CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

CHEMISTRY REVIEW(S)

TABLE of CONTENTS

Recommendation: Approval

NDA 208603
Review #1

Drug Name/Dosage Form	**ARYMO ER(morphine sulfate)/Extended Release Tablet**
Strength	**15 mg, 30 mg, 60 mg**
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	**Egalet US Inc.**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*12/14/15*	*OPQ*
Amendment	*3/22/16*	*OPQ*
Amendment	*5/3/16*	*OPQ*
Amendment	*5/20/16*	*OPQ*
Amendment	*5/23/16*	*OPQ*
Amendment	*5/24/16*	*OPQ*
Amendment	*5/27/16*	*OPQ*
Amendment	*6/13/16*	*OPQ*
Amendment	*7/1/16*	*OPQ*
Amendment	*7/7/16*	*OPQ*
Amendment	*7/8/16*	*OPQ*
Amendment	*7/15/16*	*OPQ*
Amendment	*7/20/16*	*OPQ*
Amendment	*7/26/16*	*OPQ*
Amendment	*8/10/16*	*OPQ*
Amendment	*8/18/16*	*OPQ*
Amendment	*8/30/16*	*OPQ*
Amendment	*9/1/16*	*OPQ*
Amendment	*9/2/16*	*OPQ*
Amendment	*9/8/16*	*OPQ*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh/Donna Christner	OPQ/ONDP/DNDPAPI/BII
Drug Product	Chris Hough/Julia Pinto	OPQ/ONDP/DNDPII/BIV
Process	Haitao Li/Pei-I Chu	OPQ/OPF/DPAII/BVI
Microbiology	Haitao Li/Pei-I Chu	OPQ/OPF/DPAII/BVI
Facility	Frank Wackes/Derek Smith	OPQ/OPF/DIA/BII
Biopharmaceutics	An-Chi (Angela) Lu/Haritha Mandula	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)	-	
ORA Lead	Paul Purdue	
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	Adequate	N/A	Adequate information in NDA
	Type IV			Adequate		Adequate information in NDA
	Type III			Adequate		Adequate information in NDA
	Type III			Adequate		Adequate information in NDA
	Type II			Adequate	9/21/16	
	Type III			Adequate		Adequate information in NDA
	Type III			Adequate		Adequate information in NDA
	Type III			Adequate.		Adequate information in NDA
	Type III			Adequate		Adequate information in NDA
	Type III			Adequate		Adequate information in NDA
	Type IV			Adequate		Adequate information in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117317	
NDA	019516	RLD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

Recommendations and Conclusion on Approvability

Based on the recommendations from the following disciplines, Drug Substance, Process, Microbiology, Biopharmaceutics, Drug Product, and the Office of Compliance, CMC recommends the approval of ARYMO ER (morphine sulfate) 15 mg, 30 mg, and 60 mg tablets.

Summary of Quality Assessments

Product Overview

The applicant has developed an extended-release, oral morphine formulation indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. ARYMO ER was designed using Egalet's Guardian™ Technology, which utilizes a polymer matrix tablet technology involving an injection molding process. The tablets possess controlled-release properties as well as physical and chemical features that may resist some common methods of manipulation. Guardian™ Technology is designed to make the tablets harder than typical tablets (>400 N) which in theory would make it more resistant to particle size reduction and therefore more challenging to extract morphine sulfate. In addition, the technology results in a viscous hydrogel on contact with aqueous media, making syringeability more challenging. The majority of the physical manipulation attempts on ARYMO ER tablets resulted in particle sizes > 500 microns. Among the manually operated tools, the knife appears to be the most efficient tool in terms of producing particles less than 1,000 µm, which was not possible with the spoon, mortar and pestle, pill crusher, and hammer. Household electrical tools such as spice grinder and coffee grinder appear to be moderately effective for particle size reduction, when operated intermittently to prevent overheating and damage of the equipment components. The gelling nature of the formulation in aqueous media appears to restrict morphine extraction even when significant effort was expended for particle size reduction. Additional information can be found about the in vitro evaluation of category 1 studies in the CMC review.

Swelling in vitro experiments were conducted on the 15 mg and 60 mg tablets. The tablets were submerged in 1600 mL of liquid media where they were fully submerged. When the tablets were submerged for 30 seconds, they swelled to approximately 105% of the tablets weight in the liquid media. During the first three minutes, the outer coating of the tablet started to dissolve and swelled to 114-117%. Between 3.75-4.75 hours, the range of the swelling was observed to be 249-274%.

Morphine sulfate is a white to off-white crystalline solid that is very soluble in hot water, soluble in glycerin, sparingly soluble in anhydrous ethanol. The aqueous solubility of

morphine sulfate depends on pH, but is mostly ionized at physiological pH with highest solubility at around pH 5.6- 5.7 and decreases gradually as pH of the media increases to 8.0. (b) (4) Morphine sulfate is non-hygroscopic. Morphine sulfate has a retest period of (b) (4) months. A letter of authorization was provided by the applicant to access DMF# (b) (4). The DMF is adequate for this application.

ARYMO ER are oral tablets that consist of a matrix containing the active substance, morphine sulfate, along with Polyethylene Oxide 400,000 ((b) (4)) and butylated hydroxytoluene. ARYMO ER tablets are available in three strengths: 15 mg, 30 mg and 60 mg. Each strength is coated with a color to differentiate between the strengths:

ARYMO ER tablets, 15 mg are blue film coated, capsule shaped tablets debossed with "EGLT 15".
ARYMO ER tablets, 30 mg are light purple film coated, capsule shaped tablets debossed with "EGLT 30".
ARYMO ER tablets, 60 mg are light orange film coated, capsule shaped tablets debossed with "EGLT 60".

Based on the stability data provided, an expiry of 24-months will be granted using the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature]".
All strengths of ARYMO ER tablets are packaged in 200 cc high- density polyethylene (HDPE) bottles (b) (4) Each bottle contains two oxygen absorber canisters and has a (b) (4) closure with (b) (4) seal.

A. Final Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	H	-	Acceptable	No alcohol dose dumping was observed based on in vitro data.

B. *Risk ranking applies to product attribute/CQA
C. **For example, post marketing commitment, knowledge management post approval, etc.
D. Primary Quality Review

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
Application Technical Lead
ONDP/DIVII/Branch IV

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

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Reviewer's Assessment: NA

Lifecycle Management Considerations: NA

List of Deficiencies: None

The applicant provided adequate information to ensure the identity, strength, purity and integrity of drug substance (API). From a perspective of Chemistry, Manufacturing and Controls - API, the NDA is recommended for approval.

Primary Drug Substance Reviewer Name and Date:

Debasis Ghosh, Ph.D.

Sept 02, 2016

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

I concur with Dr. Ghosh's assessment that the information on the API supports approval of the NDA.

Donna F. Christner, Ph.D.

02-Sep-2016

Donna Christner

Digitally signed by Donna Christner
Date: 9/07/2016 08:40:53AM
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Debasis Ghosh

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Date: 9/06/2016 10:50:55AM
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CHAPTER II: Drug Product

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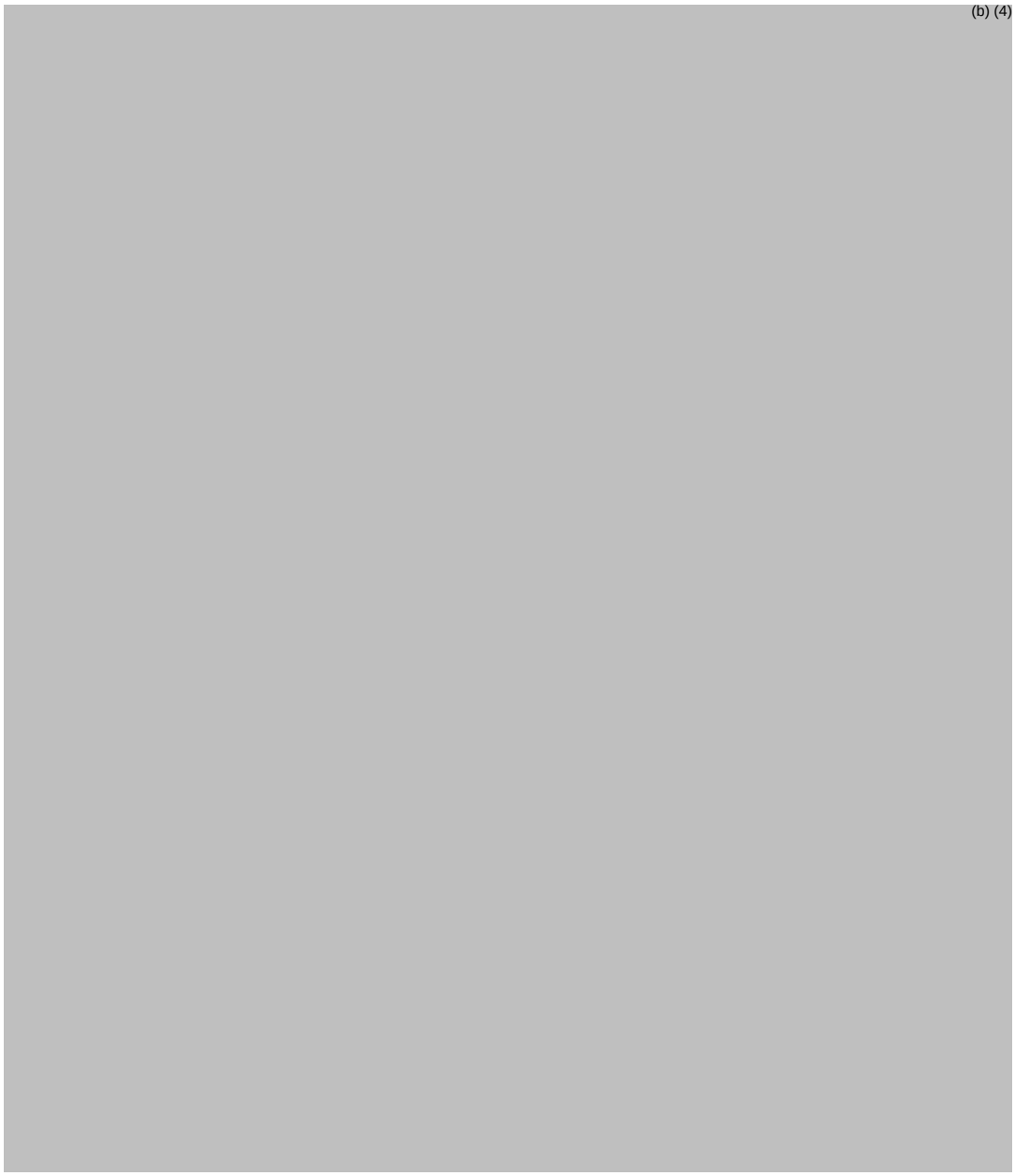

Reviewer's Evaluation: the labels and labelling are acceptable.

B. **Environmental Assessment:**

Egalet claims a categorical exclusion from the environmental assessment for the following reasons:
The approval of Arymo ER (morphine) extended release tablets will not increase the amount of active moiety into the environment because it will replace the current formulation of oral morphine sulfate.
No novel excipient will be released into the environment as a result of this approval.
To the best of Egalet's knowledge no extraordinary circumstances exist that would significantly affect the quality of the environment.

I have reviewed this new drug application and recommend its Approval.

Christopher J. Hough, Ph.D. Primary Reviewer

Julia Pinto, Ph.D. Secondary Reviewer

Julia Pinto

Digitally signed by Julia Pinto
Date: 9/26/2016 07:05:16PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Christopher Hough

Digitally signed by Christopher Hough
Date: 9/27/2016 09:00:17AM
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CMC Review for NDA 208603 – *In Vitro* Abuse-Deterrence studies

(Category 1 Laboratory Manipulation and Extraction Studies)

REVIEW NO.: 1

DATE OF REVIEW: 29-JUL-2016.

PROPRIETARY NAME: ARYMO™ ER

ALTERNATE NAMES / CODES USED IN THE REVIEW: **EG-001**

GENERIC NAME: Morphine Sulfate Extended-Release Tablets

SPONSOR: Egalet US Inc.

DOSAGE STRENGTH(S): 15 mg, 30 mg, and 60 mg.

PRIMARY CMC (DP) / QUALITY REVIEWER: Christopher Hough, Ph. D;

IN VITRO ABUSE-DETERRENT STUDIES REVIEWER:

Venkateswara R. Pavuluri, Ph. D., R. Ph.

QUALITY ASSESSMENT LEAD: Ciby J. Abraham, Ph. D;

BRANCH CHIEF, ONDP Division II, Branch IV: Julia C. Pinto, Ph. D;

Summary Evaluation of Category 1 In Vitro Studies for ARYMO™ ER Tablets

(b) (4)

Following is the summary evaluation of various category 1 laboratory based in vitro manipulations and extraction studies conducted with the to-be-marketed-product of ARYMO ER (EG-001), challenging the physical and chemical features (e.g. hardness, gelling features, burning, extraction and extended-release properties) (b) (4)

1. ARYMO™ ER (EG-001) appears to resist the most common methods of physical manipulations. The planned physical manipulation performed using tablets with and without pre-treatment, i.e. heating and freezing conditions, doesn't appear to change the outcome of the manipulations. Serial physical manipulations performed using multiple modes of size reduction, as suggested by the FDA during type A meeting, doesn't appear to significantly change the particle size distribution.

2. ARYMO™ ER appears to possess physical and chemical features that resist extraction in to small volumes (up to 10 mL) of media, from intact and pre-treated tablets. The physically manipulated tablets also appear to retain gelling properties and resist extractions in small volumes. Combined with the Syringeability and injectability studies performed using water and hypertonic saline, the small volume extraction studies on EG-001 appear to possess abuse-deterrent features that make abuse via injection route difficult."

3. The cumulative percent of morphine extracted from cut and ground tablets in a large volume (200 mL) of commonly available liquids and alcoholic solvents is significantly higher in the first two hours compared to intact tablets. The cumulative percent of morphine released from intact tablets after the first two hours period has decreased with increasing concentration of alcohol in the dissolution media.

4. Simulated smoking tests, to evaluate the likelihood of success of attempts to directly smoke (vaporize) drug from the formulation, appears to be unsuccessful releasing a very low percent of active when compared with the base and salt forms used as comparators.

5. Precipitation and isolation of morphine free base appears to be possible, using complex multi-step physical and chemical manipulations followed by extraction in to low boiling non-ingestible solvents and subsequent evaporation of solvent.

Review of Category 1 Laboratory based *in- vitro* studies

Introduction

ARYMO™ ER (morphine sulfate extended-release) tablets, hereafter referred as EG-001, are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. EG-001 is proposed to be marketed in three dosage strengths, i.e. 15 mg, 30 mg and 60 mg, differentiated mainly by color of the film coated tablets. (b) (4) made up of a matrix containing morphine sulfate, Polyethylene Oxide 400,000 (PEO) as release controlling agent, and butylated hydroxytoluene (BHT) (b) (4), and are manufactured by using an injection molding process. According to the sponsor, EG-001 was developed based on proprietary Guardian™ Technology that differentiates it from reference listed drug MS Contin® by its reduced potential for physical and/or chemical manipulations by patients and abusers.

Overview of *in vitro* Abuse-deterrent studies conducted by Sponsor

The purpose of this review is to evaluate the ease with which the potentially abuse-deterrent properties of EG-001 can be defeated or compromised against the backdrop of the physical and chemical properties of the components and drug products combined with known and potential routes of abuse for opioid extended-release products in general and morphine sulfate in particular. The potential methods of manipulations and routes of abuse for opioid include extraction into aqueous solvents intravenous injection; chewing, crushing, extraction into aqueous solvents for oral or rectal administration; snorting and inhalational via smoking. The discussion and interpretation of experimental data from category 1 studies was presented by sponsor under various subheadings, as follows.

- **Physical Manipulations and Particle size measurement**
  - Single step manipulations,
  - Multiple step manipulations using mechanical and /or electrical tools
  - Cutting EG-001 with a knife followed by physical manipulation using a mortar

  - Electrical instrument (a spice grinder), followed by a mechanical tool (a mortar and pestle).
- **Assessing Labor, Effort and Resources Required for Tampering (ALERRT™)**
- **Chemical Manipulation Studies**
  - Large volume Extraction studies: Oral / Rectal administration
  - Small volume extractions: Injectability / Syringeability Study
  - Isolation of the Active: Extraction by non-ingestible solvents and Evaporation of solvent
  - Precipitation of free base
  - Simulated Smoking study
- **Dissolution studies:**
  - in presence of Alcohol (Dose Dumping)
  - with physically manipulated EG-001

Key physicochemical Characteristics of Drug Substance, Polyethylene Oxide and Drug Product:

Morphine sulfate (MS): Morphine sulfate is very soluble in hot water, freely soluble in water, freely (and slowly) soluble in glycerin, sparingly soluble in alcohol (Source: USP/NF accessed online Dt. 3/09/2016). Aqueous solubility of MS depends on pH, but is mostly ionized at physiological pH with highest solubility at around pH 5.6- 5.7 and decreases gradually as pH of the media increases to 8.0. Except for changes in crystal bound water, MS is non-hygroscopic, (b) (4)

Polyethylene Oxide 400,000: Polyethylene oxide (PEO), the functional excipient, is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. PEO is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols (source: Handbook of Pharmaceutical Excipients, eBook accessed online Dt. 3/9/2016). (b) (4)

Drug Product: EG-001 proposed to be marketed as 15, 30, and 60 mg extended release tablets for oral administration. According to the sponsor, to-be-marketed composition of EG-001was manufactured using injection molding process resulting in tablets with hardness > 400 N that resisted abuse while releasing the drug over an extended period of time. (b) (4) as noted during pharmaceutical development.

Start of sponsor material:

Table 1: Composition of EG-001 (morphine sulfate) Extended-Release Tablets

Component	15 mg Amount per Tablet mg (%)	30 mg Amount per Tablet mg (%)	60 mg Amount per Tablet mg (%)	Function	Reference to Quality Standards
Morphine Sulfate	15.00 (1.98)	30.00 (3.94)	60.00 (7.83)	Drug substance	USP
Polyethylene Oxide 400,000 (b) (4) (b) (4)				Release controlling; Abuse-deterrent properties	USP/NF
Butylated Hydroxytoluene (b) (4)				(b) (4)	USP/NF
					Section 3.2.P.4.1- (b) (4)
					Section 3.2.P.4.1- (b) (4)
					Section 3.2.P.4.1- (b) (4)
					USP
Total	759.21 (100.0)	761.69 (100.0)	766.53 (100.0)	-	- (b) (4)

Table 4 EG-001 Batch/Lot Information for Test Articles

Test Article	Batch or Lot Numbers	Formulation
EG-001 15 mg	SB69400201	TBMP
EG-001 30 mg	SB69200201	TBMP
EG-001 60 mg	SB69300101	TBMP
	SB69300201	TBMP
EG-001 100 mg	13-0055-067	DPFF
	SB69500301	DPFF
	SB69500201	DPFF
MS CONTIN 60 mg	Lot# WYR61	

End of Sponsor material

Reviewer's Notes:

1. The category 1 *in vitro* experiments were designed and conducted by a third party laboratory, (b) (4) . and the data from these various laboratory assessments was interpreted by external consultants, (b) (4) for Egalet. A document titled "Category 1 Expert Report" was included in the submission under module 3.2. P. 2.
2. The various manipulation and extraction studies were initially conducted using development-product-final-formulation (DPFF) of EG-001and MS Contin® 100 mg. These studies were extended to EG-001 to-be-marketed-product (TBMP) composition

with optimized experimental conditions identified earlier. MS Contin® is an approved morphine sulfate extended release drug product which also served as reference listed drug (RLD).

3. Though all three proposed dosage strengths (15, 30, 60 mg), were used in these premarket studies, 60 mg dose was the focus of the in vitro studies. Some data from initial studies using 100 mg tablets with DPFF was also considered by sponsor for interpretative purposes.
4. The assay method (HPLC-MS/MS) used for morphine sulfate was stated to be qualified to ensure that it was suitable for its purpose. Linearity, limit of quantification (LOQ), recovery, accuracy, carryover and specificity were tested. The parameters tested were reported to cover all solvents and combinations of experimental conditions. The method used for assay of extracted samples appears to be acceptable for the purpose of ADF studies.

Physical Manipulation Studies

Physical manipulations performed initially on PDFF of EG-001 100 mg tablets and MS Contin® 100 mg, using a series of ten household equipment operating on principles of cutting, crushing or grinding. The characteristics of the product obtained by cutting/crushing/grinding were evaluated by photography, measurement of particle size distribution by sieving and image analysis of collected pictures, and determination of the MS content in different sieved fractions. Observations, pictures and times spent on manipulations using each of the tools, were recorded for each replicate. The information obtained from these initial experiments, on optimal experimental conditions and duration of operation for the equipment, was used in testing TBMP of EG-001 tablets using the most effective tools and optimal conditions and also repeated using pre-treated EG-001. The three pre-treatment conditions employed are heating in oven (100°C, 30 minutes), microwave (1200 W, 3 minutes), and storing in freezer (-20°C, 1 hour) prior to manipulation.

Single step manipulations: Hardness of EG-001 was reported to be above 400 N and thus the efforts to pulverize EG-001 using most common household tools were ineffective, whereas simple kitchen tools produced a large fraction of snortable powder (<500 microns) of MS Contin®. Physically manipulation of EG-001 was only partially successful and required more time and effort through the use of knife, razor blade, hammer, and electrical tools such as coffee grinder or spice grinder. The most successful procedure for particle reduction of the EG-001 tablet was with a knife (26.7% produced particles was < 1000 μm), followed by spice grinder (14.7% particles < 1000 μm). The pre-treatment of EG-001 prior to manipulation didn't significantly alter the effort required for physical manipulations or particle size distribution of manipulated products. A number of instrument failures (breakages) were reported during the physical manipulation of EG-001.

Overall, no effective methods were established to pulverize EG-001 tablets, compared to the simple kitchen tools such as spoons and a mortar and pestle that produced a large fraction of fines (<500 microns) of MS Contin®. According to sponsor, the (b) (4) density (b) (4)) of the EG-001 tablet and (b) (4) porosity (based on photographs) resulted in its resistance to particle size reduction.

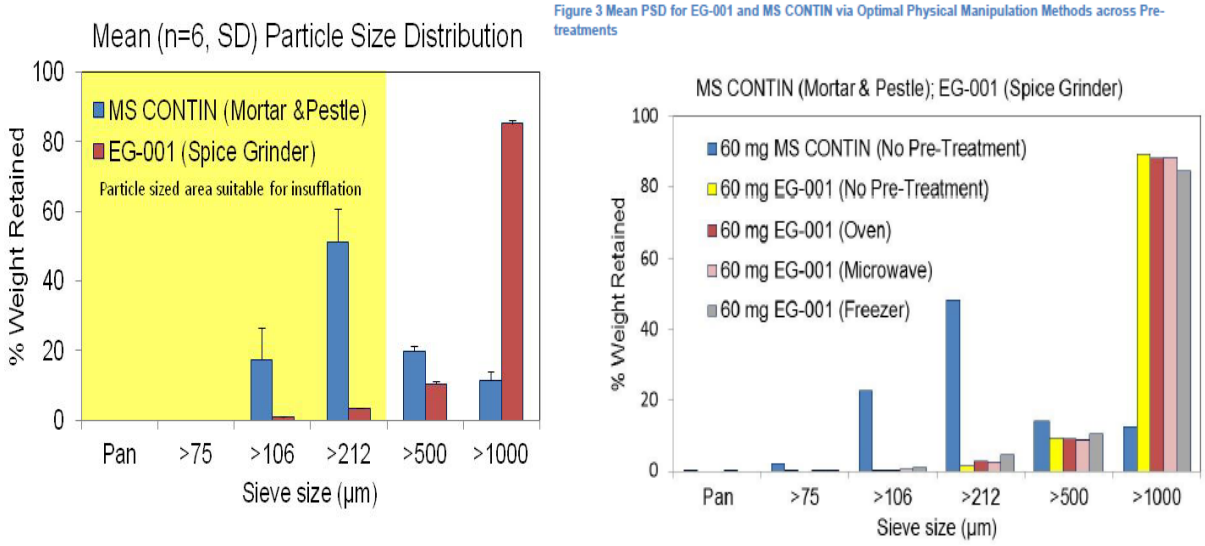
Start of Sponsor material

Table 13: Results from Physical Manipulation Testing of EG-001 versus MS Contin Using Common Household Tools

Tool	% w/w Particles <1000 Microns (EG-001)	EG-001 60 mg Outcome	% w/w Particles <1000 Microns (MS Contin)	MS Contin 100 mg Outcome
Spoons	0%	Unsuccessful[1]	78.5%	Successful[2]
Mortar and pestle	0%	Unsuccessful	77.6%	Successful
Hammer	0%	Unsuccessful	30.2%	Partially successful[3]
Foot file	4.1%	Unsuccessful	70.4%	Successful
Food grater	1.0%	Unsuccessful	89.3%	Successful
Knife	10.3%	Partially successful	79.0%	Successful
Razor blade	0.3%	Unsuccessful	96.5%	Successful
Pill crusher	0%	Unsuccessful	82.7%	Successful
Coffee grinder	6.8%	Partially successful	78.2%	Successful
Spice grinder	5.8%	Partially successful	66.7%	Successful

[1] Unsuccessful = Less than 5% of particles <1000 microns
[2] Successful = More than 50% of particles <1000 microns
[3] Partially successful = Between 5%-50% particles <1000 microns

Figure 3 Mean PSD for EG-001 and MS CONTIN via Optimal Physical Manipulation Methods across Pre-treatments



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Multi-step manipulations: Based on Agency's recommendation to confirm whether further particle size reduction could be achieved by serial, multi-step manipulation using to different particle size reduction methods, following two multi-step manipulation procedures investigated:

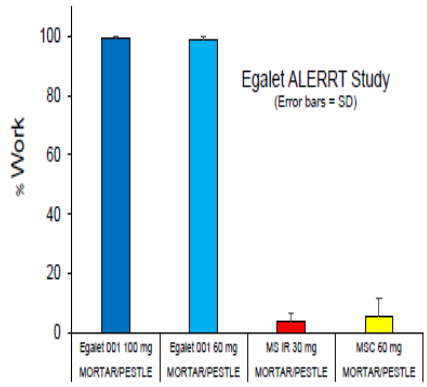
- Cutting EG-001 with a knife followed by physical manipulation using a mortar and pestle.
- Physical manipulation using an electrical instrument (a spice grinder), and followed by a mechanical tool (a mortar and pestle).

According to the sponsor, these serial manipulations were not effective in reducing the particle size any further upon subsequent grinding with mortar and pestle.

Assessing Labor, Effort and Resources Required for Tampering (ALERRT): The amount of time and effort required to manipulate EG-001 using various household tools was measured and expressed on a visual analog scale (VAS). ALERRT scales were used by sponsor to capture an additional dimension to Category 1 abuse-deterrent testing that was not otherwise reflected in the output measures from physical and chemical manipulation procedures. According to the sponsor, the 'input' as measured by ALERRT, includes speed with which drugs of abusive potential can be manipulated, ease of manipulation, and the yield that can be obtained from these efforts, and is an important real world aspect of abuse-deterrence. A single unit of EG-001 60 mg, 100 mg, MS Contin® 60 mg, or a MS 30 mg IR tablets were manipulated by individual trained technicians (n=4) using a standard procedure.

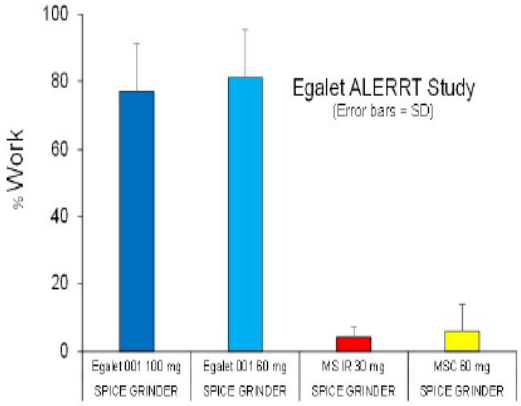
Start of sponsor material:

Figure 24: Level of Effort for EG-001, MS Contin, and a Morphine Sulfate Immediate-Release Formulation (Mortar and Pestle)



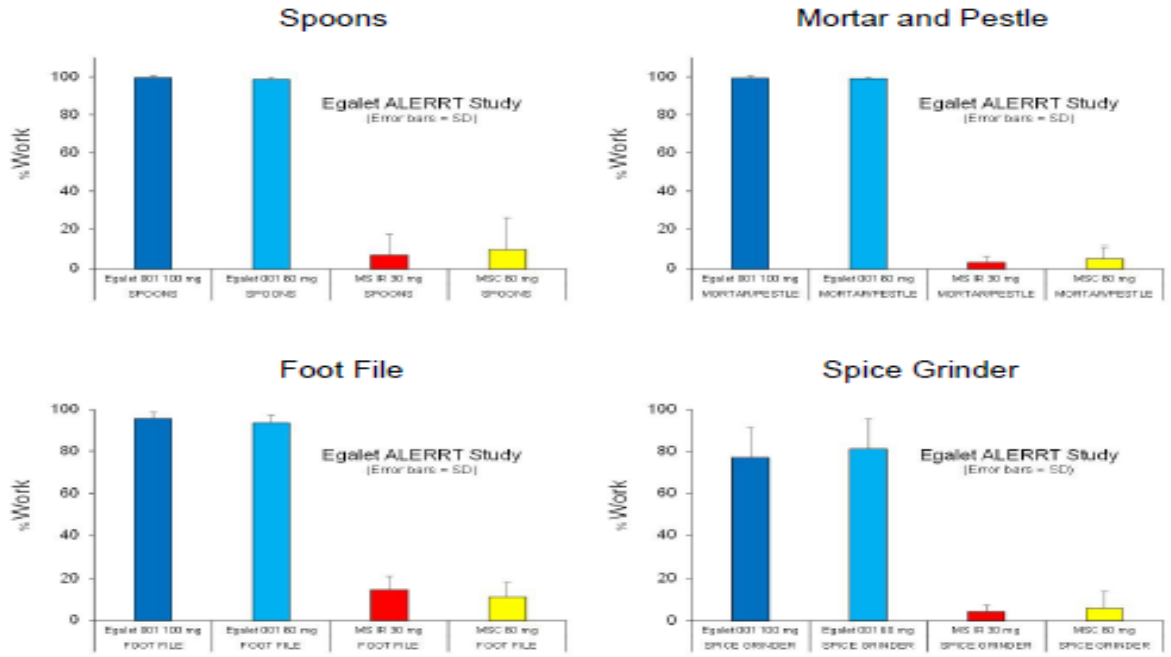
Egalet 001 = EG-001 (Blue); MS IR = Morphine Sulfate Immediate-Release (Red); MSC = MS Contin (Yellow)

Figure 25: Level of Effort for EG-001, MS Contin, and a Morphine Sulfate Immediate-Release Formulation (Spice Grinder)



Egalet 001 = EG-001 (Blue); MS IR = Morphine Sulfate Immediate Release (Red); MSC = MS Contin (Yellow)

Figure 5 Mean %Work for EG-001 100 mg, EG-001 60 mg, MS IR 30 mg, and MS CONTIN 60 mg (Ratings on a 100 mm VAS with 0 Representing Low Difficulty and 100 Representing Extreme Difficulty)



End of Sponsor Material

***Reviewer Evaluation of Physical Manipulations*: Adequate with the following comments.**

Majority of the physical manipulation attempts on EG-001 resulted in particle sizes > 500 microns. Among the manually operated tools, the knife appears to be the most efficient tool in terms of producing particles that pass the 1,000 µm, which was not possible with the spoon, mortar and pestle, pill crusher, and hammer. Household electrical tools such as spice grinder and coffee grinder appear to be moderately effective for particle size reduction, when operated intermittently to prevent overheating and damage of the equipment components.

Though ALERRT^{SM} system was used by sponsor, to measure the significant effort required for manipulation of EG-001 compared to MS Contin®, the sum of the measured values were presented as "work" on visual analog scales ranging from '0' being the easiest and '10 being the most difficult. The nature of data collection and observations made are subject to variations depending on the individuals performing the physical manipulations and are thus not amenable for standardization or validation across the range of tools used in a meaningful way. Since tablet was stated as the main premise for the abuse deterrence features of the drug product, during the review process sponsor was advised to provide a release and stability specification for minimum tablet hardness as a quality attribute of the drug product and the sponsor complied with the advice by including the test for hardness.

The rapid gelling properties of the physically manipulated formulation in aqueous media are an additional feature that deters abuse by the intranasal route. While a cumulative 77.6% of ground

MS Contin® (with mortar and pestle) had particle size diameters <1000 microns, only 5.8% of physically manipulated EG-001 with spice grinder had particle size diameters <1000 microns. Tablet size, density, hardness and resistance to particle size reduction combined with extended-release and gelling properties polyethylene oxide appear to impede abuse by various routes of administration (crushing, physical manipulation, and extraction).

Swelling Study: In response to request for information, sent with the Agency's filing communication Dt. 24-FEB-2016, a tablet swelling study was conducted using water and simulated gastric fluid (under fasting conditions) as the media and the results were reported.

Text of request for Information (IR): *"Provide data from a swelling study in water and gastric fluid demonstrating the size of the tablet over time. Provide data that includes photos and dimensions of the tablet as it swells in the fluid."*

Procedure: Initial dimensions of tablets (15 mg or 60 mg dose strength) were recorded using a caliper and placed on a fixed glass base using a small piece of adhesive tape in a transparent vessel (2L) A selected liquid media (1600 mL) was added to the vessel, covering EG-001 tablet completely. Pictures taken at relevant time points after exposing the tablet to the defined liquid media, until maximum swelling and subsequent decline was observed. Tablet dimensions were measured (length, height, width and calculated volume) for the pictures taken over time. Data for all three dimensions (i.e., length, height, and width) was used to calculate average values, for each tablet strength, liquid media and time point. The averaged length (l), height (h), and width (w) of the tablet for each strength/liquid media at each defined time point was used to calculate an approximate tablet volume (V)/time point using the calculation: $VT = l \times h \times w$.

Swelling, defined as the relative volume change (in percent) of the tablet for each strength and liquid media for each time point (T = x) relative to the average volume calculated at T = 0. Swelling was calculated according to the following formula

$$Swelling = \frac{Volume\ at\ T = x}{Volume\ at\ T = 0} \cdot 100\%$$

Maximum Swelling (S_{MAX}) observed and Time to S_{MAX} was recorded, for each of the tablet strengths. Three replicates of each strength were tested in each media, and experiments were conducted over an 8 hour time period.

Results: Reporting of the swelling was focused on two time point periods, i.e. T = 30 seconds to 3 min and T_{MAX}, time to maximum swelling of the tablet. At T = 30 seconds, all tablets swelled to approximately 105%, independent of the liquid media. During the first three minutes, the outer coat of the tablet started to dissolve and diffuse away from the tablet. Swelling during the first three minutes was linear and reached 114-117%. T_{MAX} was reached between T = 3.75-4.75 hours and the range of S_{MAX} observed was between 249-274%, and no correlation was observed for

S_{MAX} between either tablet strength or liquid media. The largest length of a tablet observed was between 22.9-24.4 mm, the largest width observed was between 11.8-12.8 mm, and the largest height was between 8.1-9.3 mm.

Reviewer Evaluation of swelling study: Acceptable. Based on the test results, EG-001 tablet doesn't swell rapidly in the first three minutes, allowing enough time for the patient to swallow the tablet without difficulty. The limited initial swelling is consistent with the erosion based release of the EG-001 tablets, which is different from diffusion-controlled release tablets. However, with lapse of time following addition of water, the outer coat starts to dissolve and tablet core may become sticky making it difficult to swallow.

Chemical Manipulation Studies

Optimized procedures developed during physical manipulation studies were used for manipulation of to be marketed drug products of EG-001 and MS Contin® for testing their resistance to various chemical manipulations. The procedures developed for EG-001 consist of cutting the tablet into quarters with a knife (which is difficult to do and takes extensive time, effort and physical force), followed by grinding of the quartered pieces in a spice grinder. The initial optimization of experimental conditions for extraction and syringeability studies was conducted with EG-001 (DPFF) and MS CONTIN®. The effects of shaking speed (agitation), filtration (to remove un-dissolved drug particles) and pre-heating were assessed for optimization of extraction efficiencies. A LC/MS/MS method was used for analysis of samples for morphine content, in chemical manipulation studies.

Extractability in Large volume (200 mL)

Extractability of MS (API) from EG-001 from intact and manipulated EG-001 (both cut and ground) was studied to assess whether extraction with a large volume of solvents could result in preparation of solutions containing dissolved morphine, which could be administered by the oral or rectal routes. Extraction studies were conducted on intact and ground EG-01 tablets and MS Contin®, in aqueous media with varying pH and in organic solvents using 200 mL of media at RT and higher temperatures near or below their boiling point, e.g. 60°C for alcohol containing media and 90°C for aqueous media. Up to ~ 70% of MS was extracted from cut EG-001, within one hour in many of the aqueous solvents at 90°C, even though it was claimed that the formulation maintained some extended release properties following manipulation. With few exceptions, the extractability of morphine (MS) from EG-001 was lower in general compared to extractability from MS Contin®. Heated extraction enhanced overall recovery from both formulations at 15 minute time point, with different degrees of efficiency for all tested forms except ground tablets. Extractability from EG-001 was similar or closer to MS Contin® under certain conditions i.e. intact tablets at room temperature (RT) with pH 6 buffer and at 90°C with pH 10 buffer; ground tablets at RT with pH 2 buffer, 50% ethanol and methylene chloride, and at

90°C with pH 4 and pH 8 buffer. Extractability of MS Contin® was lower compared to EG-001 under certain other conditions, i.e. intact tablets at RT with methylene chloride, pH 8 and pH 10 at certain time points; and ground tablets at RT with 95% ethanol at 1 h time point and above, and at 60°C with 20% and 50% ethanol.

Extraction studies using TBMP EG-001 tablets: The extraction studies described above were repeated on TBMP compositions of EG-001 tablets, across all three dosage strengths (15, 30, and 60 mg) in different manipulated forms (intact, cut into 32 pieces, and ground), using two model solvents (pH 2 buffer and 50% ethanol). EG-001 displayed comparable extraction profile across all three doses, where extended release properties of intact tablets were retained to a greater extent in 50% ethanolic solvent at RT. As expected rate of morphine extraction increased with cut and physically manipulated tablets, and was further accelerated at higher temperatures in pH 2 buffer and in presence of alcohol (50%), even though the time to reach maximum extractability of drug varied with particle size and /or solvent used. Loss of morphine observed after initial spike in pH 2 buffer at higher temperature was attributed to morphine's instability in presence of oxygen at high temperatures.

Start of sponsor material

Figure 6 Mean Extraction Data for pH 2 Buffer and 50% Ethanol for EG-001 (RT)

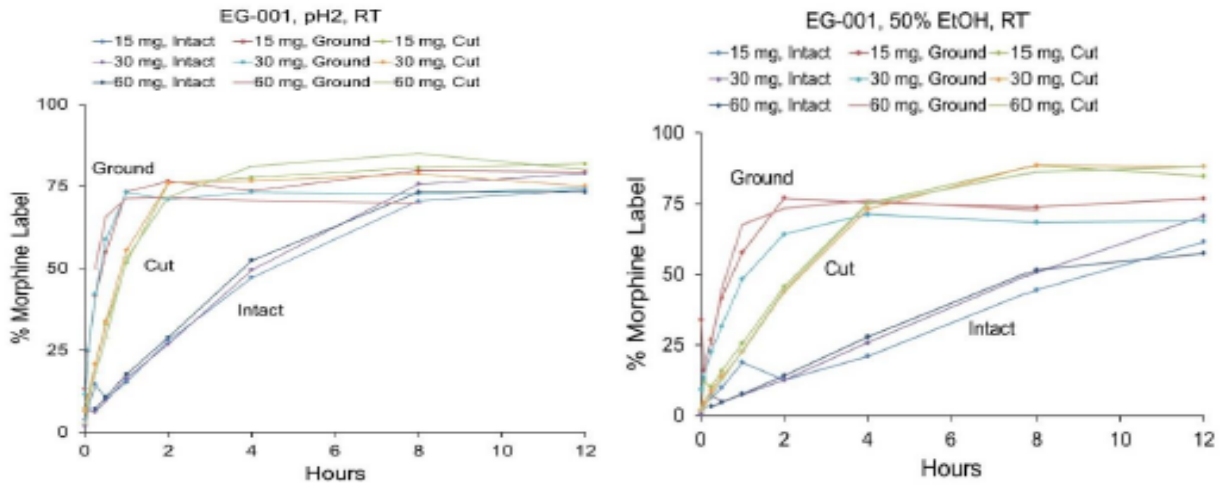
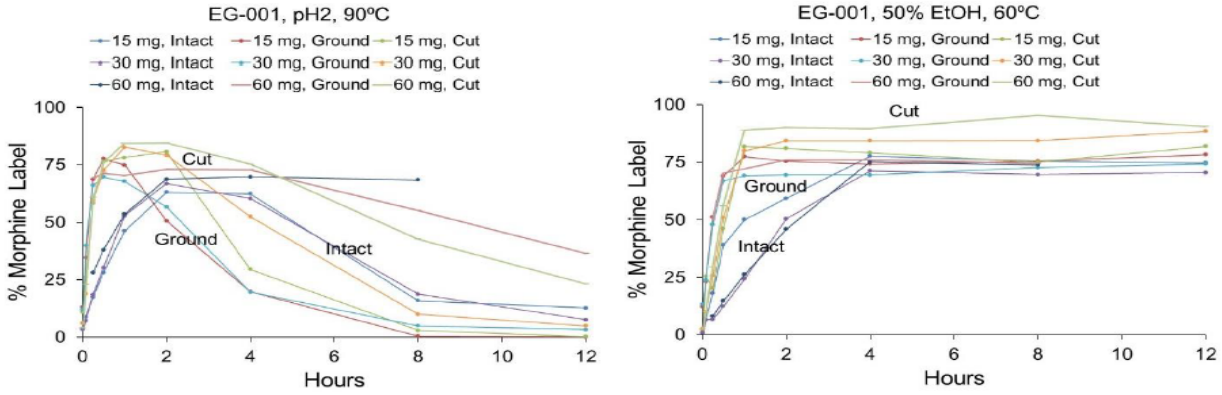


Figure 7 Mean Extraction Data for pH 2 Buffer and 50% Ethanol for EG-001 (Heated Temperature)



End of sponsor material

To evaluate the feasibility of higher percent recovery of MS in larger volumes (200 mL), extractability of EG-001 60 mg tablets, cut in to 32 pieces, was also studied in a variety of solvents with different characteristics (i.e. aqueous, organic, protic, aprotic and acidic/alkaline media) that may be used by a drug abuser. MS was readily extracted, from tablets cut into pieces, in aqueous-based solvents over a wide pH range (1- 10) at RT and reached near maximal recoveries of ~60-70% within two hours. The extractions were further accelerated under heated conditions (90ºC) reaching the plateau within 30 minutes. Ethanol-based aqueous solvents and methylene chloride also were relatively efficient media for morphine extraction, when compared to other pure organic solvents. Extraction with 95% ethanol was less efficient when compared to other ethanol concentrations.

Start of sponsor material

Figure 8 Mean Extraction Data for a Variety of Solvents for Cut EG-001 (RT and 90°C)

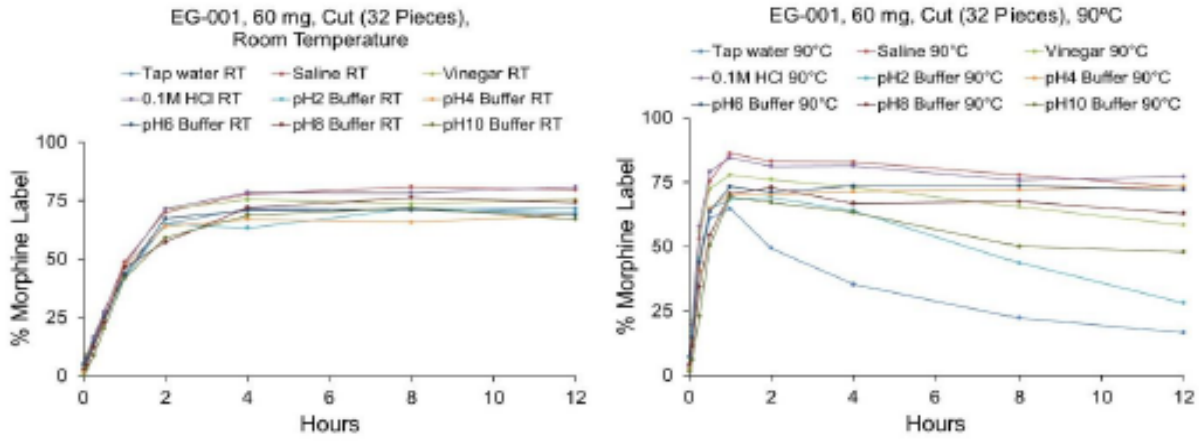
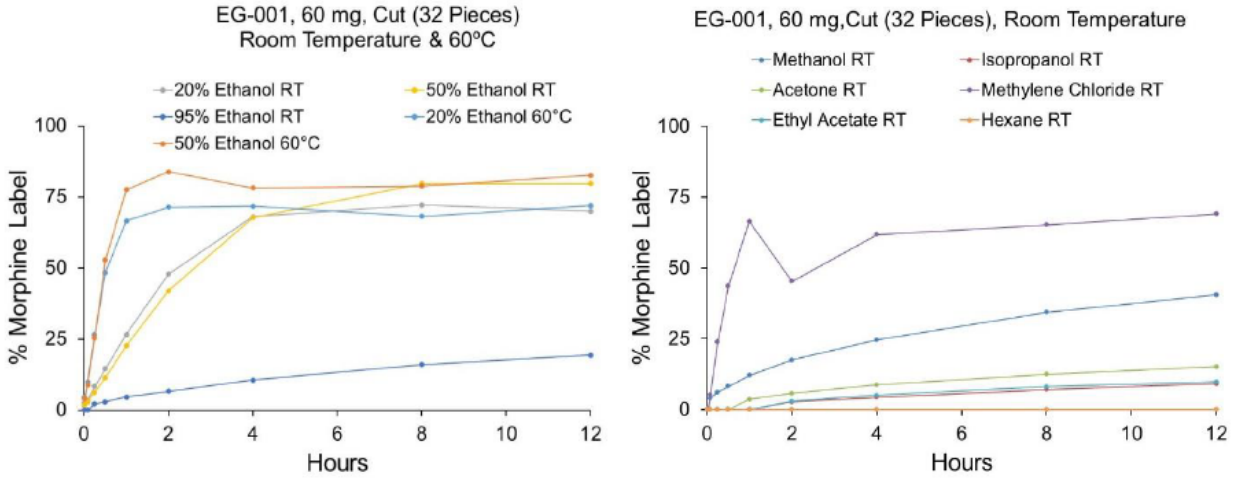


Figure 9 Mean Extraction Data with Different Strengths of Ethanol in Water and with Pure Organic Solvents for Cut EG-001 (RT and 60°C)



End of sponsor material

In response to Agency's requests for information, sponsor provided data on large volume extraction studies with 40 % and 95 % ethanol using intact and manipulated EG-001 tablets, after pretreatment (heating in oven and microwave and Freezing). The amount of MS recovered was ≤30 % at 4hours for intact pretreated tablets when compared to the amounts (~68 %, ~79 % and 84 % for freezing, microwave and oven heated) recovered at 4 hours from manipulated pretreated tablets using 40 % ethanol as the solvent. The percent recoveries of MS upon extraction with 95 % were about 10 -15 % low when compared to 40 % ethanol at 4 hour time point.

Start of sponsor material

Table 4: Extraction (% morphine from 60 mg tablets) in Large Volume (200 ml) Following Pre-Treatment of Intact Tablets (Batch # SB69300201)

Solvent	Time	Pre-Treatments		
		Microwave (% of morphine) Mean (n = 3)	Oven (% of morphine) Mean (n = 3)	Freezer (% of morphine) Mean (n = 3)
40% ethanol	0	0.0	0.0	0.0
	15 minutes	2.2	1.7	2.2
	30 minutes	3.7	2.4	3.8
	1 hour	7.1	4.9	6.7
	4 hours	30.0	19.0	27.9
	24 hours	90.6	94.3	94.2
95% ethanol	0	0.0	0.0	0.0
	15 minutes	1.5	1.5	1.4
	30 minutes	2.0	2.5	1.8
	1 hour	3.4	4.9	3.0
	4 hours	18.4	19.4	17.6
	24 hours	92.6	89.6	89.1

Table 2: Extraction (% morphine from 60 mg tablets) in Large Volume (200 mL) Following Pre-Treatment of Manipulated EG-001 Tablets (Batch # SB69300201)

Solvent	Time	Pre-Treatments		
		Microwave (% of morphine) Mean (n = 3)	Oven (% of morphine) Mean (n = 3)	Freezer (% of morphine) Mean (n = 3)
40% ethanol	0	0	0	0
	15 minutes	21.2	23.2	15.7
	30 minutes	35.4	37.2	24.2
	1 hour	57.0	57.5	35.7
	4 hours	78.7	84.0	67.9
	24 hours	87.7	92.3	97.3
95% ethanol	0	0	0	0
	15 minutes	24.4	21.2	22.4
	30 minutes	34.3	28.0	33.9
	1 hour	47.4	40.8	43.4
	4 hours	72.5	77.7	72.7
	24 hours	86.0	102.0	96.6

End of sponsor material

Reviewer's Evaluation of large volume extractions: Extraction rate of MS from EG-001 tablets cut in to 32 pieces was higher with various aqueous media including the media containing ethanol up to 50 % v/v and reached a plateau (60-70%) in most cases within two hours at room temperature (RT). Extraction rate increased under heated conditions in all aqueous media and media containing ethanol up to 50 %. Methylene chloride appears to be a relatively efficient solvent for morphine extraction when compared with other pure organic solvents, and in 95 % ethanol at RT. These findings from extraction studies using ground and cut pieces of EG-001, alone doesn't appear to present any barriers to systematic drug abusers. However, the relatively high hardness of EG-001 tablets combined with the low rate of extraction of morphine from intact EG-001 tablets in to large volumes of pH 2 aqueous media and 50 % under optimal conditions may only deter accidental misuse by patients, who are likely to grind the product or take with alcoholic drinks.

Syringeability Studies (Small volume extractions)

Solution syringeability was tested for solutions prepared at RT and 90ºC. Planned syringeability studies involved loading syringes initially with physically manipulated EG-001 along with small volumes of solvents (2, 5, and 10 mL of tap water), incubating for either, 2, 5, 10 or 30 minutes at RT with and without agitation at 200 rpm. The syringe contents (allowed to cool to body temperature before testing, when heated to 90°C) were tested for viscosity and the ability to expel (inject) the drug solution, and followed by feasibility assessment of drawing the extract into a syringe equipped with needles with different pore sizes.

The mean percent recovery of morphine with 2, 5, and 10 mL water solutions incubated for 30 minutes at RT was 0, 6.1, and 14.2% for EG-001 compared to 17.0, 39.7, and 64.9% for MS Contin. Heat pre-treatment (microwave, oven) of physically manipulated material (EG-001) continued to exhibit gelling properties. The time required to cool aspirated solutions from 90ºC to 37ºC was directly related to the amount of volume drawn into the syringe. The mean percent recovery of morphine with 2, 5, and 10 mL water solutions incubated for 30 minutes at 90ºC was 0, 20.0, and 6.8% for EG-001 compared to 54.7, 62.1, and 68.0% for MS Contin.

The viscosity of solutions prepared for injection with EG-001 appears to be higher than those prepared with MS Contin, where higher volume preparations provided lower viscosity measures while heating to 90ºC followed by cooling to 37ºC appears to increase viscosity for manipulated EG-001. Placing intact tablets, cut tablets, and physically manipulated material in a small volume of water or 3% saline without agitation for 4 hours resulted in syringeable solutions with a 27 gauge needle, but ≤5% of the API was present in solution while maximum recovery of 18.5% with an incubation time of 24 hours.

In response to Agency's request for information, sponsor provided data from small volume extractions (syringeability) studies, using intact and manipulated EG-001 with 40 % and 95 % ethanol. The viscosity and the amounts of recovered morphine were low when intact or

manipulated tablets are subjected to small volume extraction with ethanol as the solvent. Based on the data from extraction studies in small volume (10 mL) in 40% and 95% ethanol, using pre-treated (heating in oven, microwave and freezing) intact EG-001 tablets, it appears that pretreatment has no effect on extraction within first 30 min of extraction.

Start of sponsor material

Mean Viscosity (With Shaking) for EG-001 and MS CONTIN (RT and 90°C)

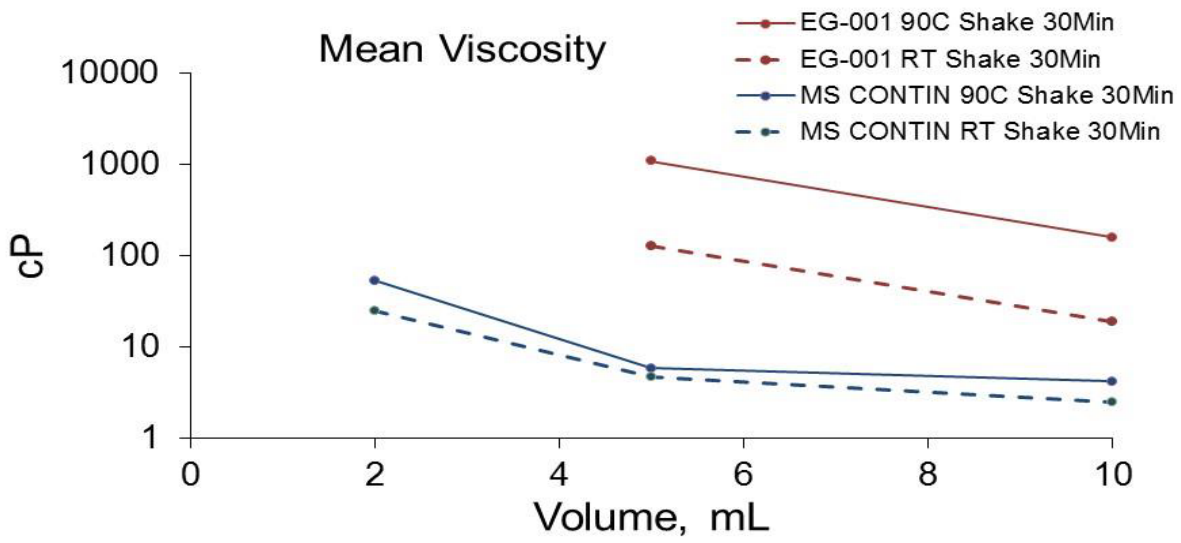


Figure 16 %Morphine Recovery (Without Shaking) for EG-001 in Saline or Tap Water Gel Blob (RT)

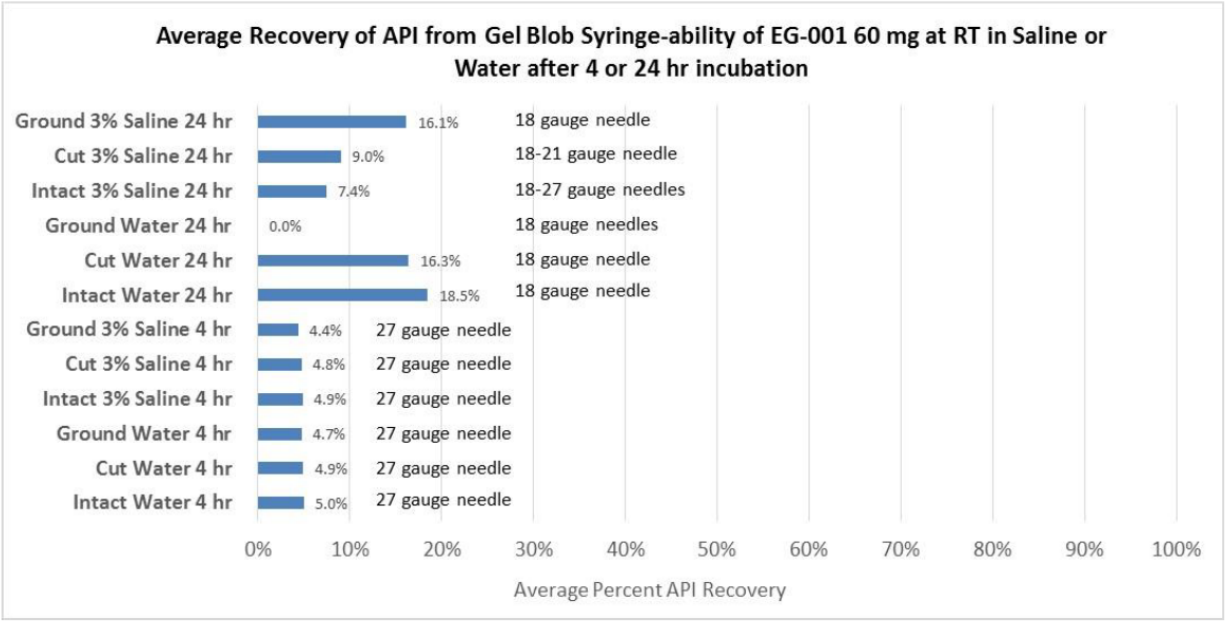


Table 1: Syringeability Study, Intact EG-001 Tablets 60 mg (Batch # SB69300201)

Solvent	Viscosity (cP) Mean (n = 3)	Needle Gauge (volume syringed, ml) Mean (n = 3)	Morphine Extracted from Volume Syringed (% of label) Mean (n = 3)
40% ethanol	3.2	27 (9 ml)	3.1
95% ethanol	1.6	27 (9 ml)	2.0

Table 2: Syringeability Study, Ground (cut and milled using optimized procedure) EG-001 Tablets 60 mg (Batch # SB69300201)

Solvent	Viscosity (cP) Mean (n = 6)	Needle Gauge (volume syringed, ml) Mean (n = 6)	Morphine Extracted from Volume Syringed (% of label) Mean (n = 6)
40% ethanol	24.6	25 (6-7 mL; n = 5) 27 (5.5 mL; n = 1)	14.9
95% ethanol	4.8	27 (8 ml)	17.9

Table 3: Extraction (% morphine from 60 mg tablets) in Small Volume (10 ml) Following Pre-Treatment of Intact Tablets (Batch # SB69300201)

Solvent	Time	Pre-Treatments		
		Microwave (% of morphine) Mean (n = 3)	Oven (% of morphine) Mean (n = 3)	Freezer (% of morphine) Mean (n = 3)
40% Ethanol	0	0.0	0.0	0.0
	15 minutes	1.9	1.9	2.0
	30 minutes	3.3	3.3	3.5
	1 hour	6.6	6.0	6.6
	4 hours	23.9	23.0	19.5
95% Ethanol	0	0.0	0.0	0.0
	15 minutes	0.9	1.5	1.5
	30 minutes	1.3	3.0	3.0
	1 hour	2.3	6.3	6.0
	4 hours	14.4	21.2	19.9

Table 1: Extraction (% morphine from 60 mg tablets) in Small Volume (10 mL) Following Pre-Treatment of Manipulated EG-001 Tablets (Batch # SB69300201)

Solvent	Time	Pre-Treatments		
		Microwave (% of morphine) Mean (n = 3)	Oven (% of morphine) Mean (n = 3)	Freezer (% of morphine) Mean (n = 3)
40% Ethanol	0	0	0	0
	15 minutes	10.6	11.4	9.4
	30 minutes	15.6	16.8	14.0
	1 hour	21.5	22.7	21.2
	4 hours	50.3	53.4	51.1
95% Ethanol	0	0	0	0
	15 minutes	20.4	20.6	12.8
	30 minutes	26.1	27.2	16.2
	1 hour	33.9	33.6	21.2
	4 hours	41.1	37.5	32.5

End of sponsor material

Reviewer Evaluation of Syringeability Studies: Extraction of MS from intact and physically manipulated EG-001 tablets appears to be low, ~with highest extraction of ~27 %) and ~ 53 % MS observed in 95 % at 30 minutes and in 450% ethanol at 4 hours respectively. Extractability in water was low for manipulated EG-001 tablets compared to ethanol 40 % and 95 % ethanol for intact and manipulated tablets that were later pretreated. The gelling nature of the formulation in aqueous media appears to restrict morphine extraction in aqueous media even when significant effort was expended for particle size reduction. It appears that small volume extraction of EG-001 intact tablets with ethanol (40% and 95%) after manipulation and pretreatment of EG-001 tablets improved the separation of morphine to some extent (<25 % from intact pretreated tablets vs > 50.0% from manipulated pretreated tablets in 40 % ethanol), and the viscosity of the extract was significantly low in the presence of ethanol.

Precipitation of free base

Attempts were made to isolate morphine free base by dissolving physically manipulated (optimized procedures) EG-001 in 0.1 M HCl followed by adjustment of pH to 10 with 12 N NaOH, and addition of acetone to the solution chilled at -20ºC. Attempts to vacuum filter resulting opaque solution with a Buchner funnel for isolation of free-base morphine were

unsuccessful. Based on these extraction / precipitation studies, it appears that isolation of free-base morphine from EG-001 by pH mediated precipitation methods was unsuccessful.

Simulated Smoking study

Simulated smoking studies using intact and physically manipulated drug product resulted in low morphine recoveries and thus it appears that smoking is unlikely to be practiced. Average percent recoveries of vaporized morphine from EG-001 at different heating conditions: 260ºC, 1.6%; 280ºC, 2.3%; 300ºC, 2.7%; and Sterno heat, 3.0%.

Reviewer Evaluation of Chemical Manipulations: Arymo™ ER tablets appears to be resist isolation of morphine using small volume extractions with water, when compared to MS Contin® in the laboratory settings. The high viscosity of the aqueous extract appears to deter syringeability and injectability. Arymo™ ER tablets also appear to resist abuse by smoking, based on the simulated smoking studies under all testing conditions when to the drug substance as base or in salt form used as comparator. Extraction studies using large volumes of various solvents with ground and cut pieces of EG-001 don't appear to drug abuse by oral route.

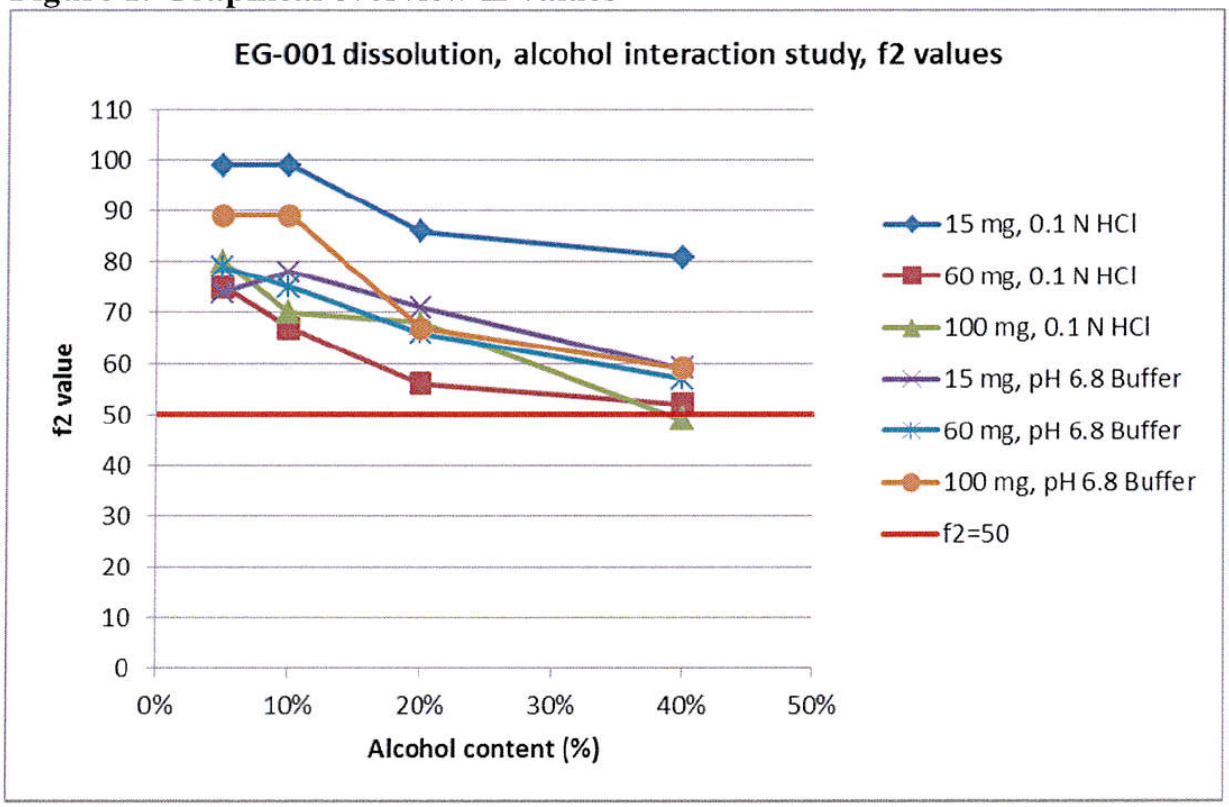
Dissolution studies with physically manipulated EG-001

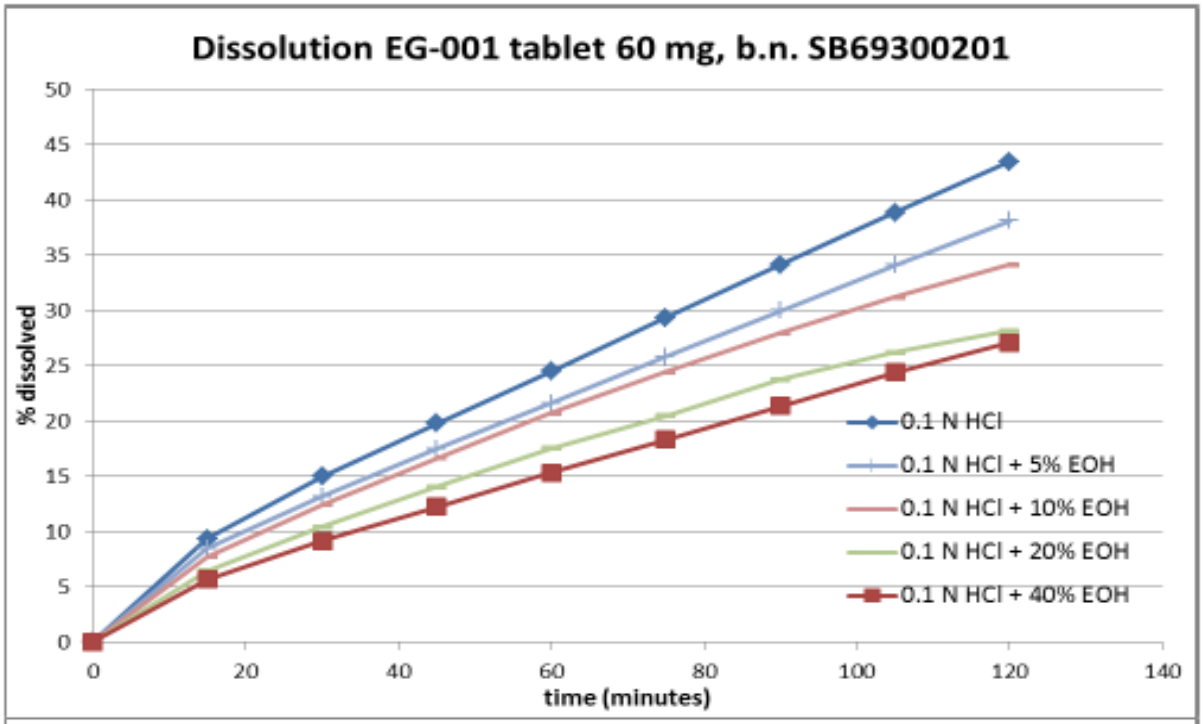
Dissolution studies with Alcohol (Dose Dumping)

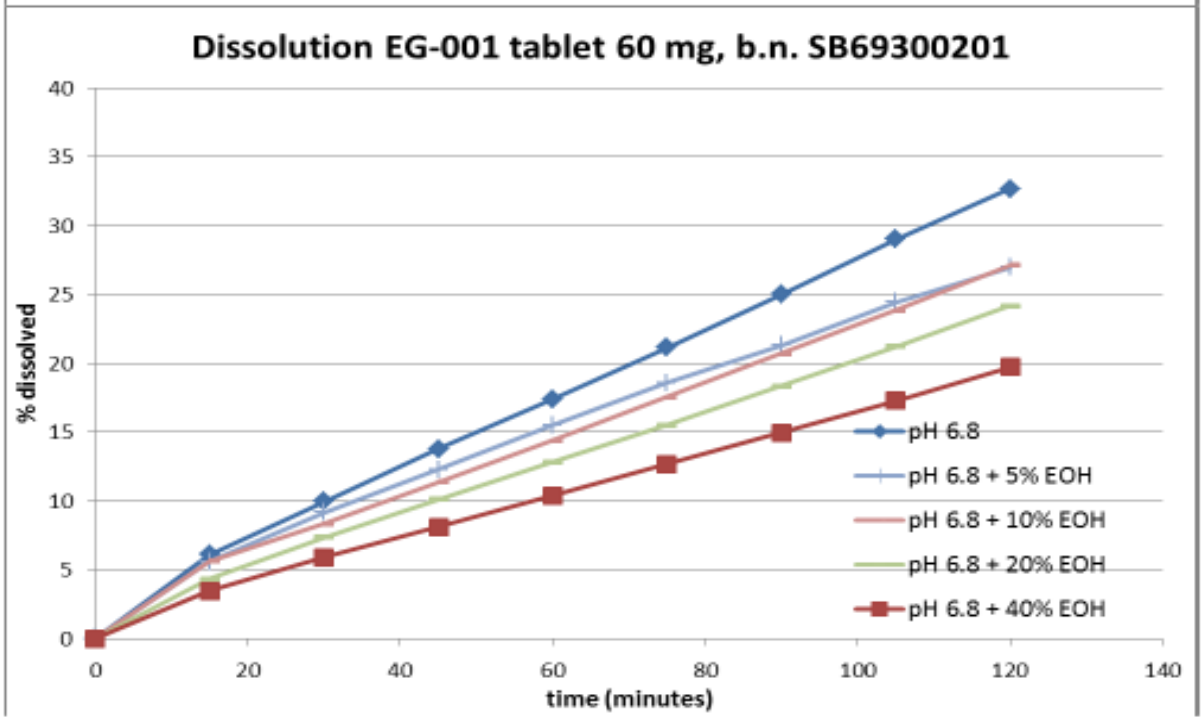
In vitro dissolution testing of EG-001 15 mg, 60 mg and 100 mg intact tablets was performed in 0.1N HCl and pH 6.8 buffers, with varying quantities of ethanol (5, 10, 20 and 40 %) with sampling at 15 minutes interval up to two hours, to assess the potential for dose dumping when ingested along with co-ingestion of alcohol. Cumulative percent of morphine released over the two hours period has decreased with increasing concentration of alcohol, in both 0.1 N HCL and Phosphate buffer pH 6.8 media, compared to the percent released in absence of alcohol.

Start of sponsor material:

Figure 1. Graphical overview f2 values







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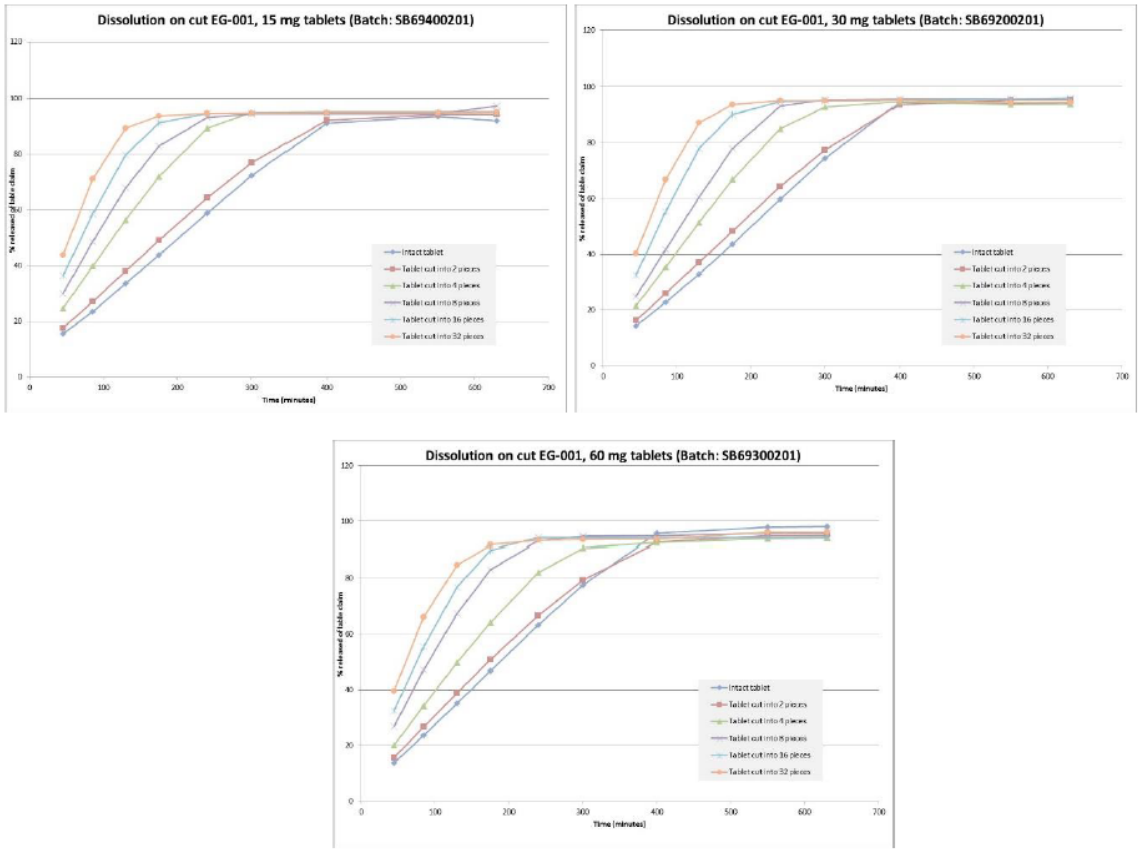
Dissolution studies on Physically Manipulated EG-001

Dissolution testing of a physically manipulated product, intact and cut to 2, 4, 8, 16, and 32 pieces of 15, 30, and 60 mg respectively, was performed in 0.1N HCl and pH 6.8 buffers with varying quantities of ethanol (5, 10, 20 and 40 %) with sampling at periodic intervals up to ten hours, to assess the effect of physical manipulation of EG-001 on dissolution rate. As expected a progressive increase in drug release was observed with increased surface area as the tablet was cut into smaller and smaller pieces.

Start of sponsor material

Figure 20 % of Morphine Released (Label Claim) for Intact and Cut EG-001 15, 30, and 60 mg Tablets in pH 6.8



End of sponsor material

Reviewer Evaluation of Dissolution Studies: Based on the in vitro dissolution profiles presented and because of the gelling of sample, the liability of EG-001 tablets for dose dumping in presence of alcohol appears to be very low.

Overall Conclusions: The Category 1 laboratory-based *in vitro* studies using intact and physical manipulated ARYMO™ (EG-001) tablets appears to be adequate to address the vulnerabilities and resistance of EG-001 for physical manipulation by various household tools and for abuse by

intravenous route of administration. The unusually higher hardness (≥ 400 N) of EG-001 makes it less susceptible to manipulation by chewing or crushing with blunt force when compared to MS Contin® by using most of the common household tools tested, i.e. extraction with small volumes of water and other ethanolic solvents under various test conditions followed by syringeability and injectability studies.

The physicochemical properties of morphine sulfate, together with the properties of the intact EG-001 tablets, i.e., tablet bulk density, hardness, extended-release properties, and gelling properties in aqueous solvents also appears to be contributing factors to deter abuse by other common routes. Based on the large volume extraction studies in most of the solvents used and at elevated temperatures, manipulated EG-001 (by cutting or grinding) appears to be liable for abuse by oral route. Susceptibility to complex liquid/liquid extractions is comparable to MS Contin® for separation of drug substance and/or preparation of concoctions by methodical abusers. Overall, the extremely hard tablet, and time and effort required for physical manipulation appears to discourage abuse of ARYMO™ tablets when compared to MS Contin®.

Request for Information

Below identified deficiencies were communicated to the Sponsor during the review period that were subsequently resolved. No additional deficiencies were identified at the time of this review.

1. In the submission under module "3.2.P.2 Pharmaceutical Development" it was stated that "tablet hardness and resistance to particle size reduction offers an impediment to abuse by multiple routes of administration". We were unable locate the measured values for Hardness of tablets, (b) (4) Please provide available information on:

   a. Hardness of the tablets as measured during development of the drug product, acceptance criteria, if any set for hardness.

   b. How the product composition and process parameters were optimized for obtaining tablets with desired hardness (within acceptable range) during product development.

   c. (b) (4)

   Or

   Indicate the location where this information can be found within the submission.

2. We recommend measuring hardness (b) (4) or another appropriate validated test method for measuring the crush/chewing resistance of tablets.

3. It was also stated under module "3.2.P.2" that "Category 1 abuse-deterrent studies of EG-001 have shown that the formulation will likely be unusually resistant to the most common forms of tampering (i.e., chewing, crushing, grinding, and extraction), as well as rigorous attempts at manipulation as demonstrated by serial, multi-step physical manipulation maneuvers employed". You have also indicated that ALERRT scales (or Visual Analog Scales) were used to measure the "work" required to prepare EG-001 into a form suitable for the various known forms of abuse. Please provide information on:

    a. Whether the ALERRT scales were used to evaluate any of the abuse-deterrent products approved by the Agency.

    b. Whether the test methods used in creating the ALERRT scales are amenable to validation/standardization.

    c. Whether the ALERRT scales can be used to compare and contrast "work" required for tampering a product using various tools (hand tools vs. electrical equipment) and/or mechanisms for tampering.

4. In the "Expert Review and Data Interpretation of Category 1 In Vitro Laboratory Assessment" on page 9 it was stated that "The findings presented herein are based on data generated by a third party laboratory, (b) (4) for full study details, see the laboratory protocols entitled In Vitro Laboratory Abuse-Deterrent Studies of Egalet's Morphine Prolonged Release [PR] 60 mg Formulation (b) (4) Study Number: (b) (4)-AD003 and In Vitro Laboratory Abuse-Deterrent Studies of Egalet's Morphine Prolonged Release [PR] Formulation [EG-001] Tablets, 60 mg – To Be Marketed Product [TBMP] (b) (4) Study Number: (b) (4)-AD004)."

    We were unable to locate the above referenced documents pertaining to (b) (4) Study Number (b) (4)-AD003 and (b) (4)-AD004. Provide these documents or indicate the location in the submission where these documents can be found.

5. Provide the simulated smoking study data for MS Contin 60 mg using the same test conditions as used for EG-001 tablets, 60 mg.

6. Provide data from small volume extraction (Syringeability) studies, using intact and manipulated EG-001 with 40% and 95% Ethanol using the different gauge needles as in other syringeability studies.

7. Provide data from extraction studies (large and small volume) in 40% and 95% ethanol, using pre-treated (heating in oven, microwave and freezing) EG-001 drug product.

8. Since hardness of the drug product is the main premise for the proposed abuse deterrence of the drug product, provide a release and stability specification for minimum tablet

hardness as a quality attribute reflective of the proposed ADF properties of the drug product.

9. In the response to Agency's request for information sent on Jun 27, 2016 for "data from extraction studies (large and small volume) in 40% and 95% ethanol, using pre-treated (heating in oven, microwave and freezing) EG-001 drug product" you have provided data from extraction studies using only pretreated intact tables, but not pretreated manipulated product. Provide data from extraction studies (large and small volume) in 40% and 95% ethanol, with manipulated EG-001 using optimized procedure followed by pre-treatment (heating in oven, microwave and freezing).

Proposed language for PMR/PMC

(b) (4)


(b) (4)

Julia Pinto

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Date: 9/19/2016 11:54:32AM
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Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 9/14/2016 11:59:22AM
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CHAPTER III: Environmental Analysis

See Chapter 2: Drug Product Page 57

CHAPTER IV: Labeling

See Chapter 2: Drug Product Page 56

CHAPTER V: Process

Primary Process Reviewer Name and Date:

Haitao Li, 9/9/16

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

Pei-I Chu, 9/9/2016

Pei-I Chu

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Date: 9/12/2016 03:48:41PM
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Haitao Li

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CHAPTER VI: Facilities

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

List of Deficiencies: **Not applicable**

Primary Facilities Reviewer Name and Date: **Frank Wackes, 07SEP2016**

Secondary Reviewer Name and Date:

I concur with this acceptable recommendation. - 07Sept2016
Christina Capacci-Daniel, PhD
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

Christina Capacci-Daniel

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Frank Wackes

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CHAPTER VII: Biopharmaceutics

BIOPHARMACEUTICS

Product Background:

NDA: 208603

Drug Product Name / Strength: Morphine sulfate Extended-release tablets/ 15 mg, 30 mg, and 60 mg

Route of Administration: Oral

Applicant Name: Egalet US Inc.

Review Summary:

The Applicant submits an NDA for Arymo (morphine sulfate) extended-release tablets, 15 mg, 30 mg, and 60 mg by 505(b)(2) pathway. Arymo ER is an abuse-deterrent, extended-release, oral morphine formulation indicated for the management of pain severe enough to require daily, around-the clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Formulation Development:

During development, the Applicant had progressed from a Preliminary Formulation (Formulation A) to an Intermediate Formulation (Formulation B) to the Commercial Formulation (Formulation C). Please refer to the body of the review for additional details about the summary of changes of the 3 formulations, quantitative composition and corresponding clinical studies.

The Applicant states that their "GuardianTM Technology" is a polymer matrix tablet technology that utilizes plastic injection molding manufacturing methodology and results in tablets with controlled release properties as well as physical and chemical features to resist both common and more rigorous methods of manipulation. Injection molding of polyethylene oxide results in tablets that are extremely hard, very difficult to chew, resistant to particle size reduction, and that inhibit/block attempts at chemical extraction of the morphine sulfate.

In Vitro Dissolution Testing:

The proposed dissolution method is shown below:

Parameter	Description
Principle	Dissolution with HPLC detection
Apparatus	USP Apparatus 1 (baskets mesh 10)
Dissolution media	Phosphate buffer pH 6.8
Medium volume	900 mL
Medium Temperature	37 ± 0.5°C
Rotation Speed	100 ± 2 rpm
Probe filter	Yes, 70 µm
Sinkers	No
Sample Volume	9 mL

The proposed acceptance criteria are:

85 min: (b) (4) % released

175 min: (b) (4) % released

400 min: ≥ (b) (4) % released

The applicant's dissolution method and specifications are found to be acceptable.

In Vitro In Vivo Correlation (IVIVC)

(b) (4)

(b) (4)

As a result, the IVIVC model is inadequate.

Alcohol Dose-Dumping Study

An in-vitro alcohol interaction study was conducted for the Arymo tablets 15 mg (Batch # SB69400201), 60 mg (SB69300201) and 100 mg (SB69500201) by comparing dissolutions profiles generated in the presences of alcohol (0%, 5%, 10%, 20%, and 40% of ethanol).

With increasing concentrations of alcohol (5%, 10%, 20% and 40%), the release rate of morphine from Arymo (morphine sulfate extended-release tablets) is progressively slower compared to morphine release from Arymo in the absence of alcohol. The f2 values appear to be lower in pH 6.8 media (proposed dissolution method) compared to 0.1 N HCl for the 15 mg, and higher in pH 6.8 media compared to 0.1 N HCl; however, the f2 values are all above 50 with the exception of the 100 mg strength tested in 40% alcohol/HCl in which the f2 value was 49. It appears that with higher dose of morphine sulfate, the higher concentration of alcohol in the dissolution media results in a slower release of morphine sulfate compared to lower dose of morphine.

This alcohol dose dumping study shows that there is no risk of alcohol induced dose dumping with Arymo ((morphine sulfate extended-release) tablets.

List Submissions being reviewed (table):

Application 208603 - Sequence 0001 - 0001 (1) 12/14/2015 ORIG-1 /Multiple Categories/Subcategories

Application 208603 - Sequence 0005 - 0005 (6) 03/22/2016 ORIG-1 /Quality/Response To Information Request

Application 208603 - Sequence 0008 - 0008 (8) 05/03/2016 ORIG-1 /Quality/Response To Information Request

Application 208603 - Sequence 0009 - 0009 (9) 05/20/2016 ORIG-1 /Quality/Response To Information Request

Application 208603 - Sequence 0010 - 0010 (10) 05/23/2016 ORIG-1 /Quality/Response To Information Request

Application 208603 - Sequence 0011 - 0011 (11) 05/24/2016 ORIG-1 /Quality/Response To Information Request

Application 208603 - Sequence 0021 - 0021 (21) 08/10/2016 ORIG-1 /Quality/Response To Information Request

Application 208603 - Sequence 0022 - 0022 (22) 08/18/2016 ORIG-1 /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:

The application is acceptable from a biopharmaceutics perspective.

The following deficiencies about In vitro-in vivo correlation (IVIVC) will be communicated to the applicant, however these deficiencies are not considered as approvability issues. (b) (4)

The In vitro-in vivo correlation is inadequate due to the following reasons:

(b) (4)

BCS Designation

Reviewer's Assessment: The Applicant has not claimed or submitted any information in support of BCS Designation for their drug product.

Solubility: Soluble in water. Slightly soluble in anhydrous ethanol. Practically insoluble in chloroform or ether.

Permeability: not provided.

Dissolution:

Parameter	Description
Principle	Dissolution with HPLC detection
Apparatus	USP Apparatus 1 (baskets mesh 10)
Dissolution media	Phosphate buffer pH 6.8
Medium volume	900 mL
Medium Temperature	37 ± 0.5°C
Rotation Speed	100 ± 2 rpm
Probe filter	Yes, 70 µm
Sinkers	No
Sample Volume	9 mL

The proposed acceptance criteria are:

85 min: (b) (4) % released

175 min: (b) (4) % released

400 min: ≥ (b) (4) % released

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

Drug Product

Arymo (morphine sulfate) extended-release tablets have been developed in tablet strengths of 15 mg, 30 mg, and 60 mg. The commercial formulation (to-be-marketed product) is presented in Table 1.

Table 1: Composition of Commercial Formulations of Arymo (Morphine Sulfate)

Strength	15 mg	30 mg	60 mg
Ingredient	**Amount per Tablet (%)**		
Morphine sulfate	1.976	3.939	7.828
Polyethylene Oxide 400,000 (b) (4) (b) (4)			(b) (4)
Butylated hydroxytoluene (b) (4			
Total	100.0	100.0	100.0

NA = not applicable

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(b) (4)

[redacted]

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: There is no application of dissolution /IVIVC in this submission

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

Reviewer's Assessment:

Alcohol Dose-Dumping Study AD 2015-R-08

An in-vitro alcohol interaction study was conducted for the Arymo tablets 15 mg (Batch # SB69400201), 60 mg (SB69300201) and 100 mg (SB69500201) by comparing dissolutions profiles generated in the presence of alcohol (0%, 5%, 10%, 20%, and 40% of ethanol).

The dissolution method is based on the proposed regulatory dissolution method, except that 0.1 N HCl medium has been added and the detection method has been modified in order to enable proper analysis of the sample solutions containing alcohol. The method is as described below:

Basket (10 mesh), 100 rpm, 900 ml, 37°C, UPLC detection

Sampling time points: 15, 30, 45, 60, 75, 90, 105 and 120 minutes.

Dissolution media:

- 0.1N HCl containing 0, 5, 10, 20 and 40% ethanol, respectively.
- Phosphate buffer pH 6.8 (QC dissolution medium) containing 0, 5, 10, 20 and 40% ethanol, respectively.

The dissolution profile of Arymo 60 mg tablets (Batch # SB69300201) with different concentrations of ethanol at 0.1 N HCl media is shown in

Figure 24: Dissolution Profile of Arymo 15 mg Tablets (Batch # SB69400201) with Different Concentrations of Ethanol in 0.1 N HCl

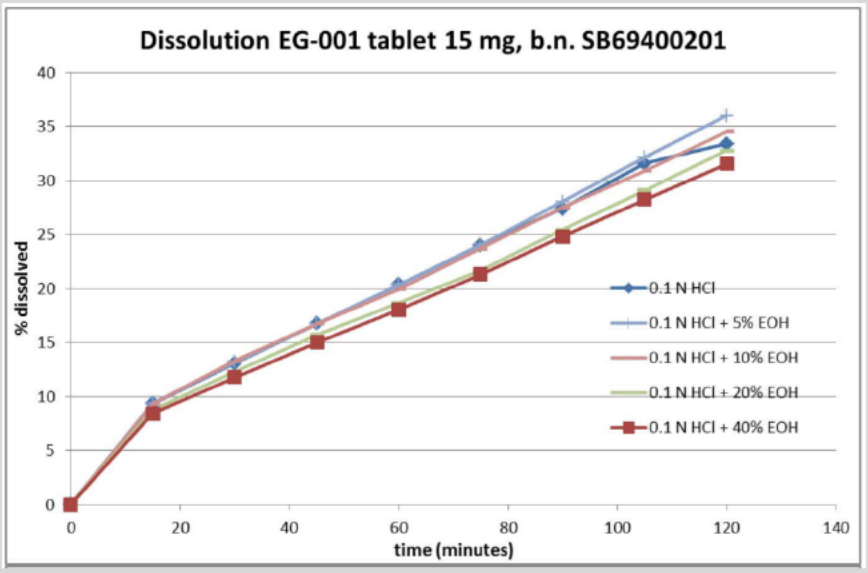


Figure 25: Dissolution Profile of Arymo 15 mg Tablets (Batch # SB69400201) with Different Concentrations of Ethanol in pH 6.8 Buffer

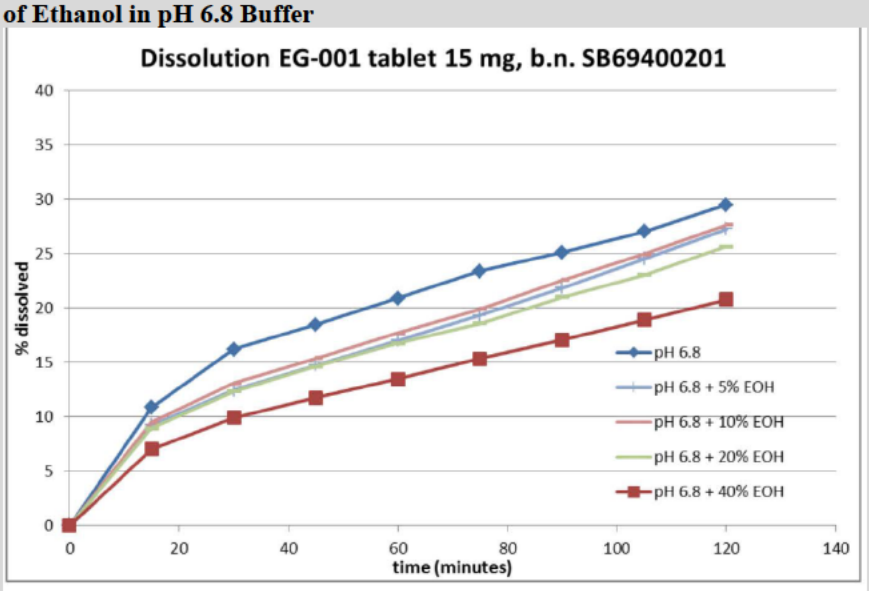


Figure 26: Dissolution Profile of Arymo 60 mg Tablets (Batch # SB69300201) with Different Concentrations of Ethanol in 0.1 N HCl

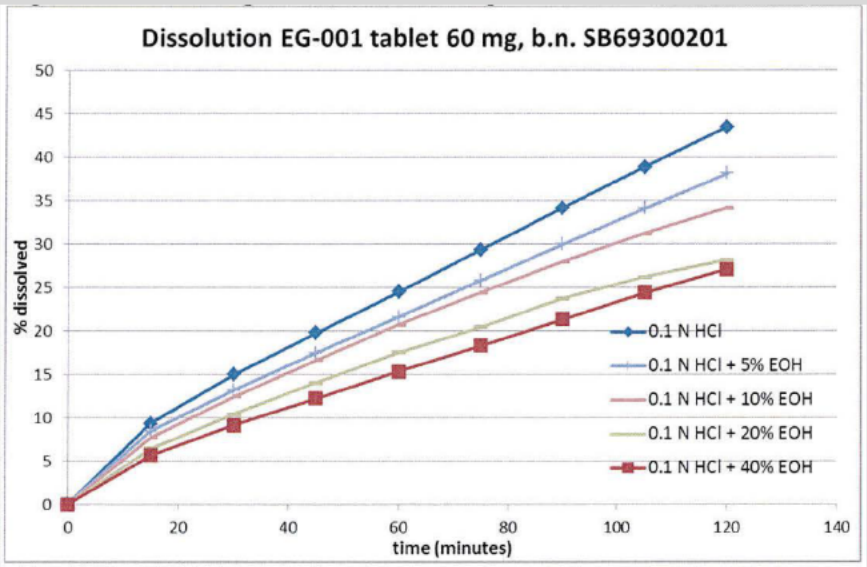


Figure 27: Dissolution Profile of Arymo 60 mg Tablets (Batch # SB69300201) with Different Concentrations of Ethanol in pH 6.8 Buffer

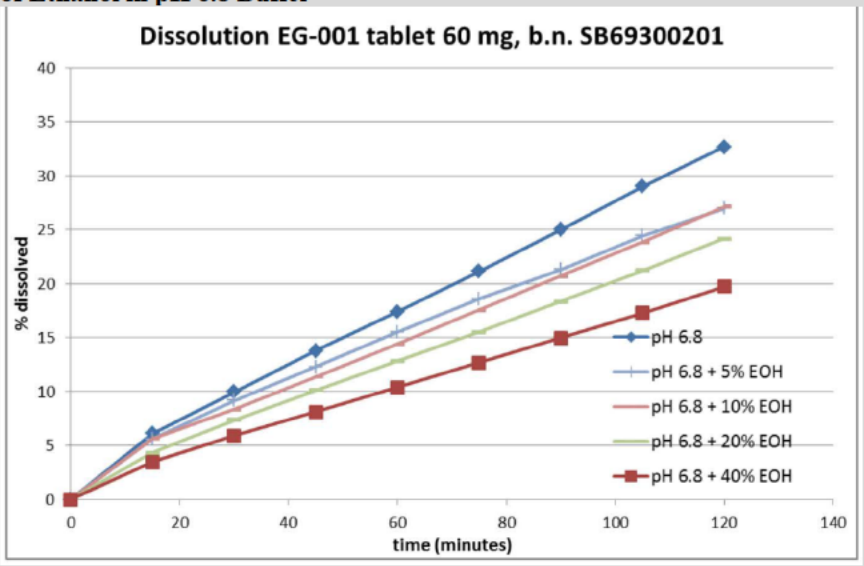


Figure 28: Dissolution Profile of Arymo 100 mg Tablets (Batch # SB69500201) with Different Concentrations of Ethanol in 0.1 N HCl

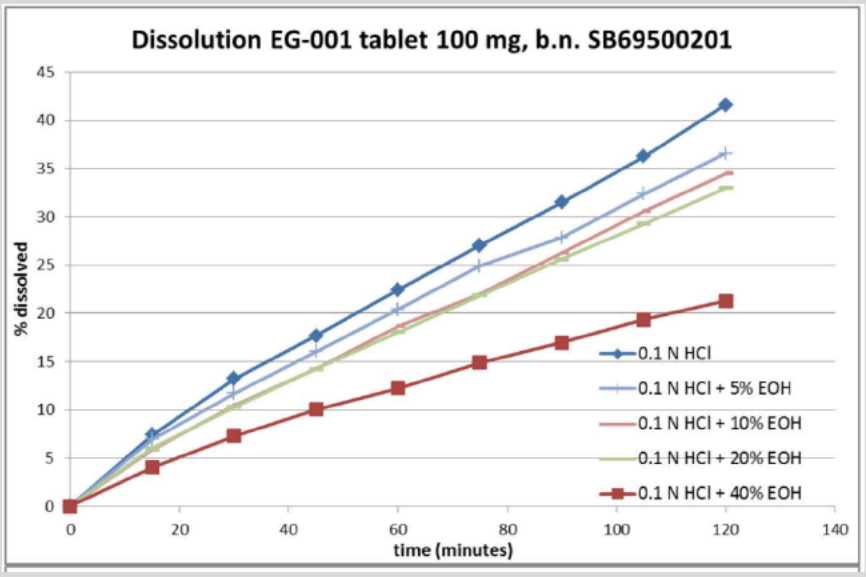
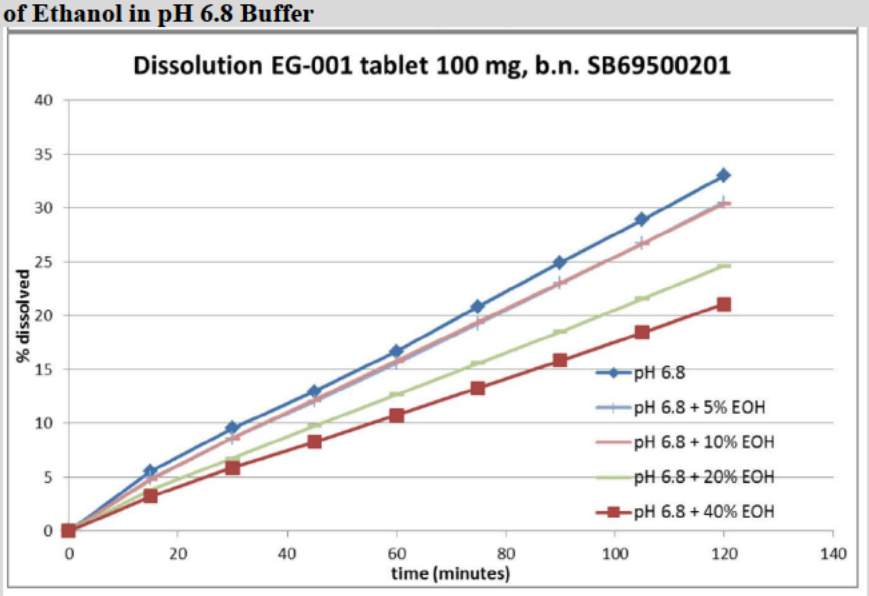


Figure 29 Dissolution Profile of Arymo 100 mg Tablets (Batch # SB69500201) with Different Concentrations of Ethanol in pH 6.8 Buffer

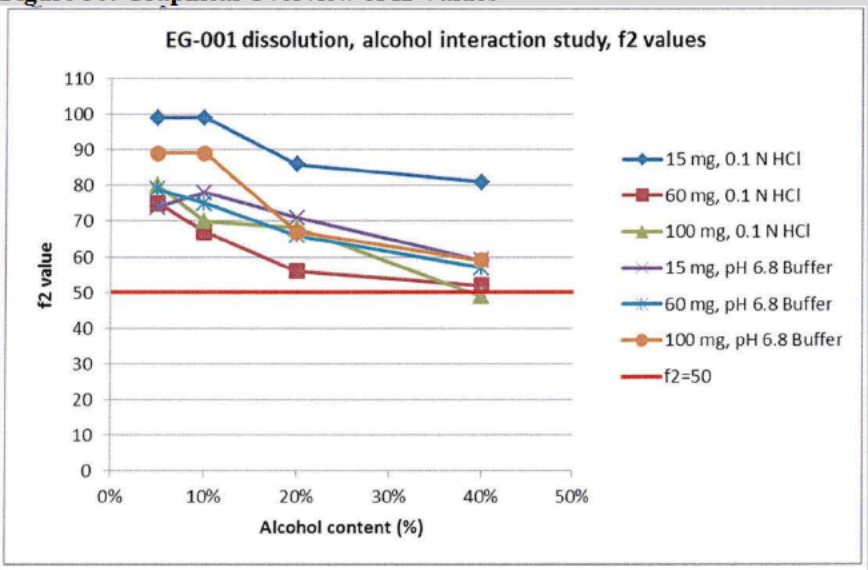


The f2 tests comparing each of the dissolution results obtained from media containing varying levels of alcohol with alcohol free media are presented in Table 16. Graphical presentation of the f2 results are shown in Figure 30.

Table 16: f2 Values Comparing Each of the Dissolution Results Obtained from Media Containing Varying Levels of Alcohol with Alcohol Free Media

Tablet strength	Dissolution Medium	% alcohol			
		5%	10%	20%	40%
15 mg	0.1 N HCl	99	99	86	81
60 mg	0.1 N HCl	75	67	56	52
100 mg	0.1 N HCl	80	70	68	49
15 mg	pH 6.8 Buffer	74	78	71	59
60 mg	pH 6.8 Buffer	79	75	66	57
100 mg	pH 6.8 Buffer	89	89	67	59

Figure 30: Graphical Overview of f2 Values



Reviewer's comments:

With increasing concentrations of alcohol (5%, 10%, 20% and 40%), the release rate of morphine from Arymo (morphine sulfate extended-release tablets) is progressively slower compared to morphine release from Arymo in the absence of alcohol. The f2 values appear to be lower in pH 6.8 media (proposed dissolution method) compared to 0.1 N HCl for the 15 mg, and higher in pH 6.8 media compared to 0.1 N HCl; however, the f2 values are all above 50 with the exception of the 100 mg strength tested in 40% alcohol/HCl in which the f2 value was 49. It appears that with higher dose of morphine sulfate, the higher concentration of alcohol in the dissolution media results in a slower release of morphine sulfate compared to lower dose of morphine.

This alcohol dose dumping study shows that there is no risk of alcohol induced dose dumping with Arymo ((morphine sulfate extended-release) tablets.

In-Vitro Soft-food Interaction Study

Reviewer's Assessment:

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: The same formulation was used in invivo studies. Therefore, no additional bridging is needed.

Biowaiver Request

Reviewer's Assessment:

No biowaiver requests were submitted in this NDA application.

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

Reviewer's Assessment: n/a

List of Deficiencies:

The application is acceptable from a biopharmaceutics perspective.

The following deficiencies about In vitro-in vivo correlation (IVIVC) will be communicated to the applicant, however these deficiencies are not considered as approvability issues. (b) (4)

The In vitro-in vivo correlation is inadequate due to the following reasons:

(b) (4)

Primary Biopharmaceutics Reviewer Name and Date: An-chi (Angela) Lu, Pharm D. 9/1/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D. 09/09/2016

Haritha Mandula

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An-Chi Lu

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CHAPTER VIII: Microbiology

See Chapter 5: Process page 142

Ciby Abraham

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