ejpmr, 2024, 11(8), 406-417

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

DEVELOPMENT AND BIOEQUIVALENCE STUDY OF ESOMEPRAZOLE BIPHASIC MICRO PELLETS TABLETS

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Article Received on 20/06/2024 **Article Revised on 10/07/2024** **Article Accepted on 31/07/2024**

ABSTRACT

The development of Esomeprazole Biphasic Micro Pellets Tablets, 20 mg & 40 mg, followed a structured approach based on the US FDA Guidance "Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms." This encompassed defining the Pharmaceutical Product Target Profile (PPTP), identifying Critical Quality Attributes (CQAs), conducting formulation development, optimizing formulation and process, and establishing a control strategy for commercial manufacturing. The formulation included enteric-coated micro pellets with different pH-dependent dissolution profiles, designed to deliver Esomeprazole in two distinct phases. The first phase releases 70% of the drug in the proximal duodenum, providing conventional delayed release, while the second phase releases the remaining 30% in the stomach environment, extending acid suppression. A randomized, open-label, two-way crossover bioequivalence study compared Esomeprazole Biphasic Micro Pellets Tablets (40 mg) with Nexium 40 mg gastro-resistant tablets. Pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, Kel, $t_{1/2}$) were assessed in healthy adult males under fasting conditions using non-compartmental analysis. The study demonstrated bioequivalence with 90% confidence intervals for Esomeprazole within acceptance criteria for C_{max}, AUC_{0-t}, and AUC_{0-inf}. This randomized, open-label, two-treatment, two-period crossover study compared the bioequivalence of 40 mg Esomeprazole Biphasic MUPS tablets to Nexium in healthy adults. Blood samples were collected at 21 time points over 24 hours and analyzed using LC/MS/MS. Both formulations reached peak plasma concentrations (C_{max}) at 3 hours, with Esomeprazole Biphasic MUPS showing an additional peak at 4 hours and sustained higher levels until 16 hours. The AUC_{0-t} and AUC_{0-inf} for Esomeprazole Biphasic MUPS were 5711.549 ng/mL and 5751.938 ng/mL, respectively, compared to 5615.535 ng/mL for both parameters with Nexium. C_{max} was 1416.570 ng/mL for Esomeprazole Biphasic MUPS versus 1670.887 ng/mL for Nexium. Esomeprazole Biphasic MUPS provided 17.3% higher drug availability between 4 and 16 hours, suggesting a longer mean residence time and extended acid suppression compared to Nexium. In conclusion, Esomeprazole Biphasic Micro Pellets Tablets exhibited enhanced absorption characteristics and demonstrated bioequivalence to Nexium. The formulation was well-tolerated and provided extended acid suppression, offering potential clinical advantages in the management of acid-related disorders.

KEYWORDS: Esomeprazole, MUPS, Proton Pump Inhibitor (PPI), gastroesophageal reflux disease (GERD), Quality by Design (QbD), Formulation Development, Bioequivalence.

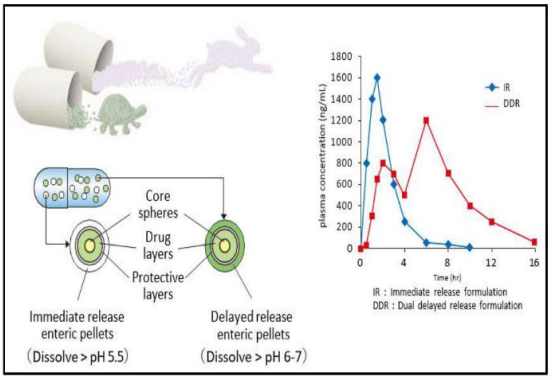

Fig. 1: Graphical Abstract.

INTRODUCTION

Esomeprazole is a type of medication called a proton pump inhibitor (PPI) that lowers the amount of acid your stomach makes. It's mainly used to help with gastroesophageal reflux disease (GERD), where stomach acid causes heartburn and can damage the esophagus. This drug works for both adults and children over one year old. Esomeprazole also helps prevent ulcers in people who take nonsteroidal anti-inflammatory drugs (NSAIDs) and is used with other medicines to treat and prevent stomach ulcers caused by the bacteria Helicobacter pylori in adults. Additionally, it treats conditions where the stomach makes too much acid, like Zollinger-Ellison syndrome, and is useful for managing

frequent heartburn that happens two or more times a week in adults.[1-3]

Esomeprazole offered more effective control of intragastric pH compared to omeprazole, lansoprazole, and pantoprazole.[4]

PPIs (proton pump inhibitors) are known to have a short half-life of less than 2 hours. Their long-lasting effect comes from their ability to permanently shut down active proton pumps while they are in the bloodstream. On average, traditional PPIs block about 70% of these pumps with a once-daily dose. However, since not all proton pumps are active at the same time, about 25% of them regenerate each day. Because PPIs stay in the bloodstream for only 1 to 2 hours, their presence decreases throughout the day, leading to a complete absence in the later part of the 24-hour period. This allows new or restored pumps to start producing stomach acid again. Moreover, how quickly proton pumps regenerate can vary from person to person, making it harder to control stomach acid in those with faster pump turnover compared to those with slower turnover.[5]

"Acid breakthrough" happens when stomach acid levels rise to a pH below 4 for at least 60 minutes during the night (from 10:00 PM to 6:00 AM). In a study of 45 patients who took PPIs twice a day, the researchers found that 70% of them experienced acid breakthrough during the nighttime.[6]

Multi-particulate systems (MUPS) are oral dosage forms made up of many small, separate units, each with specific properties. In these systems, the drug dose is divided into numerous smaller subunits, usually consisting of thousands of tiny spherical particles.[7]

MUPS provide several benefits compared to other drug delivery systems, such as lowering the risk of local irritation and toxicity, ensuring more predictable bioavailability, reducing the chance of dose dumping, stabilizing plasma drug levels, and allowing for the administration of higher doses.[8]

The current research involves developing Esomeprazole MUPS tablets using Quality by Design (QbD). This method is a structured approach that embeds quality into the product right from the start of development. It aims to understand the key factors affecting the performance and quality of the drug. By identifying and managing these factors, QbD ensures that the final product consistently meets its quality standards.

QbD includes defining the desired quality attributes, analyzing how formulation variables affect product performance, and designing robust processes based on this understanding. It emphasizes proactive quality management, ongoing monitoring, and adjustments based on real-time data, rather than relying only on testing the final product.[9-10]

A new type of Esomeprazole Biphasic MUPS Tablets has been developed utilizing QbD concept that releases the medication in two stages from a single tablet. This method uses two different types of enteric-coated micro pellets with distinct pH levels to control when the drug is released.

The first layer of pellets is designed to break apart quickly in the upper part of the small intestine (where the pH is above 5.8), releasing 70% of the drug within 1-2 hours after taking it. This is similar to traditional delayed-release tablets.

The second layer of pellets is made to float and break down in the stomach, releasing the remaining 30% of the drug further down the small intestine (where the pH is above 6.5) within 3-5 hours. This helps to keep the drug working longer and provides extended relief from acid.

Additionally, the second layer of pellets is coated with substances that resist acid and neutralize it, maintaining the right pH level to help relieve occasional heartburn quickly.

Overall, this new biphasic formulation of Esomeprazole MUPS offers a longer duration of action in the bloodstream compared to conventional Esomeprazole tablets, due to its extended release and absorption time.

MATERIALS AND METHODS

The development process begins with defining the Quality Target Product Profile (QTPP) for Esomeprazole Biphasic MUPS Tablets. The QTPP is a comprehensive description of the desired characteristics and performance of the drug product. The QTPP includes both critical and non-critical elements. Critical elements are those that directly impact the product's efficacy, safety, and quality, while non-critical elements are less influential but still important for overall product performance. A key part of the QTPP is the Critical Quality Attributes (CQAs). CQAs are specific properties or characteristics that must be controlled within defined limits to ensure the drug product meets its intended quality, safety, and efficacy. Table 1 presents the QTPP for Esomeprazole Biphasic Micro Pellets (MUPS) Tablets in both 20 mg and 40 mg doses**.** This table provides a detailed overview of the critical and non-critical elements defined during the development process.

A thorough risk assessment is performed to identify Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). CMAs are the essential characteristics of the materials used in the formulation, while CPPs are the key variables in the manufacturing process. Both CMAs and CPPs play a vital role in ensuring that the CQAs are met. Proper control and optimization of these attributes are necessary for achieving consistent product quality.

A Design of Experiments (DoE) study is conducted to systematically evaluate the impact of CMAs and CPPs on the formulation. The goal is to determine how variations in these factors affect the CQAs. The DoE involves planning and conducting a series of experiments to understand the relationships between the CMAs, CPPs, and CQAs. This helps in identifying the optimal conditions and formulation parameters. Table 2 summarizes the quality attributes of Esomeprazole Biphasic Micro Pellets (MUPS) Tablets, 20 mg & 40 mg.

For this product, assay, content uniformity, dissolution, and degradation products are identified as subsets of Critical Quality Attributes (CQAs) that may be influenced by formulation and/or process variables. Therefore, the impact of these CQAs will be investigated by altering variables derived from Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs).

Based on the results from the DoE, high-risk formulation variables and material attributes are optimized. This means making adjustments to the formulation and process to ensure that all CQAs are consistently met. After optimization, a final risk assessment is conducted to verify that the adjusted formulation and process parameters meet all required CQAs. This assessment ensures that the final product specifications are achieved.

Bioequivalence Study

This study was a randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover bioequivalence trial involving healthy adult subjects under fasting conditions. The aim was to evaluate the bioequivalence of a single 40 mg dose of either Esomeprazole Biphasic MUPS tablets or Nexium, administered with 250±2 ml of water in each period, while subjects were seated.

The study adhered to multiple ethical and regulatory guidelines, including those set by the Indian Council of Medical Research (ICMR), New Drugs and Clinical Trials Rules (India, 2019), Good Clinical Practice (GCP), and other international standards.

Blood samples were collected from each subject at 21 time points: pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 hours post-dose. Each sample consisted of 5 mL of blood collected in vacutainers with K2EDTA. To maintain IV cannula patency, 0.5 mL of blood was discarded before each sample collection, and 0.5 mL of normal saline was injected afterward.

Post-collection, the blood samples were centrifuged at 4000 RPM for 10 minutes at 5±2°C. Plasma was then divided into two aliquots and stored at -25±5°C for up to 12 hours before being transferred to -75±10°C with dry ice for further storage.

Plasma samples were analyzed using a validated LC/MS/MS method (Thermo Discovery Max) to quantify esomeprazole levels. The method demonstrated linearity from 4.014 to 10,034.983 ng/mL. Esomeprazole and its internal standard, Esomeprazole D6, were extracted using 2.5 mL of ethyl acetate. Precision and accuracy of the method were within 15% of the nominal values, except for the lower limit of quantification (LLOQ) quality control, which was within 20% of nominal values.

In the study, all subjects' plasma samples were analyzed using a Non-Compartmental Analysis (NCA) model with Phoenix® WinNonlin software, version 8.0, to evaluate the pharmacokinetic parameters of esomeprazole. The parameters assessed included peak plasma concentration (Cmax), area under the plasma concentration-time curve (AUC), time to reach peak concentration (Tmax), elimination half-life (t½), and elimination rate constant (Kel), among others.

For statistical analysis, ANOVA was performed on the log-transformed pharmacokinetic parameters Cmax, AUC0-t, and AUC0-inf for esomeprazole. This analysis was conducted using Proc GLM in SAS Statistical Software, Version 9.4 or higher, from SAS Institute Inc., Cary, USA.

RESULTS AND DISCUSSION

The Quality Target Product Profile (QTTP) was established through reverse engineering and analysis of innovator products. The parameters defining the QTTP are detailed in Table 1. This approach provided a comprehensive understanding of the product characteristics and performance criteria necessary for meeting the desired quality standards.

Table 1: Quality Target Product Profile of the Esomeprazole Biphasic Micro Pellets (MUPS) Tablets, 20 mg & 40 mg.

QTPP Elements	Target	Justification
Dosage form	Delayed Release MUPS Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design	Oral	Immediate release design needed to meet label claims
Route of administration	Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength	Eq. base 40 mg, Eq. base 20 mg	Commercial requirement

Pharmacokinetics	Fed Study 90% confidence interval of the PK parameters, AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} should fall within BE limits (80.00%-125.00%)	Bioequivalence requirement
Stability	At least 18 Month shelf life at room temperature	Needed for commercialization
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Meeting the same or compendia or other applicable (quality) standards (i.e., identity, assay, purity, and quality).
	Identification	
	Assay	
	Content Uniformity	
	Dissolution	
	Degradation Products	
	Water Content	
	Microbial Limits	
Container closure system	Alu-Alu Blister	Needed to Commercialization

Rationale of Critical Quality Attributes (CQA)

The assay was identified as a Critical Quality Attribute (CQA) due to its significant impact on both the safety and efficacy of the drug product. Variability in the assay can directly affect the product's performance, making it essential to monitor and control this parameter rigorously. Process variables have the potential to influence the assay results, which is why it has been closely evaluated throughout both product and process development phases. Ensuring consistent and accurate assay measurements helps mitigate risks associated with variability and ensures the drug product meets its quality standards.

Content uniformity was deemed a Critical Quality Attribute (CQA) because variability in this parameter can significantly impact the safety and efficacy of the drug product. Given that both formulation and process variables—especially during the blending of Multi-Unit Pellet System (MUPS) pellets for compression—can affect content uniformity, this attribute has been thoroughly evaluated throughout the product and process development stages. Consistent content uniformity is crucial for ensuring that each dose of the product delivers the intended therapeutic effect and maintains overall product quality.

Dissolution was identified as a Critical Quality Attribute (CQA) for both immediate-release and modified-release enteric-coated Multi-Unit Pellet System (MUPS) pellets, given its critical role in influencing bioavailability. Failure to meet the dissolution specifications can significantly affect the drug's therapeutic efficacy. Both formulation and process variables impact the dissolution profile, necessitating rigorous evaluation throughout the formulation and process development phases.

For immediate-release pellets, the dissolution specifications were set as follows.

1. Acid Resistance (0.1N HCl): At least 80% of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) must be recovered after 2 hours of acid treatment.

2. Buffer Stage (pH 6.8): At least 70% of the labeled amount of esomeprazole must be dissolved after 45 minutes in the buffer solution.

For modified-release pellets, the dissolution criteria were identical for acid resistance and buffer stage.

1. Acid Resistance (0.1N HCl): The recovery requirement is the same as for immediate-release pellets, with a minimum of 80% of the labeled amount of esomeprazole recovered after 2 hours of acid treatment.

2. Buffer Stage (pH 6.8): Similar to immediate-release pellets, at least 70% of the labeled amount must be dissolved after 45 minutes.

Additionally, for modified-release MUPS pellets, dissolution was also assessed at a Buffer Stage (pH 6.0) with a specification that no more than 10% of the labeled amount of esomeprazole should dissolve under these conditions.

This thorough evaluation of dissolution specifications ensures that both immediate-release and modified-release formulations meet the required standards for bioavailability, ultimately supporting the efficacy and safety of the drug product.

Degradation products were designated as a Critical Quality Attribute (CQA) due to their potential impact on safety and the necessity to control their levels to minimize patient exposure, as outlined by ICH guidelines and Reference Listed Drug (RLD) characterization. The acceptable limits for degradation products are set in accordance with ICH standards to ensure product safety and efficacy.

Since both formulation and process variables can influence the formation of degradation products, these factors have been closely monitored throughout the product and process development phases.

Compliance was assessed against the following specifications.

- **Individual Impurity**: No more than 0.5% of any single impurity.
- **Total Impurities**: No more than 2.0% for all impurities combined.

These criteria are crucial for ensuring that degradation products remain within acceptable levels, thereby maintaining the safety and quality of the drug product. Summary reports of CQA identification with individual justification is presented in Table 2.

Table 2: Critical Quality Attributes (CQAs) of Esomeprazole Biphasic Micro Pellets (MUPS) Tablets, 20 mg & 40 mg.

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Acceptable color and shape to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Oval & acceptable to patient	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens.
	Score configuration	Unscored	No	Unit dose of 20 mg & 40 mg will be administered at a time, so scoring is not considered in design.
Identification		Positive for Esomeprazole	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of Label claim	Yes	Assay variability can impact both safety and efficacy. Process variables may influence the assay of the drug product. Therefore, the assay has been assessed throughout product and process development.
Content uniformity		Conforms to USP <905> Uniformity of Dosage Unit	Yes	Variability in content uniformity can impact safety and efficacy. Since both formulation and process variables, particularly during the blending of MUPS pellets for compression, affect content uniformity, this Critical Quality Attribute (CQA) has been evaluated throughout product and process development.
Dissolution		Acid Stage- NMT 10 % drug dissolved Buffer Stage- NMT 70% drug dissolved	Yes	Failure to meet the dissolution specification can affect bioavailability. Both formulation and process variables influence the dissolution profile. Therefore, this Critical Quality Attribute (CQA) has been examined throughout the formulation and process development stages.
Degradation Products		ny individual impurity- NMT 0.5% Total impurities: NMT 2.0%	Yes	Degradation products can affect safety and must be controlled to limit patient exposure, in accordance with ICH guidelines or Reference Listed Drug (RLD) characterization. The acceptable levels for degradation products are established based on ICH requirements. Since formulation and process variables can influence the formation of degradation products, these have been evaluated throughout product and process development.
Residual Solvents		USP <467> option 1	Yes*	Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Therefore, formulation and process variables are unlikely to impact this CQA.

Water Content by KF	NMT 5.0% w/w	No	Water content can influence degradation and microbial growth of the drug product, making it a potential Critical Quality Attribute (CQA). Therefore, maintaining moisture levels within this range is essential to ensure that stability is not compromised.
Microbial Limits	Meets relevant pharmacopoeia criteria	Yes*	Non-compliance with microbial limits will impact patient safety. However, in this case, the risk of microbial growth is very low because granules will dry at high temperature. Therefore, this CQA will not be discussed in detail during formulation and process development

* Formulation and process variables are unlikely to Impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and should be addressed accordingly.

Selection of excipients and its composition

The selection of excipient grade and supplier was based on intended manufacturing process as well as supplier technical guide.

Esomeprazole Magnesium Trihydrate (Micronized) is utilized as an Active Pharmaceutical Ingredient (API), providing the primary therapeutic effect of the formulation. Microcrystalline Cellulose Spheres, specifically Vivapur MCC Spheres 200, serve as starter beads, offering initial structure and consistency in tablets. Hypromellose 2910 USP, known commercially as HPMC 5cps, functions as a binder to hold the formulation together, a barrier agent for controlled release, and a cushioning agent in top coatings to enhance protection.

Povidone K30 USP, branded as Kollidon 30, is a key binder that ensures the cohesion and integrity of the formulation. Mannitol Milled, or Pearlitol 25C, is employed as a diluent to increase volume and a static charge remover to improve flow properties. Simethicone Emulsion 30% USP, known as BC Simethicone Antifoam PD30S, acts as an anti-foaming agent, reducing foam formation during processing.

Sodium Lauryl Sulfate, branded as Kolliphor Fine, functions as a surfactant to improve the solubility and mixing of ingredients. Potassium Hydroxide Pellets, provided by Emprove Essential, are used to adjust and maintain the formulation's pH. Purified Talc Micronized, under the brand Luzenac M, serves as an antistatic agent to prevent static electricity build-up.

Hydroxy Propyl Cellulose EP, USP NF, or Klucel EF, acts as a barrier coating agent, protecting active ingredients and controlling release rates. Propylene Glycol BP functions as a plasticizer, enhancing the flexibility and processing characteristics of the formulation.

Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion 30% EP, USP NF, branded as Eudragit L30D-55, is used as an enteric coating agent that dissolves at pH levels above 5.8 to safeguard active ingredients from stomach acid. PlasACryl HTP20 provides a thixotropic dispersion with anti-tacking, plasticizing, and stabilizing agents, serving as a processing aid during the enteric coating stage.

Triethyl Citrate acts as a plasticizer, improving the flexibility and processing properties of coating materials. Methyl Methacrylate and Methacrylic Acid Copolymer Dispersion 30%, or Acrycoat FS 30D, functions as an enteric coating agent that dissolves at pH levels above 7.0, facilitating controlled release.

Polyethylene Glycol 6000, known as Macrogol BP Type 6000, is used as a cushioning agent to improve the formulation's texture and handling. Quinoline Yellow Lake serves as a coloring agent, providing visual appeal. Lastly, Sodium Alginate, branded as Manucol LKX, functions as a binder, enhancing ingredient cohesion and formulation stability.

Methacrylic Acid and Ethyl Acrylate Copolymer, branded as Eudragit L 100-55, functions as a functional coating agent that provides gastric resistance and enteric protection, dissolving at pH levels above 5.5. Microcrystalline Cellulose 105, known commercially as Comprecel® M105, serves as both a binder and diluent, enhancing the formulation's structural integrity and volume. Hypromellose 100 mPas, or Methocel K 100 Premium LV DC2, acts as a binder and film former, helping to bind ingredients together while forming a protective film.

Silicified Microcrystalline Cellulose HD 90, branded as Prosolv SMCC HD 90, is used as a diluent, improving the flow properties and compressibility of the formulation. Sodium Bicarbonate acts as an alkalizing and floating agent, adjusting pH levels and promoting buoyancy in the formulation. Iron Oxide Red is utilized as a coloring agent, providing a distinctive color for visual identification.

Microcrystalline Cellulose 200LM, known as Comprecel® 200LM, also functions as a binder and diluent, contributing to the formulation's cohesion and volume. Hydrogenated Vegetable Oil, branded as Lubritab®, serves as a lubricant, facilitating the manufacturing process by reducing friction between

components. Crosspovidone Type A, or VIVAPHARM® PVPP XL, acts as a disintegrant, aiding in the rapid disintegration of tablets in the digestive system.

Opadry II clear, with the identifier 85F190000, is used as a coating agent, providing a clear, protective layer over the formulation. Each ingredient plays a crucial role in ensuring the stability, efficacy, and usability of the final pharmaceutical product.

The composition of materials in esomeprazole biphasic MUPS tablets was optimized through a systematic approach involving Design of Experiments (DoE). This approach was guided by the criticality of material attributes and critical process parameters. The experimental outcomes, which optimized the batch composition, are detailed in Table 4. This optimization ensured that both the formulation and manufacturing processes were refined to meet the necessary quality standards and performance requirements for the tablets.

Development of Manufacturing process and defined Process Parameters

The development of the manufacturing process and the definition of process parameters were guided by the outcomes obtained from Design of Experiments (DoE). This systematic approach ensured that the final product consistently met the identified Critical Quality Attributes (CQAs). By aligning the manufacturing process with the experimental findings, we were able to refine the process parameters to achieve a product that adheres to the required quality standards and performance criteria. Step by step process is presented in Table 3.

Table 3: Manufacturing Process Flow.

Materials Addition	Manufacturing steps	Process Parameters to be recorded during routine manufacturing
Common Manufacturing Steps		
Microcrystalline Cellulose Sphere (MCC Sphere 200), Esomeprazole Magnesium Trihydrate, Hypromellose 2910 5cps, Povidone K-30, Purified Talc, Mannitol, Simethicone Emulsion 30%, Sodium Lauryl Sulfate (Fine), Disodium hydrogen phosphate dihydrate, Sodium hydroxide and Isopropyl Alcohol	 **Drug Loading**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Hypromellose 2910 5cps, Mannitol (milled), Mannitol, Simethicone Emulsion 30%, Purified Talc, Propylene Glycol , Sodium hydroxide and Titanium Dioxide.	 **Seal Coating**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Methacrylic Acid Copolymer Type-C (Acrycoat ERD)	 **Enteric Coating-I**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Immediate Release Enteric Coating step		
Methacrylic Acid Copolymer Type-C (Acrycoat ERD), Polyacrylate Dispersion 30% (Eudragit NM 30D), Ethyl Acrylate & Methyl Methacrylate Copolymer 30% Dispersion (Acrycoat FS 30D), Citric Acid Monohydrate, Propylene Glycol,	 **Enteric Coating-II**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Opadry II Clear	**Top Coating-I**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
	Top Coating-II	Inlet Air volume Inlet Air

Hypromellose 2910 5cps , Povidone K- 30, Purified Talc, Simethicone Emulsion 30%, Quinolone Yellow Lake		temperature Spray rate Atomizing air pressure Relative humidity
Methacrylic Acid Copolymer Type-C (Acrycoat ERD)	**Top Coating-III**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Modified Release Enteric Coating step		
Methacrylic Acid Copolymer Type-C (Acrycoat ERD), Ethyl Acrylate & Methyl Methacrylate Copolymer 30% Dispersion (Acrycoat FS30D), Propylene Glycol;	 **Enteric Coating-II**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Opadry II Clear	 **Top Coating-I**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Hypromellose 2910 5cps , Purified Talc, Simethicone Emulsion 30%, Sodium Alginate, Quinolone Yellow Lake	 **Top Coating-I**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Immediate Release Top spray Granulation		
Microcrystalline Cellulose (Vivapur 301), Lactose Monohydrate 200 M, Silicified Microcrystalline (SMCC 50), Crospovidone Type-A, Citric Acid Monohydrate, Croscarmellose Sodium, Sodium Bicarbonate, Mannitol 200 SD, Povidone K 30,	 **Top Spray Granulation**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity
Immediate Release Enteric coated pellets, Immediate Release top spray granules, Mannitol 200 SD, Silicified Microcrystalline (SMCC 50), Silicified Microcrystalline (SMCC HD90), Croscarmellose Sodium, Crospovidone Type-A, Purified Talc, Hydrogenated Vegetable Oil.	 **Extra granular blending & Lubrication**	Blending time Blending speed
Modified Release Top spray Granulation		
Modified Release Enteric coated pellets, Hypromellose 2910 5cps, Hypromellose 2208-100 cps, Hypromellose 2208-4000 cps, Methacrylic Acid and Ethyl Acrylate Copolymer 1:1 (Acrycoat L 100D),Sodium alginate, Microcrystalline Cellulose (Vivapur 301), Lactose Monohydrate 200 M, Silicified Microcrystalline (SMCC HD90), Sodium bi	 **Top Spray Granulation**	Inlet Air volume Inlet Air temperature Spray rate Atomizing air pressure Relative humidity

carbonate, Croscarmellose Sodium, Povidone K 30, Ferric oxide, Povidone and Quinolone Yellow Lake.		
Modified Release top spray granules, Hypromellose 2208-100 cps, Silicified Microcrystalline (SMCC HD90), Microcrystalline Cellulose (Vivapur 301), Sodium Bicarbonate, Purified Talc, Ferric oxide, Magnesium Stearate	 **Extra granular blending & Lubrication**	Blending time Blending speed
	 **Compression**	**Pre & main compression force Main Compaction Force Feeder type & force Turret speed, Depth of filling Room RH (%) & Room temp.**
Opadry II Clear, Ethanol 96%	 **Coating**	**Pan speed Atomizing Air pressure Solid content Pump speed Inlet air temperature &RH Air volume**
Alu-Alu Blister	 **Packaging**	Machine speed

Table 4: Raw Materials Details and Composition used for Manufacturing of Scale up of esomeprazole Biphasic Micro Pellets (MUPS) Tablets, 20 mg & 40 mg.

Composition	**Quantity (mg) /Biphasic Micro Pellets Tablets**	
	40 mg	**20 mg**
Each Biphasic Micro Pellets Tablets contains		
A. Active Ingredient:		
Esomeprazole Enteric Coated Micro Pellets (14.0 % w/w as Esomeprazole)*	285.713 (Eqv. to 40 mg Esomeprazole as Magnesium TrihydrateUSP)	235.294 (Eqv. to 20mg Esomeprazole)
B. Immediate Release Enteric Micro Pellets Layer with Cushioning Agents		
Esomeprazole Enteric Coated Micro Pellets (70% of the total enteric coated micro pellets)	199.999	164.707
Povidone K 30	8.306	6.840
Microcrystalline Cellulose (Vivapur 301)	35.991	29.640
Lactose Monohydrate (Pharmatose 200M)	34.607	28.500
Silicified Microcrystalline Cellulose (SMCC 50)	55.629	45.813
Crospovidone (Type A)	11.536	9.500
Citric Acid Monohydrate	6.921	5.700
Sodium Bicarbonate	6.921	5.700
Croscarmellose Sodium	4.614	3.800
Mannitol (Spray Dried)	69.213	57.000
Purified Talc	2.307	1.900
Hydrogenated Vegetable Oil	2.307	1.900
Silicified Microcrystalline Cellulose (SMCC HD90)	q.s to 461.423 mg (Approx. 23.072)	q.s to 380.00 mg (Approx. 19.000 mg)
C. Modified Release Enteric Micro Pellets Layer		

with Cushioning Agents		
Esomeprazole Enteric Coated Micro Pellets (30% of the total enteric coated micro pellets)	85.714	70.589
Hypromellose 2910-5 cps	14.662	12.075
Hypromellose 2208-100 cps	65.631	54.050
Hypromellose 2208-4000 cps	5.586	4.600
Purified Talc	1.396	1.150
Sodium Alginate	3.910	3.220
Sodium Bicarbonate	34.910	28.750
Methacrylic Acid and Ethy Acrylate Copolymer 1:1 (Acrycoat L100D)	3.910	3.220
Lactose Monohydrate	19.550	16.100
Microcrystalline Cellulose (Vivapur 301)	18.684	15.387
Croscarmellose Sodium	3.910	3.220
Ferric Oxide (Iron Oxide Sicovit Red 30 E172)	0.154	0.127
Povidone K 30	5.865	4.830
Quinoline Yellow Lake	0.039	0.032
Magnesium Stearate (Veg)	1.396	1.150
Silicified Microcrystalline Cellulose (SMCC HD 90)	q.s. to 279.282 mg (Approx. 13.965 mg)	q.s to 230.00 mg (Approx. 11.500 mg)
D. Coating Agents		
Opadry II Clear (85F190000)	14.814	12.200
Ethanol 96%	74.070	61.00
Purified Water	QS	q.s.
Average Weight of Coated Biphasic Micro Pellet tablets	755.517	622.200 mg
***Composition of the Enteric Coated Micro Pellets**		
Microcrystalline Cellulose Spheres (Vivapur MCC Speheres 200)	42.857	35.294
Esomeprazole Magnesium Trihydrate	44.600 (Eqv. To 40mg Esomeprazole)	22.301 (Eqv. to 20mg Esomeprazole)
Sodium Lauryl Sulfate (Kolliphor SLS Fine)	1.143	0.941
Disodium Hydrogen Phosphate Dihydrate	1.286	1.059
Sodium Hydroxide	0.486	0.400
Hypromellose 2910-5cps	38.129	31.400
Povidone K 30	8.714	7.176
Purified Talc	6.571	5.412
Simethicone Emulsion 30%#	0.806	1.747
Propylene Glycol	1.429	1.176
Titanium Oxide	0.857	0.706
Methacrylic Acid Copolymer Type C Dispersion 20% (Acrycoat ERD)#	112.971	465.175
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion 30% (Eudragit NM 30D)#	3.427	9.413
Quinoline Yellow Lake	0.100	0.082
Citric Acid Monohydrate	1.000	0.824
Sodium Alginate	0.429	0.353
Methyl Methacrylate and Methacrylic Acid Copolymer Dispersion 30% (Acrycoat FS-30D)#	17.571	48.237
Isopropyl Alcohol	11.827	11.827
Mannitol (milled)	q.s. to 285.713 mg (Approx. 3.337 mg)	q.s to 235.294 mg (Approx. 17.176 mg)

Bioequivalence Study Outcome

From the data presented in Table 5, it is clear that the participants in the study fall within the specified criteria outlined in the study protocol. The age range of the subjects was between 18 and 45 years, and their Body Mass Index (BMI) ranged from 18.5 to 24.9 kg/m², both of which are within the acceptable ranges set by the study protocol.

Table 5: Mean Demographic Data.

	Age	Height	Weight	BMI
Min	21	160.3	55.85	18.9
Max	42	181.3	77.70	24.8
Mean	33.08	170.7	65.28	22.4
SD	6.23	6.0	6.13	1.7
%CV	18.60	3.5	9.35	7.7

Fig. 2 illustrates the mean plasma concentration versus time profiles over a 24-hour period for both the test formulation (Esomeprazole Biphasic MUPS Tablets 40 mg) and the reference formulation (Nexium 40 mg). The graph shows that both formulations achieve peak plasma concentrations at 3 hours. However, the Esomeprazole Biphasic MUPS Tablets exhibit an additional peak at 4 hours, with elevated drug concentrations maintained until 16 hours. This extended exposure indicates that the biphasic formulation design of the Esomeprazole Biphasic MUPS Tablets results in a prolonged presence of the drug in the systemic circulation.

The data also reveals a 17.3% higher drug availability for Esomeprazole Biphasic MUPS Tablets between 4 and 16 hours compared to Nexium 40 mg. This increased drug availability suggests a longer mean residence time (MRT), which is beneficial for extended acid suppression. Therefore, the biphasic release characteristics of the Esomeprazole Biphasic MUPS Tablets provide a longer duration of effective drug presence in the bloodstream compared to the conventional delayed-release formulation of esomeprazole.

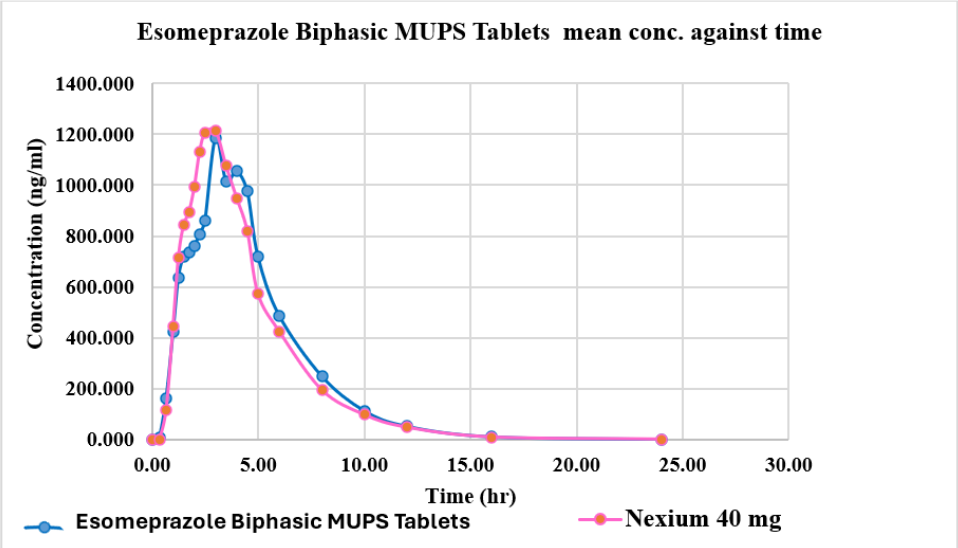

Fig 2: The mean plasma concentration of esomeprazole vs. time profile over 24 hours on linear scale for Esomeprazole Biphasic MUPS Tablets and Nexium.

The pharmacokinetic analysis of the study indicated that the Esomeprazole Biphasic Micro Pellets tablet formulation demonstrated a longer Tmax compared to Nexium 40 mg. Specifically, the arithmetic mean and standard deviation of the pharmacokinetic parameters for Esomeprazole Biphasic Micro Pellets and Nexium 40 mg were as follows.

- **AUC0-t**: 5711.549 (3397.785) ng/mL and 5615.535 (3302.086) ng/mL
- **AUC0-inf**: 5751.938 (3409.709) ng/mL and 5615.535 (3302.086) ng/mL
- **Cmax**: 1416.570 (722.397) ng/mL and 1670.887 (651.569) ng/mL
- **Median Tmax**: 3.0 hours and 2.125 hours, respectively

Additionally, secondary pharmacokinetic parameters such as the elimination rate constant (Kel) and the half-life (t1/2) were recorded, including their arithmetic means and standard deviations for all participating subjects. Detailed Pharmacokinetic summary reports are presented in Table 6.

Table 6: Pharmacokinetic data comparison after single dose administration of Esomeprazole Biphasic MUPS Tablet 40 mg and Nexium 40 mg Mean (±SD) of PK parameters of Esomeprazole.

Parameters (unit)	Treatment T (Othera 40 mg)	Treatment R (Nexium 40 mg)
#T_{max} (hr)	3.000 (1.250 - 5.000)	2.125 (1.250 - 3.500)
AUC_{0-t} (ng*hr/ml)	5711.549 ± 3397.785	5615.535 ± 3302.086
AUC_{0-inf} (ng*hr/ml)	5751.938 ± 3409.709	5651.511 ± 3304.642
C_{max} (ng/ml)	1416.570 ± 722.397	1670.887 ± 651.569
K_{el} (1/hr)	0.574 ± 0.272	0.569 ± 0.263
$t_{1/2}$ (hr)	1.421 ± 0.519	1.411 ± 0.500

#T_{max} is represented in median (min-max) value

SUMMARY

This new formulation of Esomeprazole, known as Biphasic MUPS Tablets, has been developed using a Quality by Design (QbD) approach. This innovative tablet releases medication in two stages via enteric-coated micro pellets with distinct pH-triggered dissolution profiles. The first layer of pellets releases 70% of the drug within 1-2 hours in the upper small intestine, akin to traditional delayed-release tablets. The second layer, designed to float and dissolve in the stomach, releases the remaining 30% of the drug over 3-5 hours further down the small intestine. This dual-stage release provides extended acid suppression and maintains effective pH levels to alleviate heartburn.

A randomized, open-label, two-way crossover bioequivalence study compared 40 mg Esomeprazole Biphasic MUPS Tablets with Nexium 40 mg gastro-resistant tablets. The study found that the new formulation was bioequivalent to Nexium in terms of key pharmacokinetic parameters (AUC0-t, AUC0-inf, Cmax). Both formulations reached peak plasma concentrations at 3 hours, with the Biphasic MUPS Tablets showing a secondary peak at 4 hours and sustained higher levels until 16 hours. The Biphasic MUPS Tablets demonstrated a 17.3% higher drug availability between 4 and 16 hours, indicating a longer mean residence time and more extended acid suppression compared to Nexium.

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