CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210296Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210296
Review # 01

Drug Name/Dosage Form	Monomethyl Fumarate Delayed Release Capsules
Strength	95 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Banner Life Sciences LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	18-JAN-2018	*Amendment*	24-SEP-2018
Amendment	13-APR-2018	*Amendment*	26-SEP-2018
Amendment	20-APR-2018	*Amendment*	01-OCT-2018
Amendment	29-JUN-2018	*Amendment*	11-OCT-2018
Amendment	20-JUL-2018	*Amendment*	23-OCT-2018
Amendment	13-SEP-2018	*Amendment*	01-NOV-2018

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rajan Pragani	Suong Tran	ONDP
Drug Product	Dan Berger	Wendy Wilson-Lee	ONDP
Environmental			
Labeling			
Process	Peter Krommenhoek	Nallaperumal Chidambaram	OPF
Microbiology			
Facility	Peter Krommenhoek		OPF
Biopharmaceutics	Kaushal Dave	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	IV		(b) (4)	Not reviewed		Sufficient information provided in NDA
	II			Adequate	12-SEP-2018	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	126454	Monomethyl fumarate delayed release capsules
NDA	204063	Tecfidera (dimethyl fumarate) delayed release capsules

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210296, as amended.

II. Summary of Quality Assessments

A. Product Overview

Banner Life Sciences LLC (Banner) submitted a 505(b)(2) application seeking approval of monomethyl fumarate for the treatment of patients with relapsing forms of multiple sclerosis. Several treatment options are currently marketed for this indication, including the listed drug TECFIDERA (dimethyl fumarate). Monomethyl fumarate is the active metabolite of dimethyl fumarate. Banner developed a 95 mg strength delayed release capsule with a recommended dosing regimen of 190 mg or 2 capsules twice daily for a maximum daily dose of 380 mg.

The initial risk assessment identified alcohol dose dumping as a high risk attribute for this drug product due to is modified release characteristics. Assay and dissolution were found to be moderate risk attributes due to the poor stability of the drug substance and modified release characteristics of the drug product, respectively. Solid state of the drug substance is another attribute of interest as no known polymorphs were identified. Confirmation of this characteristic will be a review issue. Another review issue was the filing and acceptance of a USAN name for the drug substance. Monomethyl fumarate was not listed in the USAN database at the time of filing.

Proposed Indication(s) including Intended Patient Population	***Relapsing forms of multiple sclerosis***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***380 mg***
Alternative Methods of Administration	***None***

B. Quality Assessment Overview

Monomethyl fumarate (MMF) was accepted as the USAN name by the USANC on April 13, 2018. The control strategy to maintain MMF drug substance quality is acceptable. The (b) (4) structural alert was deemed not significant since MMF and its prodrug dimethyl fumarate (DMF) are both stated to be non-mutagenic in the approved TECFIDERA (dimethyl fumarate) delayed-release capsules label. The justification for (b) (4), which has a structural alert, was acceptable. MMF has good solubility and shows no polymorphism. Although it is not a critical quality

attribute because of the high solubility of MMF, particle size is monitored in the drug substance specification. The control strategy and quality of MMF drug substance is adequate. **A retest period of (b) (4) months (b) (4) is supported by provided stability data.**

The drug product consists of monomethyl fumarate soft gelatin capsules at a single 95 mg strength to be dosed at up to 380 mg maximum daily dose (190 mg twice a day) orally. Each capsule has a (b) (4) Formulation development required (b) (4) All excipients are compendial, present in safe quantities and BSE/TSE free. The specifications are adequate to ensure drug product quality and drug product batches meet specified acceptance criteria at release. Commercial packaging consists of an HDPE bottle enclosed with a (b) (4) closure and an induction seal. The container closures that contact with the drug product are suitable for pharmaceutical or food contact per 21 CFR regulations. The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited as 21 CFR 25.31(a) is appropriate for the submitted application, and a statement of no extraordinary circumstances has been submitted. **The claim of categorical exclusion is acceptable.**

Although the drug substance can react with excipients and water, registration drug product batches met all acceptance criteria on release and during long-term stability studies for 18 months at 5°C ± 3°C. At 25°C/60%RH, trends are noted for assay, degradants and particle size. (b) (4) impurity acceptance criteria are met for up to 12 months, but not 18 months. The trends were more pronounced at intermediate conditions (30°C/65% RH), with some misshapen capsules after 6 months, and specifications met for up to 9 months. Under accelerated conditions (40°C/75% RH), capsules became misshapen at the beginning of the study, with assay, degradants and dissolution not meeting specifications from 2 months onward. In-use stability studies (with bottle induction seal compromised) and stability studies in bulk cartons performed at 25°C/60%RH show similar trends to drug product stored in bottles. **The data submitted, which includes extrapolation plots based on long term stability data, provides adequate support for a shelf-life of 24 months at refrigerated conditions (5°C ± 3°C). As the hold time for bulk storage of the capsules is up to (b) (4) months at room temperature, a 3-month room temperature storage period is assigned to drug product after the bottles are opened to ensure drug product integrity.**

To support the approval of this 505(b)(2) submission, the Applicant conducted a pivotal bioavailability/bioequivalence (BA/BE) study to bridge the proposed BAFIERTAM™ (95 mg x 2 capsules) to Tecfidera® 240 mg under fasted and fed conditions. Additionally, the Applicant provided data/information for the proposed dissolution testing for quality control of the proposed delayed-release drug product at batch release and during stability testing, as well as for alcohol-induced dose-dumping potential. The Biopharmaceutics review is focused on the evaluation of the 1) proposed dissolution

method and acceptance criteria, 2) in vitro alcohol-induced dose-dumping study results, and (3) formulation bridging.

Dissolution Method: (b) (4) the Applicant modified the dissolution method based on the method approved for the List Drug (LD) Tecfidera®. The proposed dissolution method [900 mL of acid stage (0.1N HCl; during 0-2 hours) and buffer stage (pH 6.8 phosphate buffer; during 2-4 hours) using USP Apparatus 2 (paddle) with a Stationary Basket over the Paddle at 100 rpm] has been demonstrated to be sufficiently discriminating (b) (4) . Based on the provided information/data, the proposed dissolution method is deemed acceptable for quality control of the proposed finished drug proposed product.

Dissolution Acceptance Criteria: The Applicant's proposed dissolution acceptance criterion for the acid stage (not more that (b) (4)% in 120 minutes) is reasonable. However, the Applicant's originally proposed dissolution acceptance criterion of 'not less than (b) (4)% (Q) in 90 minutes' for the buffer stage testing was not appropriately selected. As the proposed product exhibits high variability in drug release during the first hour of the buffer stage dissolution testing, the Division determined that an additional acceptance criterion at an earlier (60 minute) time point is necessary for the quality control. The Applicant has agreed to implement the FDA's recommended dissolution acceptance criteria [Acid Stage: Not more that (NMT) (b) (4)% in 120 minutes; Buffer Stage: Not less than (NLT) (b) (4)% in 60 minutes, and NLT (b) (4)% (Q) in 90 minutes] on 09/26/2018 for quality control of the finished drug product at batch release and during stability testing.

Alcohol-Induced Dose-Dumping Potential: The provided data show that ethanol at 5-40% v/v has minimal effects on the drug release of the proposed product in 0.1N HCl for 2 hours, indicating the lack of dose-dumping potential in the gastric environment with the consumption of alcohol/alcohol beverages. The potential impact of alcohol on the drug release beyond 2 hours is unknown due to the lack of study. Restriction pertaining to the alcohol consumption is not described in the approved labeling of LD Tecfidera® or of the proposed BAFIERTAM™. In view of the much faster drug release of the LD Tecfidera® after 2 hours in the buffer stage, as reflected by the steeper dissolution profile, and the totality of information related to dosing and disease, this Reviewer determines that the increase in drug release from the BAFIERTAM™ after 2 hours (b) (4) if there is any, in the presence of alcohol will unlikely result in clinical concerns for safety or efficacy.

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

The method proposed for manufacturing Monomethyl Fumarate Delayed Release Capsule, 95 mg, involves the following unit operations: (b) (4) stages of manufacturing have high risk that could affect certain drug product critical quality attributes. Although identified as high risk, the Applicant employed sufficient risk mitigation strategies to reduce the risk for these unit operations to low as detailed below:

(b) (4)

The Applicant has implemented in-process controls during each process step that were optimized during development and will be validated at a commercial scale. The recommended process parameters fell within specified the ranges. (b) (4)

(b) (4) These parameters and in-process controls will be validated at commercial scale. The Applicant proposes a planned commercial batch size of (b) (4) capsules. This is approximately 10X the size of the largest registration batch. The design and operating principles of all the equipment proposed in the commercial batches are same as that of registration batches. (b) (4)

A risk-based assessment of the proposed facilities concluded that the operations were low risk and no inspections were needed. There is no evidence to warrant withholding approval, **therefore the facilities are found adequate for this NDA.**

C. Special Product Quality Labeling Recommendations

The recommended long-term storage condition is refrigerated. An in-use storage of room temperature for up to three months after dispensing to patients is supported by available drug product stability data. Additional precaution statement added to discourage storage at elevated temperatures to avoid deformation.

D. Final Risk Assessment

From Initial Risk Identification		Review Assessment		
Attribute/ CQA	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	**Medium**	Long-term storage condition reduces potential for degradation	**Acceptable**	
Solid State	**Low**		**Acceptable**	
Content Uniformity	**Low**		**Acceptable**	
Microbial Limits	**Low**		**Acceptable**	
Dissolution	**Medium**	Proposed dissolution method deemed acceptable	**Acceptable**	
Alcohol Dose Dumping	**High**	In vitro data provided to demonstrate risks associated with potential dose dumping are minimal	**Acceptable**	
Appearance/Shape	**Medium**	Labeling statement added to avoid exposure to elevated temperatures	**Acceptable**	
Particle Size	**Low**		**Acceptable**	

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LABELING

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Adequate
Dosage form, route of administration	Adequate
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Adequate

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Adequate

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Adequate with edits made
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Adequate with edits made
Chemical name, structural formula, molecular weight	Adequate with edits made
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Adequate with edits made

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	Adequate
Storage conditions	Adequate with edits made
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer's Assessment of Package Insert: ***Adequate***
Section 11 has been edited to add the chemical class, molecular weight, physical properties and listing of inactive ingredients in alphabetical order. Section 16 has been edited to include updated storage conditions and an alert that capsules can become deformed at high temperatures. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Bottle Label***
    a. ***Front label:***

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate	Adequate
Dosage strength	Adequate	Adequate
Net contents	Adequate	Adequate
"Rx only" displayed prominently on the main panel	Adequate	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate	Adequate
Lot number and expiration date (21 CFR 201.17)	Adequate with edits made	Adequate
Storage conditions	Adequate with proposed edits	Adequate with proposed edits
Bar code (21CFR 201.25)	Adequate with edits made	Adequate
Name of manufacturer/distributor	Adequate with edits made	Adequate with edits made
And others, if space is available		

Reviewer's Assessment of Labels: ***Adequate***
In response to an Information Request, the drug product bar code, lot number and manufacturer information was added to the bottle label, and manufacturer information was added to the carton. Storage conditions were additionally revised to USP controlled room temperature. As a further revision of storage conditions is required, DMEPA has prepared a recommendation to amend the storage conditions. With the updates made, the labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies:

None.

Overall Assessment and Recommendation:

All deficiencies have been addressed. The Prescribing Information and labels, as revised, comply with all regulatory requirements from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Dan Berger November 7, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Wendy Wilson November 7, 2018

Dan Berger

Digitally signed by Dan Berger
Date: 11/07/2018 04:35:29PM
GUID: 56e6e1b5001a2fedae663c62a5ce7513

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 11/07/2018 04:42:00PM
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BIOPHARMACEUTICS

PRODUCT BACKGROUND

NDA: 210296; 505(b)(2)
Drug Product Name / Strength: BAFIERTAM™ (Monomethyl Fumarate) Delayed Release Capsules/95 mg
Route of Administration: Oral
Indication: Treatment of patients with relapsing forms of multiple sclerosis
Submission Date: 01/18/2018 (Original)
Applicant Name: Banner Life Sciences LLC

BACKGROUND

The proposed drug product, BAFIERTAM™ (Monomethyl Fumarate) Delayed Release Capsules, 95 mg (designated as BLS-11 by the Applicant during the development), is an opaque-white, oval-shaped, soft gelatin capsule (b) (4) The active ingredient in the proposed product is monomethyl fumarate (MMF) which is an active metabolite of dimethyl fumarate (DMF). The Listed Drug (LD), Tecfidera® (Dimethyl Fumarate Delayed Release Capsule), was approved by the FDA in 2013 under NDA 204063 for the treatment of relapsing forms of multiple sclerosis (MS).

The Applicant's 505(b)(2) NDA submission for BAFIERTAM™ (monomethyl fumarate) Delayed Release Capsules, 95 mg, relies on the FDA's safety and efficacy findings of the LD, Tecfidera® (dimethyl fumarate) Delayed Release Capsules, 240 mg (approved under NDA 204063). The proposed starting dose of the proposed drug product is 95 mg twice a day, orally, for 7 days and maintenance dose after 7 days is 190 mg twice a day. To support the approval of this 505(b)(2) submission, the Applicant conducted a pivotal bioavailability/bioequivalence (BA/BE) study to bridge the proposed BAFIERTAM™ (95 mg x 2 capsules) to Tecfidera® 240 mg under fasted and fed conditions. Additionally, the Applicant provided data/information for the proposed dissolution testing for quality control of the proposed delayed-release drug product at batch release and during stability testing, as well as for alcohol-induced dose-dumping potential.

The Biopharmaceutics review is focused on the evaluation of the 1) proposed dissolution method and acceptance criteria, 2) in vitro alcohol-induced dose-dumping study results, and (3) formulation bridging, as presented below.

REVIEW SUMMARY

Dissolution Method: (b) (4) , the Applicant modified the dissolution method based on the method approved for the List Drug (LD) Tecfidera®. The proposed dissolution method [900 mL of acid stage (0.1N HCl; during 0-2 hours) and buffer stage (pH 6.8 phosphate buffer; during 2-4 hours) using USP Apparatus 2 (paddle) with a Stationary Basket over the Paddle at 100 rpm] has been demonstrated to be sufficiently discriminating (b) (4) Based on the provided information/data, the proposed dissolution method is deemed acceptable for quality control of the proposed finished drug proposed product.

Dissolution Acceptance Criteria: The Applicant's proposed dissolution acceptance criterion for the acid stage (not more that (b) (4)% in 120 minutes) is reasonable. However, the Applicant's originally proposed dissolution acceptance criterion of 'not less than (b) (4)% (Q) in 90 minutes' for the buffer stage testing was not appropriately selected. As the proposed product exhibits high variability in drug release during the first hour of the buffer stage dissolution testing, the Division determined that an additional acceptance criterion at an earlier (60 minute) time point is necessary for the quality control. The Applicant has agreed to implement the FDA's recommended dissolution acceptance criteria [Acid Stage: Not more that (NMT) (b) (4)% in 120 minutes; Buffer Stage: Not less than (NLT) (b) (4)% in 60 minutes, and NLT (b) (4)% (Q) in 90 minutes] on 09/26/2018 for quality control of the finished drug product at batch release and during stability testing.

Alcohol-Induced Dose-Dumping Potential: The provided data show that ethanol at 5-40% v/v has minimal effects on the drug release of the proposed product in 0.1N HCl for 2 hours, indicating the lack of dose-dumping potential in the gastric environment with the consumption of alcohol/alcohol beverages. The potential impact of alcohol on the drug release beyond 2 hours is unknown due to the lack of study. Restriction pertaining to the alcohol consumption is not described in the approved labeling of LD Tecfidera® or of the proposed BAFIERTAM™. In view of the much faster drug release of the LD Tecfidera® after 2 hours in the buffer stage, as reflected by the steeper dissolution profile, and the totality of information related to dosing and disease, this Reviewer determines that the increase in drug release from the BAFIERTAM™ after 2 hours ((b) (4) if there is any, in the presence of alcohol will unlikely result in clinical concerns for safety or efficacy.

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

Conclusion and Recommendation: From the Biopharmaceutics perspective, NDA 210296 for Monomethyl Fumarate Delayed Release Capsules, 95 mg, is recommended for **APPROVAL**.

The approved dissolution method and acceptance criteria for the quality control of the finished delayed release drug product at batch release and during stability testing:

FDA's Approved Dissolution Method and Acceptance Criteria for BAFIERTAM™ **(Monomethyl Fumarate) Delayed Release Capsules, 95 mg**	
Apparatus	USP Apparatus 2 (paddle) with a Stationary Basket over the Paddle
Paddle Speed	100 rpm
Volume	900 mL
Medium	0.1N HCl (Acid Stage; 0-2 Hours) pH 6.8 Phosphate Buffer (Buffer Stage; 2-4 Hours)
Temperature	37.0 ± 0.5˚C
Acceptance Criteria	**Acid Stage:** Not more that (NMT) (b) (4) in 120 minutes **Buffer Stage:** Not less than (NLT) (b) (4)% in 60 minutes, and NLT (b) (4)% (Q) in 90 minutes

Primary Biopharmaceutics Reviewer Name and Date

Kaushalkumar Dave, Ph.D. (10/11/2018)
Division of Biopharmaceutics, ONDP, OPQ

Secondary Reviewer Name and Date

I concur with Dr. Dave's Biopharmaceutics assessment and recommendation.

Ta-Chen Wu, Ph.D. (10/11/2018)
Division of Biopharmaceutics, ONDP, OPQ

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	01/18/2018	Original NDA Submission
0010	06/29/2018	Quality/Response to Information Request
0014	09/13/2018	Quality/Response to Information Request
0018	09/26/2018	Quality/Response to Information Request

2. DRUG PRODUCT

The proposed product is a delayed-release capsule comprised of a [redacted] (b) (4) The Applicant developed and optimized the proposed product for the pivotal clinical studies based on in vitro and pilot in vivo studies. Based on the pilot bioequivalence study results, the Applicant modified their product [redacted] (b) (4) The composition of the proposed delayed release capsules (fill and shell) and the capsule [redacted] (b) (4) is provided in ***Appendix 1***. There were no product/process related changes between the pivotal clinical study batch and the proposed commercial batch which would require bridging studies.

The delayed release mechanism of the proposed product is attributed to [redacted] (b) (4)

All the pivotal clinical studies were performed with the same batch of the proposed drug product (Batch 147000847M) which is one of the three exhibit/registration batches (Batch 147000841M, Batch 147000847M and 147000852M).

3. BCS DESIGNATION: *NOT APPLICABLE*

Solubility

The Applicant studied the solubility of MMF in the physiological pH range of 1.2–7.2. The results of the experimental solubility summarized in Table 1 indicate that MMF is a highly soluble drug substance, per the BCS criteria, and exhibits pH independent solubility across the studied physiological pH range.

Table 1: Aqueous Solubility of MMF (20-25ºC)

Media	Room Temperature (20-25°C)
0.1N Hydrochloric acid	10.9
Acetate Buffer pH 4.5	17.7
Acetate Buffer pH 5.5	19.0
Phosphate Buffer pH 6.8	15.0
Phosphate Buffer pH 7.2	19.2

Permeability

No information of permeability of the drug substance was provided for this application.

4. DISSOLUTION INFORMATION

(b) (4)

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[1] GSR Link: Application 210296 - Sequence 0010 - FDA Letter-15Jun2018

[2] GSR Link: Application 210296 - Sequence 0010 - Cover Letter-29Jun2018

(b) (4)

[redacted]

Discriminating ability of the selected dissolution method:

The Applicant investigated the discriminating ability of the selected dissolution method (Table 5) by varying 1) (b) (4) [redacted].

Table 5: Testing conditions for the selected dissolution method

Apparatus	USP Apparatus 2 (paddle) with a Stationary Basket over the Paddle
Paddle Speed	100 rpm
Volume	900 ml
Medium	0.1N HCl (Acid Stage; 2 Hours) pH 6.8 Phosphate Buffer (Buffer Stage; 2 Hours)
Temperature	37.0 ± 0.5°C

The provided dissolution data (Figure 4) suggest that the dissolution profile of the test product with the (b) (4) [redacted] is different from those of the products with (b) (4) [redacted] (reviewer calculated similarity factor $f_2 = 40.8$) and (b) (4) [redacted]" (reviewer calculated $f_2 = 47.9$). However, no significant difference in the dissolution profiles was observed for the products with the (b) (4) [redacted] (reviewer calculated $f_2 = 68.0$).

Figure 4: Dissolution profiles of the test products with different (b) (4)

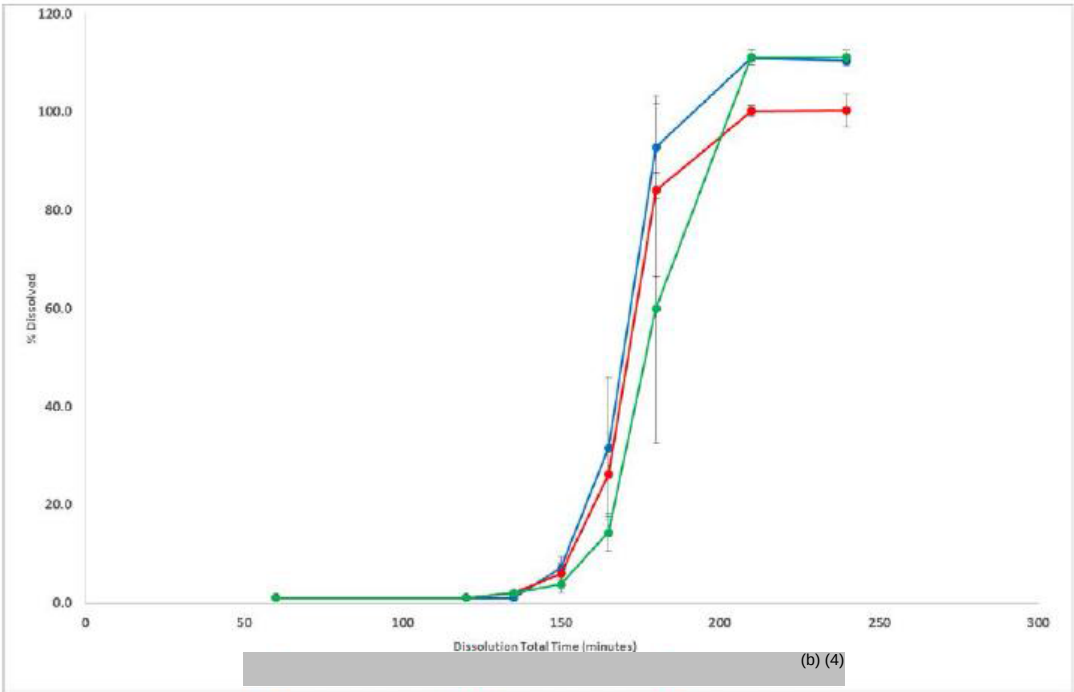

Table 6: Dissolution profiles of the test products with different (b) (4)

Media Time (min)	Total Time (min)	(b) (4)					
		Average Percent Dissolved	Std. Dev.	Average Percent Dissolved	Std. Dev.	Average Percent Dissolved	Std. Dev.
Acid 60	60	1.0	0.0	1.0	0.0	1.0	0.0
Acid 120	120	1.0	0.0	1.0	0.0	1.0	0.0
Buffer 15	135	1.0	0.0	2.0	0.0	2.0	0.0
Buffer 30	150	7.2	2.3	6.0	2.1	3.8	1.7
Buffer 45	165	31.5	14.4	26.2	8.4	14.3	3.8
Buffer 60	180	92.8	10.4	84.0	17.5	60.0	27.6
Buffer 90	210	111.0	0.6	100.2	1.2	111.2	1.6
Buffer 120	240	110.5	1.0	100.3	3.3	111.2	1.5

As shown in Figure 5, the dissolution profile of the test product with the (b) (4) was significantly different from that of the product with (b) (4) (reviewer calculated f_2 = 40.8). However, no significant difference in dissolution profile was observed between the products with the (b) (4) (reviewer calculated f_2 = 52.0), and between (b) (4) (reviewer calculated f_2 = 58.2).

Figure 5: Dissolution profiles of the test products with different levels (b) (4)

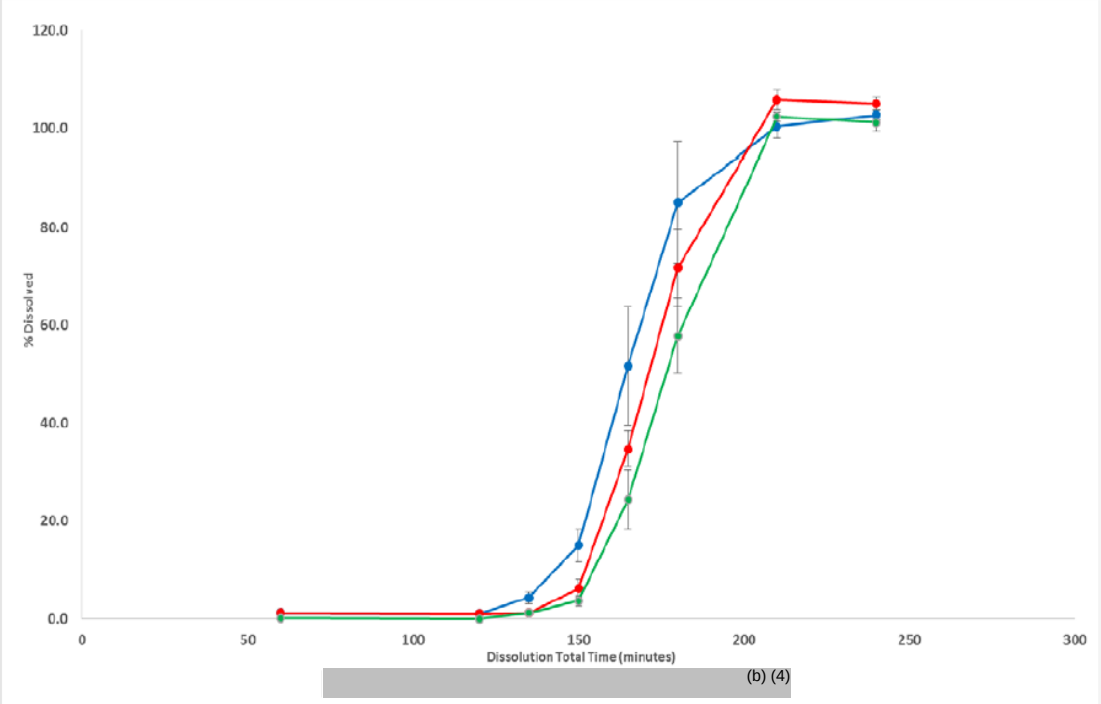

Table 7: Dissolution profiles of the test products with different levels (b) (4)

Media Time (min)	Total Time (min)	(b) (4) Average Percent Dissolved	Std. Dev.	Average Percent Dissolved	Std. Dev.	Average Percent Dissolved	Std. Dev.
Acid 60	60	1.2	0.8	1.2	0.4	0.2	0.4
Acid 120	120	1.0	0.0	1.0	0.0	0.0	0.0
Buffer 15	135	4.3	1.2	1.2	0.4	1.2	0.4
Buffer 30	150	15.0	3.3	6.2	1.8	3.7	1.0
Buffer 45	165	51.7	12.1	34.7	3.7	24.3	6.1
Buffer 60	180	85.0	12.4	71.7	7.9	57.8	7.8
Buffer 90	210	100.3	2.3	105.8	2.0	102.3	1.0
Buffer 120	240	102.7	1.0	105.0	1.4	101.2	1.7

The proposed product is a (b) (4) soft gelatin capsule with a delayed release (b) (4) are the critical parameters for dissolution performance of the product. The Applicant's selection of these parameters for testing and demonstrating the discriminating ability of the proposed dissolution method is reasonable. The Applicant's provided dissolution data demonstrate that the proposed dissolution method can discriminate between products with meaningful variations in terms of the (b) (4)

Dissolution profile data for the pivotal clinical (bioequivalence; BE) study batch and the registration batches:

Table 8: Dissolution profile of Pivotal Bioequivalence Study (BLS-11-104) Batch (14700847MA)

Dissolution Results (Percent Dissolved)								LOT:		14700847MA (1 capsule equivalent)					
Total Time	Time Point	Capsule Number												Avg. (T)	%RSD
(min)	(min)	1	2	3	4	5	6	7	8	9	10	11	12		
60	60	(b) (4)												2	14.7
120	120													2	8.3
135	15													3	8.9
150	30													10	16.6
165	45													33	22.6
180	60													69	22.5
210	90													99	2.8
240	120													101	2.5

Table 9: Dissolution profiles of Registration Batches (147000841M, 147000847M, 147000852M)

Stage	Time (min)	95 mg Strengths		
		Lot # 147000841M	Lot # 147000847M	Lot # 147000852M
Acid	60	1	0	1
	120	2	0	1
Buffer	15	3	1	5
	30	7	10	11
	45	40	31	32
	60	70	75	80
	90	99	100	110
	120	99	101	111

As shown in Tables 8 and 9 above, the BE and registration batches of the proposed product remained essentially intact at 2 hours in the acid stage, as reflected by the nearly zero drug release. However, the dissolution data for the clinical and registration batches showed highly variable dissolution in the buffer medium, especially at 30 min (RSD of 16.6%), 45 min (RSD of 22.6%) and 60 min (RSD of 22.5%). It was not made clear by the Applicant whether the variability in the dissolution is due to the product itself (e.g., variability in the (b) (4)) or the dissolution

methodology (e.g., pH of the dissolution medium, sampling technique, etc.). A Biopharmaceutics IR comment was conveyed to the Applicant (dated 09/06/2018[4]) to investigate the source(es) of the observed high variability in dissolution testing and implement appropriate mitigation measures for it.

In response[3], the Applicant stated that the observed high variability in the dissolution in the buffer stage is primarily from the following sources: (b) (4) [redacted]. It was not clear why the variability in the dissolution was not controlled despite these controls in place.

Subsequently, a teleconference was held between the Applicant and the FDA on 09/20/2018 to discuss the high variability in the dissolution despite the controls (b) (4) [redacted] in place, as well as the mitigation strategies. The Applicant explained that the capsules were observed to (b) (4) [redacted] Considering the nature of the proposed product and its dissolution behavior, this Reviewer believes that studying the '(b) (4) [redacted]' earlier in the drug development (during the IND stage), in addition to the dissolution testing, could have provided useful information for understanding the source of variability and for better quality control.

The Applicant justified that the high variability associated with the dissolution data at 30-, 45- and 60-minute time-points is not expected to have significant effect on AUC of the MMF and the product's clinical performance or therapeutic effect. The proposed product dissolves completely in the buffer-stage at the 90-minute time-point. The Applicant's provided pivotal BA/BE study results (BLS-11-104; Table 10) show that the proposed product is bioequivalent to Tecridera® in terms of AUC and Cmax while the Tmax is different by approximately 1.5 hours. The median Tmax (min, max) observed in the pivotal study (Study BLS-11-104) was 4.03 (1.02, 6.01) hours following administration of the proposed dose (2 x 95 mg capsules) to fasted subjects. Dosing with food prolonged the median Tmax to 10.75 (3.00, 24.00) hours (Study BLS-11-106). Tecfidera® can be taken with or without food, per the approved labeling. The median plasma Tmax (min, max) following administration of single 95 mg capsules to fasting healthy subjects was 4.00 (3.85, 29.37) hours (Study BLS-11-108).

[4] GSR Link: Application 210296 - Sequence 0014 - FDA Information Request

Table 10: Summary of Plasma Pharmacokinetics of Plasma MMF Following a Single Oral Dose of BLS-11 190 mg (2 × 95 mg) MMF (Treatment A) and a Single Oral Dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Treatment B)

	Treatment A		Treatment B	
Pharmacokinetic Parameters		**n**		**n**
AUC0-t (ng*hr/mL)	AM: 3051 (26.3%) GM: 2952 (26.4%) 1578, (3025,5894)	49	AM: 3145 (25.3%) GM: 3051 (25.0%) 1888, (3077,5679)	49
AUC0-inf (ng*hr/mL)	AM: 3081 (26.0%) GM: 2984 (25.9%) 1615, (3046,5916)	49	AM: 3203 (24.3%) GM: 3116 (23.9%) 1988, (3136,5707)	48
AUC%extrap (%)	1.29 ± 0.27	49	1.27 ± 0.35	48
Cmax (ng/mL)	AM: 1860 (32.5%) GM: 1760 (34.8%) 524, (1810,4060)	49	AM: 1770 (32.7%) GM: 1680 (33.8%) 763, (1650,3500)	49
tmax (hr)	4.03 (1.02, 6.01)	49	2.50 (1.01, 5.04)	49
Kel (1/hr)	1.2940 ± 0.2747	49	1.2722 ± 0.3488	48
t½ (hr)	0.566 ± 0.154	49	0.591 ± 0.185	48

Treatment A: A single oral dose of BLS-11 190 mg (2 × 95 mg) MMF
Treatment B: A single oral dose of Tecfidera® 240 mg (1 × 240 mg) DMF
AUC and Cmax values are presented as arithmetic mean (CV%), Geom Mean (Geom CV%), and median (min, max).
tmax values are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD)
AM = Arithmetic mean; GM = Geometric mean
Source: Tables 14.2.1.3 and 14.2.1.4
Program: /CA20782/sas_prg/pksas/intext-pk-tables.sas 24MAY2017 9:28

This Reviewer acknowledges the Applicant's justification for the observed variability and determines that the proposed dissolution method (described in Table 5) is adequate for quality control of the proposed delayed-release product, based on the provided information/data. Meanwhile, this Reviewer believes that appropriately selected dissolution acceptance criteria with an additional time-point at the 60 minutes is important from a drug product quality control standpoint (see "**Dissolution Acceptance Criteria**" section).

Dissolution Acceptance Criteria

Considering the target release profile having minimal drug release in the acidic environment while achieving complete release in buffer (b) (4)) environment, the Applicant proposed the following dissolution acceptance criteria for the proposed product at batch release and during stability testing:

Acid Stage: Note more that (NMT) (b) (4)% in 120 minutes

Buffer Stage: Not less than (NLT) (b) (4)% (Q) in 90 minutes

The Applicant's proposed dissolution acceptance criterion for the acid stage is reasonable. The Applicant's proposed dissolution acceptance criterion for the buffer stage is not considered as appropriate by this Reviewer based on the provided dissolution data with high variability during the first hour in the buffers stage. Consequently, this Reviewer recommended the following dissolution acceptance criteria to the Applicant during the T-Con on 09/20/2018 and obtained the Applicant's agreement:

Acid Stage: Note more that (NMT) (b) (4)% in 120 minutes

Buffer Stage: Not less than (NLT) (b) (4)% in 60 minutes, and

NLT (b) (4)%(Q) in 90 minutes

In an IR Amendment dated 09/26/2018, the Applicant revised the dissolution acceptance criteria as per the FDA recommendation. As per the provided data, the proposed product meets the FDA recommended dissolution acceptance criteria during the stability testing period of 6 months at accelerated and 12 months at room-temperature/long-term and intermediate study conditions.

5. IN-VITRO ALCOHOL-INDUCED DOSE DUMPING

The Applicant submitted in-vitro dissolution results (up to 2 hours only) for the alcohol-induced dose-dumping potential with alcohol concentrations (5%, 10% 20% and 40% v/v) in 0.1N HCl medium for the proposed product (see ***Appendix 5***). The provided data indicate that ethanol at 5-20% v/v has no effect on the dissolution of the proposed product in 0.1N HCl for 2 hours and the product remains undissolved during this period, and ethanol at 40% v/v concentration leads to total 3% dissolution of the proposed product in 0.1 N HCl at 2 hours. The Applicant did not propose any relevant labeling language with respect to the results of the in-vitro testing. The provided dissolution data indicate that ethanol is not expected to have a significant effect on the release of the proposed product in gastric/acidic environment. The potential impact of alcohol on the drug release beyond 2 hours is unknown due to the lack of study. Restriction pertaining to the alcohol consumption is not described or recommended in the approved labeling of LD Tecfidera® or proposed for BAFIERTAM™. In view of the much faster drug release of the LD Tecfidera® after 2 hours in the buffer stage, as reflected by the steeper dissolution profile, reaching ≥85% within 10 minutes (Figure 2), as well as the totality of information related to dosing, PK property, and disease, this Reviewer believes that any potential increases in drug release in vitro from the BAFIERTAM™ after 2 hours ((b) (4)) in the presence of alcohol will unlikely result in clinical concern for safety or efficacy.

6. FORMULATION BRIDGING

In-vitro and/or in-vivo bridging studies are not needed for the following reasons:

- There were no changes in the composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches.
- There was no change in the manufacturing site for the proposed product. Clinical and exhibit batches were manufactured at the same site as the proposed site for the commercial batches.
- There were no major changes in the manufacturing process in the scale-up.

According to Dr. Jagan Parepally, Clinical Pharmacology Reviewer from the Office of Clinical Pharmacology, results of the pivotal BA/BE study to bridge the proposed drug product to LD are acceptable.

7. BIOWAIVER REQUEST

Only one strength (95 mg capsules) is proposed under the current NDA and therefore no biowaiver request is submitted or is necessary.

8. LIST OF DEFICIENCIES

None

Appendix 1

Table: Composition of capsule fill and shell for Monomethyl Fumarate Delayed Release Capsules/95 mg

Capsule Fill Formulation			
Component	**Function**	**Amount per capsule (mg)**	**Quality Standard**
Monomethyl Fumarate	Active Ingredient	95.0	Specifications See 3.2.S.4.1
(b) (4)		(b) (4)	National Formulary (NF)
			United States Pharmacopeia (USP)
			USP
Lactic Acid		(b) (4)	USP
Theoretical Total Fill Weight			
Capsule Shell Formulation			
Component	**Function**	**Amount per capsule (mg)[1]**	**Quality Standard**
Gelatin, (b) (4)		(b) (4)	NF
(b) (4) -Sorbitol and Sorbitans Solution			NF, European Pharmacopeia (EP)
			(b) (4)
Titanium Dioxide		(b) (4)	USP
			(b) (4)

Table: Composition of delayed release coating for Monomethyl Fumarate Delayed Release Capsules/95 mg

(b) (4)

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Appendix 5

Dissolution of the proposed product in 0.1N HCl with different concentrations of ethanol

Figure 1: 0% versus 5% alcoholic 0.1N HCl

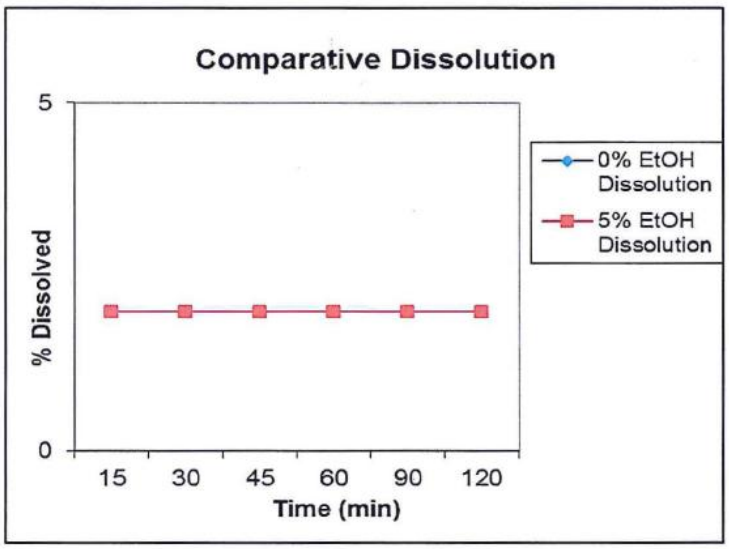


Figure 2: 0% versus 10% alcoholic 0.1N HCl

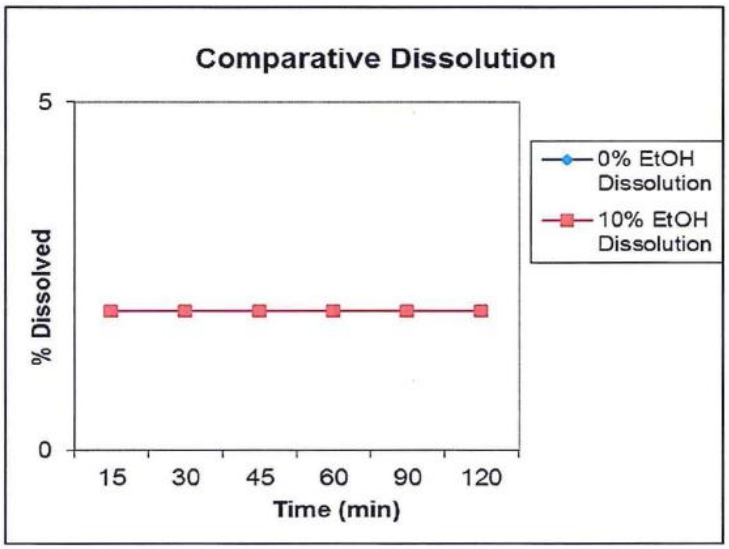


Figure 3: 0% versus 20% alcoholic 0.1N HCl

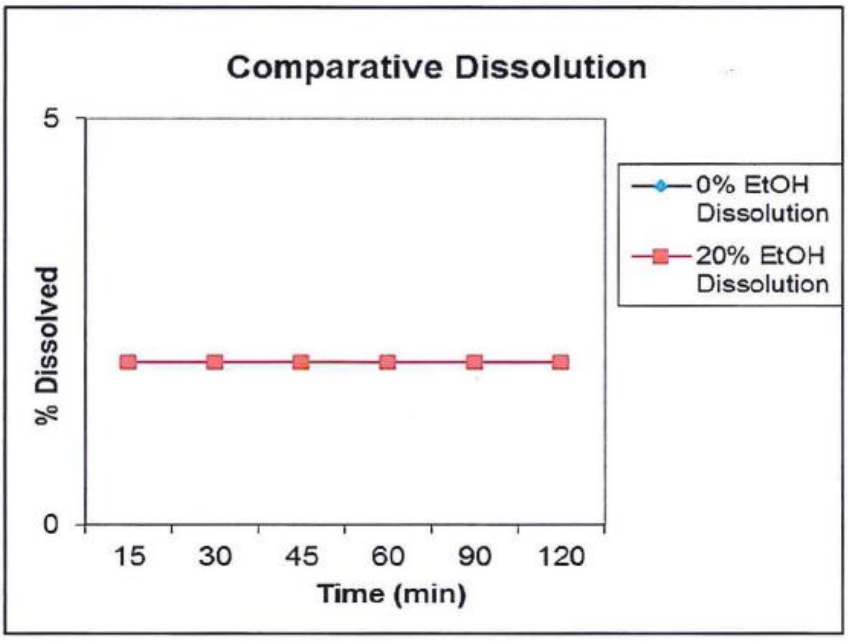
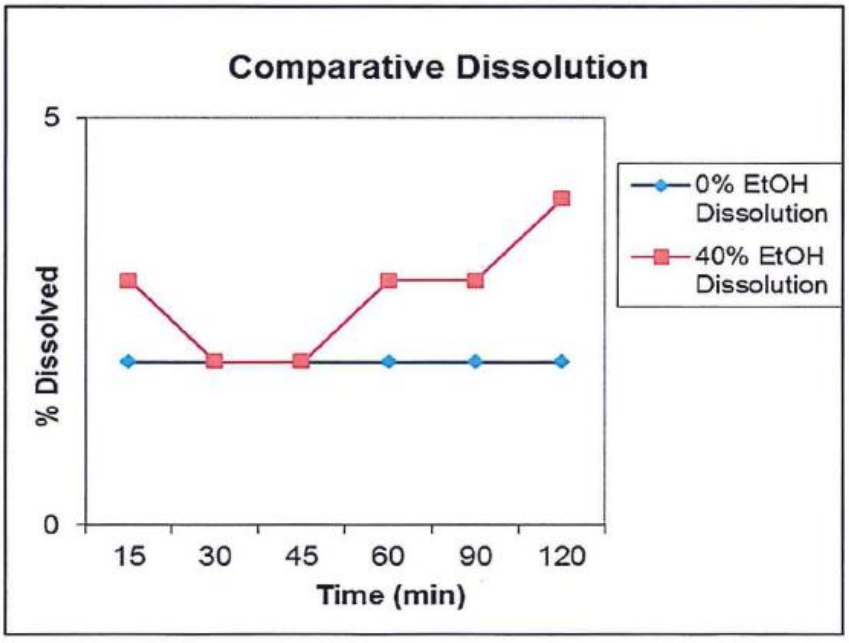


Figure 4: 0% versus 40% alcoholic 0.1N HCl



Kaushalkumar Dave

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