100 mg FDC tablets could be granted, considering empagliflozin layer as an immediate release product.

Furthermore, empagliflozin shows linear pharmacokinetics following single oral doses over the dose range from 0.5 mg to 800 mg and after multiple oral doses ranging from 2.5 mg to 100 mg once daily (*Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses (0.5 mg to 800 mg) of BI 10773 as tablets administered to healthy male subjects. A randomized, placebo-controlled (within dose groups) and double-blind trial; Safety, tolerability, pharmacokinetics and pharmacodynamics of 4 multiple rising oral doses (2.5 mg to 100 mg) of BI 10773 tablets in male and female type 2 diabetic patients)*. Systemic exposure of empagliflozin increased in a dose proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time (FDA label for Jardiance® (empagliflozin), initial U.S. Approval 2014). Based on demonstrated BE from BA/BE studies conducted on highest strength 25 mg /1000 mg and medium strength 10 mg /1000 mg, the PK linearity of empagliflozin over the range from 2.5 mg to 100 mg may suggest the similar PK for 5 mg /1000 mg FDC compared to the respective free combination.

Overall, the biowaiver request for 5 mg/1000 mg and 12.5 mg/1000 mg strengths are acceptable, pending on the acceptance of BE studies 1276.15 and 1276.28 by the reviewer of Office of Clinical Pharmacology (please refer to clinical pharmacology review for additional details).

List of Deficiencies:

N/A

From Biopharmaceutics perspective, NDA 208658 is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date: Peng Duan, Ph.D. 09/21/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D. 10/26/2016.

Haritha Mandula

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Peng Duan

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CHAPTER VIII: Microbiology

See Chapter V Process

CHAPTER IX: Additional Quality Discipline

n/a

ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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