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DEVELOPMENT OF DELAYED RELEASE CAPSULES CONTAINING ENTERIC COATED MINI-TABLETS OF ESOMEPRAZOLE

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ABSTRACT

Now a day's innovative dosage forms like mini-tablets which having diameter ≤ 3mm attaining more eminence due to their simplicity of manufacturing and effective way of drug release mechanisms. They are more effective and patient friendly dosage forms than conventional dosage forms like tablets/capsules due to smaller size. They are manufactured just by modification in compression step using application of multi-tips tooling. Even they are more economical compare to complex and delicate pellets manufacturing process. Primary study shows that esomeprazole accomplishes better and more sustained acid control than other proton pump inhibitors but major problems accompanying are rapid degradation in gastric acid, BCS class III drug, short biological half-life and wide inter-intra individual variability in the bioavailability (50-90%) due to its low permeability. Enteric coated mini-tablets dosage form serves as promising approach as they can protect the drug substance from degradation in gastric media and avoids premature drug release due to smaller size, rapid transit time, higher surface area and higher dispersability in gastro-intestinal tract which leads to improved drug absorption compare to conventional dosage forms. Esomeprazole mini-tablets are manufactured using direct

compression technique and further evaluated for optimization of barrier coat and enteric coat using different types and levels of polymers to prepare robust and effective delayed release mini-tablets of esomeprazole.

Keywords: Direct compression, Multi-tips tooling, Barrier coat optimization, Enteric coating polymers

INTRODUCTION:

Mini-tablets are innovative and effective dosage forms among oral solid formulations having diameter ≤ 3 mm. They have wide application area. They can be administered by filling into capsules or by compressed within larger tablets or as such in mini-tablets form. Manufacturing process of mini-tablets is easy, robust and reproducible due to minor alternation in conventional compression process by application of specialized multi-tips tooling **[1,** Error! Reference source not found.**]**.

Table 1: Comparison of oral controlled release drug delivery systems [1-3]

Single units' dosage forms (Tablets, capsules)	Multi-units' dosage forms (Granules, pellets, mini-tablets)
Low effective surface area	High effective surface area
Gastric emptying rate is highly variable and also dependent on presence or absence of food	Gastric emptying is more predictable and less dependent on presence or absence of food
Higher inter-intra individual variability in absorption rate	Lesser inter-intra individual variability in absorption rate
Higher risk of overdose and local irritation	Lower risk of overdose and local irritation
Simple manufacturing process	Complicated manufacturing process

Suitability of multi-tip tooling compare to conventional manufacturing requirements **[**Error! Reference source not found.**, [6]]**

- No need for specialized manufacturing equipments, only multi-tips tooling required instead of conventional compression tooling.
- High efficiency and low cost (Higher output in short period of time) compare to complex granule/pellet manufacturing techniques.

Figure 1: Multi-tips tooling

Prominence of mini-tablets compare to other dosage forms **[**Error! Reference source not found.**,** Error! Reference source not found.**-** Error! Reference source not found.**]**

- Uniformity in dimensions (Shape and size) helpful in trouble free handling during coating/packaging.
- Easy, robust and reproducible manufacturing process compare to granules/pellets. Simplicity in manufacturing methods gives uniform dosage units so batch to batch variability is lower.
- Patient centric drug delivery systems for targeted population due to lesser inter-intra individual variability, better swallowing, flexible dosing regimen, lesser chances of dose dumping.
- Mini-tablets can be modified to impart different drug release kinetics and doses. Different incompatible drug substances can be combine into single drug delivery unit which decreases dosing frequency and/or polypharmacy therapy issues.
- Miniature size leads to extensive dispersability throughout gastrointestinal tract is accountable for consistent drug release kinetics and lower local irritation.
- Pellets are spherical units which are produced by complex techniques like fluid bed granulation or extrusion-spheronization techniques, while mini-tablets are manufactured by conventional compression methods. This ultimately saves time and money.
- Higher stability of mini-tablets due to no requirement of any specific solvent system or high shearing techniques in manufacturing process.
- Mini tablets having smooth and stable surface along with high mechanical resistance compared to granules. Easy of handling during process like coating and requires less coating material than granules.

Esomeprazole is a benzimidazole derivative belonging to a group of proton pump inhibitors. It inhibits gastric acid secretion by acting at the final step of the acid secretory pathway. It is extensively used in the treatment of dyspepsia, peptic ulcer disease, gastro esophageal reflux disease and zollinger-ellison syndrome **[[16], [17]]**.

Esomeprazole having higher potency in acid inhibition than other proton pump inhibitors.

The greater clinical efficacy of esomeprazole compared with omeprazole is due to its higher systemic bio-availability **[[18], [19]]**. Primary studies have shown that esomeprazole accomplishes better and more sustained acid control with a comparable acceptability and safety profile. Besides, Esomeprazole shows a more rapid onset of acid-suppression effect than Omeprazole and less inter-individual variation in acid control **[[19]]**. Moreover, a recent crossover study proved that Esomeprazole at a standard dose of 40 mg once daily provides more effective control of gastric acid at steady state than standard doses of Pantoprazole, Lansoprazole and Rabeprazole in patients with symptomatic gastroesophageal reflux disease (GERD). Esomeprazole treatment profits higher erosive esophagitis healing rates and provides better resolution of heartburn in more patients than any other **[[19], [20]]**.

The major problems associated with esomeprazole are as per below: **[[21]]**

- Rapid degradation in gastric media
- BCS class III drug so it having high water solubility and low permeability
- Short biological half-life (Around 1-1.5 hours)
- It shows wide inter- intra individual variability in the bioavailability (50-90%) due to its low permeability

Drug degradation in acidic media issue can be overcome by applying enteric coating on dosage form. Enteric coated dosage forms, once reach to the intestinal atmosphere activates the drug release mechanism which improve absorption at intestinal site. But premature drug release in the gastric region possibly results in the degradation of the drug or may cause local irritation of the gastric mucosa. Multiple unit dosage forms like mini-tablets can overcome such difficulties due to miniature size of units leads to rapid gastric transit time compared to enteric coated single unit conventional dosage forms. Multiple unit dosage forms disperse in gastro-intestinal tract more homogeneously than the conventional single unit dosage forms which leads to decreasing inter-intra individual variability of absorption. Mini-tablet formulation will intensify systemic bioavailability of esomeprazole due to smaller size and high effective surface area leads to higher dissolution. Delayed release mini tablets will serve as a promising approach for the delivery of the drugs like esomeprazole which having poor water solubility and permeability **[22]**.

Earlier studies show that there is a direct interaction between esomeprazole and eudragit polymers, so there is a need of barrier level – intermediate layer which

separates drug layer from enteric coating layer **[22]**.

Ideal properties of the candidate polymer for barrier coating are as following [22].

- It should appropriately separate both the drug layer and enteric coating layer without any incompatibility.
- It should be rapidly disintegrating in intestinal pH.
- It should not hinder the release of active material from the drug layer.
- It should have good film forming properties rendering its suitability for coating process.
- It should provide moisture barrier to the drug layer.

Application of enteric coating is most common to prepare delayed release dosage forms. Eudragit polymers are most widely used for this purpose. Among all eudragit polymers Eudragit L100, Eudragit L100-55, Eudragit L 12,5, Eudragit L30D-55 and Eudragit FL30D-55 are specially used to prepare delayed release dosage forms which having absorption site at upper-middle intestine part. These polymers are not dissolved or degraded in the acidic conditions but readily dissolves in the buffer having pH beyond 5.5 i.e. duodenal pH **[[21]]**.

Enteric coated dosage forms must have to pass acid resistance test - "The active ingredient should not be released or degraded more than 10 % in the 0.1 N HCl within 2 hours ". Lesser than optimal level of enteric coat may not provide sufficient shield to drug substance and higher than optimal level of enteric coat may retard the dissolution of drug substance. So optimal level of enteric coat plays very crucial role in designing of delayed release dosage forms.

MATERIAL AND METHODS:

Materials: Esomeprazole magnesium trihydrate (Raks Pharma Pvt. Ltd.), Microcrystalline cellulose (Avicel PH-102, FMC BioPolymer), Startab (DC starch 1500, Colorcon), Crospovidone (Polyplasdone XL-10, Ashland), Colloidal silicon dioxide (Aerosil 200, Evonik), Magnesium stearate (Ligamed MF-2V, Peter Greven). Kollidon VA 64 (BASF), Kollicoat IR (BASF), Kollicoat protect (BASF), Eudragit L30D-55 (Evonik), Eudragit NE 30 D (Evonik), Triethyl citrate (Indo-nippon chemicals), Talc (Luzenac pharma M, Imerys), Glyceryl monostearate (Spectrum chemical), Polysorbate 80 (Kolliphor PS 80, BASF). All materials used were of pharmaceutical grade.

Methods: Based on prior work it was concluded that drug substance esomeprazole is very cohesive in nature. Due to poor flow

properties in most of work conventional tablets were prepared either using wet granulation technique or by drug layering of pellets using fluid bed process. In present work mini-tablets of esomeprazole were formulated using simple and easy direct compression technique by selection of proper excipient having targeted particle size and particle size distribution. Compressibility, blend particle size distribution and flow properties are critical quality attribute for mini-tablets formulation. They play very crucial role in compression step of manufacturing process.

Flow property evaluation of drug substance: Bulk density, tapped density, carr's index, hausner ration and ring shear test were performed to evaluate flow properties of drug substance. Drug substance particle size is 166µ (Less than 250µ) so excipients were selected based on their particle size and flow properties in such way that final lubricated blend have desired particle size distribution.

- Fine blends with small PSD may have poor flow properties that do not support consistent die filling.
- Particle agglomeration through granulation increases particle size and improves flow properties. Granulated blends with large and wide PSD were shown to have inadequate die filling despite excellent flow properties.

Drug excipient compatibility study: This study was performed with all excipients used in present work, as alone and as binary mixture with drug substance (1:1 ratio) as per below mentioned pack style and storage condition. Physical observation carried out for any odd observation

- Pack details - White colored glass vials with rubber stopper & aluminum seal
- Storage condition - 40ºC/75% RH (Open/closed condition), 30ºC/65% RH and 25ºC/60% RH for 4 weeks.
- Test to be performed – Physical observations (Any color change or lump formation)

Force degradation study: This study was performed to evaluate chemical stability of drug substance. Details of study are mentioned in below table.

Table 2: Force degradation study of drug substance

Sr. No.	Stress condition		Condition
1	Hydrolysis	Acid hydrolysis	API treated with 0.1N HCl (5%w/v) and stir for 1Hr. at RT
		Alkali hydrolysis	API treated with 0.1N NaOH (5%w/v) and stir for 1Hr. at RT
2	Oxidation	Peroxide oxidation	API treated with 0.1N H_2O_2 (5%w/v) and stir for 1Hr. at RT
3	Heat	Thermal degradation	Exposed at 100°C ±2°C in oven for 24 Hrs.
4	Humidity	Humidity degradation	Exposed at 40°C ±2°C and 75% ±5% RH for 24 Hrs.
5	Light	Photo degradation	Exposed at 1.2 million Lux fluorescence for 7 days

Spectrophotometric analysis of drug substance: In the present work, esomeprazole was estimated by UV/Visible spectroscopy. The drug release study was carried out using phosphate buffer pH 6.8 as dissolution media.

Preparation of 0.1N hydrochloric acid: Solution of 0.1 N HCl prepared by diluting 8.5 mL of concentrated hydrochloric acid to 1000 mL with distilled water.

Preparation of phosphate buffer pH 6.8: 250 mL of 0.2 M monobasic potassium phosphate solution and 112 mL of 0.2 M sodium hydroxide solution was mixed in 1000 mL of volumetric flask and volume was made to 1000 mL with distilled water.

Preparation of standard stock solution in dissolution media: Accurately weighed 100 mg of esomeprazole was dissolved in 100 mL volumetric flask containing freshly prepared dissolution medium. From the obtained solution of esomeprazole (1000 µg/ mL), 10 mL of solution was taken and further diluted to 100 mL. The obtained solution of esomeprazole (100 µg/ mL) was used as standard stock solution.

Standard curve in phosphate buffer pH 6.8: From the stock solution 5, 10, 15, 20 and 25 mL were withdrawn and diluted to 100 mL with phosphate buffer pH 6.8 to yield concentration of 5, 10, 15, 20 and 25µg/mL respectively. Absorbance of each solution was measured at 302 nm using Shimadzu 1800 UV/Visible spectrophotometer. Samples were analyzed in triplicate, and the average values were used for plotting the graph of absorbance versus concentration µg/mL).

Mini-tablet core formulation:

(Figure 2)

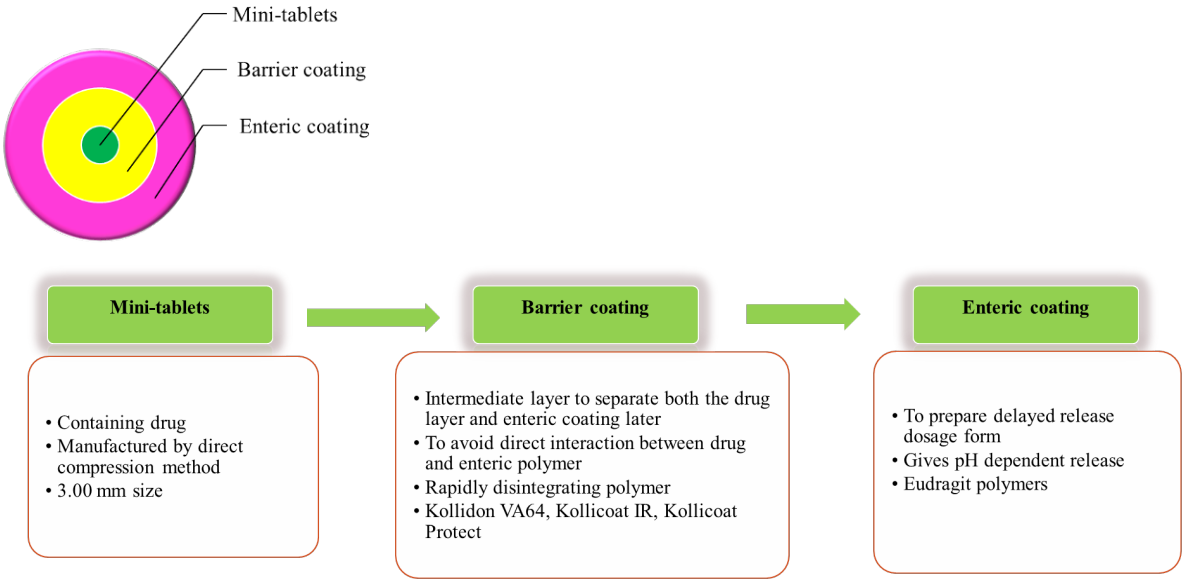

Figure 2: Esomeprazole mini-tablets formulation overview

Mini-tablets were manufactured using below mentioned optimized composition. Due to cohesive nature of drug substance first it was co-sifted (#25 sieve) and blended with colloidal silicon dioxide and then again co-sifted and blended with micro crystalline cellulose, startab and crospovidone. This blend was again passed through co-milling process (1016-micron screen, 1000 RPM) to improve content uniformity of drug substance. And finally blend was lubricated with magnesium stearate (Pre-sifted with #60 sieve). Blend was compressed into mini-tablets using 3.0 mm round, standard concave, embossing less multi-tips (10 tips) and counter bore die tooling by Korsch-XL 100 compression machine. These mini-tablets were evaluated IPQC parameters of lubricated blend as well as compressed mini-tablets. Further they were also evaluated for optimization of barrier coat and enteric coat.

Table 3: Composition of mini-tablet formulation by direct compression process

Batch number		F01	
Sr. No.	**Ingredients**	**mg/mini-tablet**	**%w/w (Individual)**
	Mini-tablet core (Size - 3.0 mm)		
1	**Esomeprazole mg trihydrate**	**2.50**	**10.00**
2	**Microcrystalline cellulose (Avicel PH-102)**	**5.38**	**21.50**
3	**Startab (DC starch 1500)**	**15.38**	**61.50**
4	**Crospovidone (Polyplasdone XL-10)**	**1.25**	**5.00**
5	**Colloidal silicon dioxide (Aerosil 200)**	**0.25**	**1.00**
6	**Magnesium stearate (Ligamed MF-2V)**	**0.25**	**1.00**
	Total (Mini-tablet core)	**25.00**	**100.00**

Barrier coat optimization trials: Different type of rapidly disintegrating polymers in different levels along with different anti-adherent agents (single or in combination) evaluated for barrier coat optimization as per below mentioned table. Barrier coating polymers having rapid disintegrating polymers so there is no major impact on drug release from dosage forms. Only visual observations were taken into consideration for process feasibility instead of going for chemical analysis of barrier coated mini-tablets.

Preparation of barrier coat dispersion: All the ingredients were weighed accurately. The stirrer and homogenizer were cleaned thoroughly. Purified water was weighed sufficient to prepare 10% w/w coating dispersion. Polymer was dissolved into half quantity of purified water under continuous stirring. Talc, magnesium stearate and iron oxide yellow disperse into half quantity of purified water using homogenizer for 10 minutes. Homogenized dispersion added into polymer solution under continuous stirring for 5 minutes. This dispersion was used for barrier coating. The colorant (Iron oxide yellow) was added to evaluate barrier coating uniformity by physical observation.

Table 4: Process parameters for barrier coating optimization trials

Process parameters	Range	Process parameters	Range
Pan	275 mm, 1 mm perforated	Gun	1.0 mm
Pre-warming			
Pan RPM	3 rpm (Jogging mode)	Time	5 minutes
Inlet air temperature	50°C to 55°C		
Coating			
Pan RPM	3 – 10 rpm	Spray rate	5 g/min to 10 g/min per kg
Inlet air temperature	50°C to 60°C	Product temperature	40°C to 50°C
Atomization air pressure	1 to 1.2 bar	Fan air pressure	1 to 1.2 bar
Post coating drying		10 minutes at 50°C	

Enteric coat optimization trials: Application of enteric coating is most common to prepare delayed release dosage forms. Eudragit polymers are most widely used for this purpose.

Composition of enteric coating

Eudragit L30D-55 was used as the enteric coating polymer to provide pH dependent release property to the mini-tablets. This polymer is not dissolved or degraded in the acidic conditions but readily dissolves in the buffer having pH beyond 5.5 i.e. duodenal pH. For enteric coatings, the addition of a plasticizer is essential to get effective coatings without cracks. Plasticizers are added to polymeric solutions or dispersions

to increase the workability and flexibility of the polymer. Triethyl citrate (TEC) was used as the plasticizer as it provides good flexibility to the Eudragit L30D-55 film. The concentration of TEC was taken 10 to 30% w/w of the dry polymer weight. Eudragit dispersion possesses sticky nature which may form lumps of mini-tablets during the coating. To prevent such occurrence an anti-adherent agent should be incorporated into the coating dispersion. Glyceryl monostearate (GMS) was used as the anti-adherent agent in the concentration 5% to 7.5 w/w of dry polymer weight. To disperse it effectively in water, a small amount of polysorbate 80 was also incorporated into the dispersion. Purified water was used in quantity sufficient to prepare 20 %w/w coating dispersion.

Lesser than optimal level of enteric coat may not provide sufficient shield to drug substance and higher than optimal level of enteric coat may retard the dissolution of drug substance. So optimal level of enteric coat plays very crucial role in designing of delayed release dosage form.

Preparation of coating solution: All the ingredients were weighed accurately and the stirrer and homogenizer were cleaned thoroughly. Purified water was weighed sufficient to prepare 20%w/w coating dispersion. Eudragit L30D-55 is a 30%w/w aqueous dispersion of Eudragit L100, so it already contains water. Hence, this quantity was deducted from the total quantity of water required to prepare 20%w/w coating dispersion.

Eudragit L30D-55 was weighed accurately and transferred in a beaker. 80%w/w of the purified water was boiled to 70-80ºC and taken in another beaker and was kept under homogenization. Polysorbate 80, glyceryl monostearate and triethyl citrate was added sequentially in the boiled water and the homogenization was carried out for 15 minutes. Remaining 20%w/w of the purified water was added to the homogenized mixture and it was cooled to room temperature. This homogenized mixture was then added to the Eudragit dispersion under gentle stirring and was mixed slowly for 5 minutes. This final dispersion was then filtered through 100# screen and used for the coating process with intermittent stirring.

Enteric coated mini-tablets were evaluated for the following parameters: [[16]]

- In-process quality control parameters
  - Physical description
  - Diameter and thickness
  - Hardness
- Chemical analysis
  - Assay

- Dissolution
  - Acid resistance test (Acid stage)
  - In-vitro dissolution (Buffer stage)

Chemical analysis: As per USP enteric coated dosage form should meet following acceptance criteria. The active ingredient should not be released or degraded more than 10% in the 0.1 N HCl within 2 hours to pass the acid resistance test. Enteric coated mini-tablets were filled in capsules equivalent to the dose of the esomeprazole. Acid resistance test was performed for 6 units with following process parameters.

- Media: 0.1 N Hydrochloric acid, pH 1.2
- Volume: 300 mL
- Apparatus: Type II (Paddle), 100 RPM
- Duration: 2 hours

After 2 hours, mini-tablets are carefully transferred into alcohol ensuring that no any acid droplets are carried with mini-tablets. Mini-tablets are dissolved thoroughly with the help of stirring and assayed for the drug content.

In vitro drug release studies of enteric coated mini-tablets were performed in automatic USP dissolution apparatus type II (Paddle). The dissolution tester USP was connected with electrolab peristaltic pump, for automatic sample withdrawal and replacement of media and electrolab fractional collector for collection of sample.

- Media: pH 6.8 sodium phosphate buffer
- Volume: 1000 mL
- Apparatus: Type II (Paddle), 100 RPM
- Time point: 5, 10, 15, 30, 45 and 60 minutes

The reservoir for the replacement of the media was also filled with phosphate buffer. The enteric coated mini-tablets were placed in the bowls when temperature was achieved to 37±0.5ºC and the dissolution apparatus was started. The collected samples were filtered through the 0.45 µm filter and analyzed by HPLC UV detection method. Cumulative percentage release of the drug was calculated from the area of the peak using the established formula.

Eudragit dispersion possesses sticky nature so different feasibility trials were taken to finalize the composition of enteric coat composition with respect to different level of anti-adherent agents and plasticizers. Visual observations were taken throughout the enteric coating process in all feasibility trials for below targeted checkpoints

- Gun blockage
- Sticking of mini-tablets with pan
- Lump formation within mini-tablets

Table 5: Process parameters for enteric coating optimization trials

Process parameters	Range	Process parameters	Range
Pan	**275 mm, 1 mm perforated**	**Gun**	**1.0 mm**
Pre-warming			
Pan RPM	**3 RPM (Jogging mode)**	**Time**	**5 minutes**
Inlet air temperature	**50°C to 55°C**		
Coating			
Pan RPM	**3 – 10 rpm**	**Spray rate**	**5 g/min to 10 g/min per kg**
Inlet air temperature	**40°C to 50°C**	**Product temperature**	**25°C to 30°C**
Atomization air pressure	**1 to 1.2 bar**	**Fan air pressure**	**1 to 1.2 bar**
Post coating drying/curing		**30 minutes at 50°C**	

Capsule size selection: Esomeprazole dose is 20 mg per day. Diameter of uncoated mini-tablet is 3.0 mm. To achieve near to spherical shape (For uniform coating) tablet thickness was set around 3.0 mm. Final dosage form – capsule size will be selected based on number of enteric coated tablets required to equivalent dose 20mg of esomeprazole.

Reproducible batch/Confirmatory batch for stability study (Finalized composition): A reproducible batch was manufactured by optimized composition for mini-tablets, barrier coating, enteric coating and optimized process. This batch was characterized for physical parameters, chemical analysis and load for stability study.

Stability study of reproducible batch/confirmatory batch: As per ICH guideline the reproducible batch (F28) was packed in 60cc, round, white HDPE bottle with child-resistant closure containing 1g desiccant (30 capsules per bottle) and kept on stability as per below…

Short term study (Stress condition): 40°C±2°C/75%RH ±5 % RH for 1 month

Time points for each condition – 1month

RESULTS AND DISCUSSION

Flow property evaluation of drug substance: As per below table it can be concluding that drug substance have poor flow as well cohesive nature.

Drug excipient compatibility study: Initially, all the samples showed off white blend characteristic. Physical observation of sample was done at every week for any color change or lumps formation and flow. There was a slight color change in the API alone from off white to light yellow in the conditions 40ºC/75% RH (Open & closed condition). Most of the samples of 40ºC/75% RH showed color change to light yellow from the off white blend. This may be attributed to the discoloration tendency of the API. There was no any color change or lumps formation observed in the samples of 30ºC/65% RH and 25ºC/60% RH. Samples

containing eudragit polymers turned into brown cake and brown granules.

Force degradation study: Data generated from this study are mentioned in **Table 7**.

Based on drug-excipient compatibility study and force degradation study it was concluded that…

1) API is relatively stable under condition of alkali, heat, humidity and light while it shows degradation under acidic and oxidative condition.

2) Eudragit polymers are acidic in nature so during drug-excipient compatibility drug substance shows interaction with eudragit polymers. So, it is concluded that there is direct interaction between drug and eudragit, so there is need to separate both the drug and enteric coating later by incorporating an intermediate layer – barrier layer of rapidly disintegrating polymer.

Spectrophotometric analysis of drug substance: (Table 8)

Mini-tablet core formulation: Results obtained for batch F01 are mentioned in **Table 9**.

Barrier coat optimization trials: (Table 10)

Visual observations from batch number F02 were sticking of mini-tablets with coating pan as well as with other mini-tablets and static charge development. Sticking of mini-tablets can be resolved by reducing polymer level and increasing level of talc. Static charge development was not diminished by modifying process parameters.

Therefore, it was decided to find a suitable alternative having all required properties to function as an effective barrier against acrylate polymers. Kollicoat IR and Kollicoat protect were such alternatives. They rapidly disintegrate in the pH 6.8 buffer and immediately release the drug. They possess good film forming properties as well as, they function as effective moisture barrier so they may also help in acid resistance mechanism.

Feasibility trials were carried out for assessing the feasibility of coating with these polymers. Also polymer level reduced and talc level increased to resolve sticking issue. Kollicoat IR showed sticking tendency and as a result, lumps were generated. However, trial with kollicoat protect demonstrate slight sticking issue but there was no any static charge development throughout the process. Hence to reduce sticking issue further polymer level optimization trials with reduced polymer level and small amount of magnesium stearate was also added in the coating dispersion to impart hydrophobicity to the coating layer which may in turn reduce the adherence of mini-tablets. (It was co-homogenized with talc during coating dispersion preparation). Sticking issue was

not observed with this composition of dispersion for barrier coating. So this composition of dispersion was finalized for barrier coating and further evaluated for optimization of level of barrier coat.

Another trial was executed with dispersion composition as per batch number F06. Samples were withdrawn for physical observation from auto-coater upon achieving of 5%, 10%, 15%, 20%, 25% and 30% weight gain from the single trial.

The barrier coat was optimized by keeping following targets: **(Table 11)**

- There should be no damage or erosion of barrier-coated tablets when they are rotated in a same pan coater for 15 minutes at 10 RPM.
- Tablets should be disintegrated within 15 minutes

Tablets surface covered poorly in case of batch F07 and F08 but in case of batch F09, F10, F11 and F12 it was satisfactory. Tablet defects observed in case of batch F07, F08 and F09. No tablet defects in case of F10, F11 and F12. Further tablets were disintegrated within 15 minutes in all the batches. Hence, it can be concluded that 20%, 25% and 30% levels of barrier coating are necessary. Therefore, 20% level of barrier coating was finalized for further enteric coating evaluation. The colorant was not added in further trials.

Enteric coat optimization trials: Results and discussion for enteric coating optimization trials mentioned in **Table 12**.

Visual observations of batch F16 were satisfactory with respect to enteric coating processing issues, but further handling of enteric coated mini-tablets may generate issues due to brittle nature of eudragit polymers. To reduce the brittle characteristic of the eudragit film, the concentration of plasticizer can be increased (Batch F15) as it imparts more flexibility to the film. However, it may also lead to develop rapid film forming tendency of the coating dispersion. As such the coating process suffers from the problem of gun choking. So, some other alternative should be exercised. One more feasibility trial was taken in combination with Eudragit NE 30D.

Eudragit NE 30D is a polymer having the highest flexibility among all the acrylate polymers. It has the elongation power of 365 times. It was decided to take Eudragit L 30D-55 and Eudragit NE 30D in the ratio of 9:1 in the coating dispersion. Remaining excipients level taken as per batch number – F16. Eudragit L 30D-55 dispersion was prepared by the same method described before. This

dispersion is added to the Eudragit NE 30D under gentle stirring. The final coating dispersion was filtered through 100# sieve and used for the coating process **(Table 13)**.

The enteric coated mini-tablet were evaluated for physical strength by using tablet friabilator. This test was performed to evaluate the physical strength of enteric coated mini-tablets so we can avoid the damage of enteric coat of mini-tablets during further handling of mini-tablets before capsule filling which may leads to dose dumping during dissolution test. Enteric coated mini-tablets from batch F16 and F17 (Equivalent to 6.5 g) were rotated for 500 rotations and evaluated for physical appearance **(Table 14)**.

Hence, it can be concluded that mini-tablets with enteric coat composition of batch F17 is selected for further enteric coat level optimization trials.

In order to optimize the level of enteric coating, same enteric composition as batch of F17 was used to manufacture below trial and samples were withdrawn for chemical analysis from auto-coater upon achieving of 20%, 30%, 40%, 50%, 60%, 70% and 80% weight gain from the single trial. Physical observations for batches all batches were same as batches F16 and F17. Satisfactory processing parameters obtained up to 80% level enteric coating. Enteric coated mini-tablets were counted with the use of manual tablet counter and filled into hard gelatin capsules to perform dissolution test **(Table 15)**.

Capsule size selection: Compressed mini-tablet weight was 25.0 mg. 8 uncoated mini-tablets was fillable into size 1 capsule but after barrier coating and enteric coating process, volume of mini-tablets was increased. So size 1 capsule was not preferable. 8 enteric coated mini-tablets was fillable into Size 0 capsule. Size 0 capsule is finalized as final dosage form **(Figure 4)**.

Confirmatory and fine tuning trials carried out to finalize the optimal level of enteric coat required to protect the dosage form in acidic media. Samples were withdrawn for chemical analysis from auto-coater upon achieving of 53%, 56% and 60% weight gain from the single trial **(Table 17)**.

From results **(Figure 5)** it can be concluded that minimum 60% level of enteric coat is required to protect the drug substance in gastric media.

Reproducible batch/Confirmatory batch for stability study (Finalized composition) (Table 18).

Table 6: Flow property evaluation of drug substance

Sr. No.	Parameters	Result	Conclusion
1	Bulk density	0.30	-
2	Tapped density	0.43	-
3	Carr's index	29.85	Poor flow
4	Hausner ratio	1.43	Poor flow
5	FFC value – Ring shear test - Flow function coefficient (RST-XS Dr. Dietmar Schulze)	2.9	Cohesive material

Table 7: Force degradation study results (Related substance by HPLC)

Sr. No.	Stress condition	Total known impurities			Total unknown impurities	Total impurities
		Omeprazole N-oxide	5-Methoxy-2-Mercapto benzimidazole	Omeprazole sulfone		
	Limit (As per COA)	NMT 0.1	NMT 0.15	NMT 0.2	NMT 0.1	NMT 0.5
1	Acid hydrolysis	ND	0.09	ND	14.15	14.24
	Alkali hydrolysis	ND	ND	ND	0.05	0.05
2	Peroxide oxidation	ND	ND	1.35	0.03	1.38
3	Thermal degradation	ND	0.01	ND	0.05	0.06
4	Humidity degradation	ND	0.01	ND	0.04	0.05
5	Photo degradation	ND	0.10	ND	0.04	0.14

Table 8: Spectrophotometric analysis of drug in phosphate buffer pH 6.8 at 302 nm

Conc.(µg/mL)	Absorbance (Average)
5	0.148
10	0.337
15	0.522
20	0.707
25	0.885

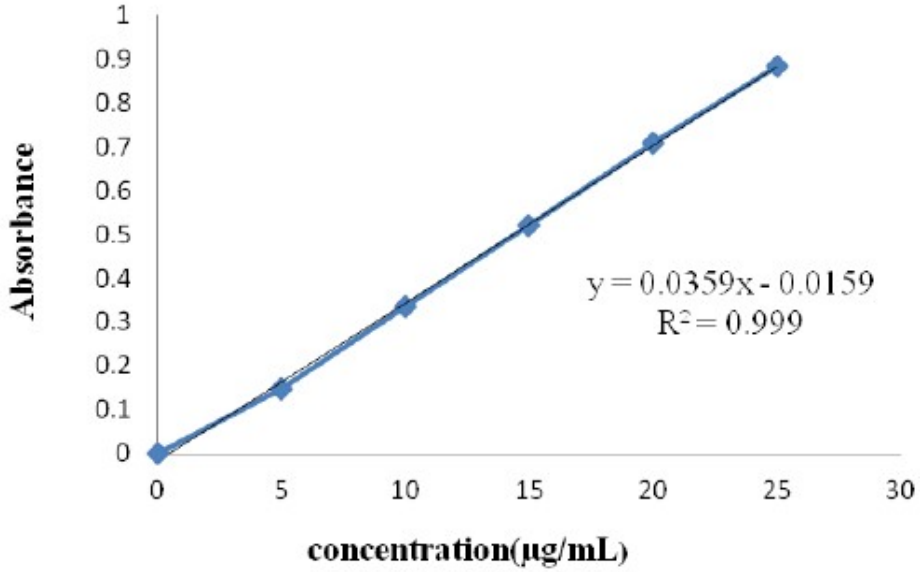

Figure 3: Spectrophotometric analysis of drug substance

Table 9: In process quality control (IPQC) parameters of batch number F01

IPQC parameters of lubricated blend											
Bulk density (g/mL)						0.45					
Tapped density (g/mL)						0.56					
Carr's index (%)						19.64 (Fair)					
Hausner ratio						1.24 (Fair)					
FFC value						15 (Free flowing)					
Flodex value						166 (Good)					
IPQC parameters of compressed mini-tablets											
Sr. No.	1	2	3	4	5	6	7	8	9	10	Average
Weight (mg)	9.60	11.40	11.00	10.50	10.70	10.00	10.40	11.00	10.80	9.70	10.51
Thickness	2.40	2.38	2.45	2.44	2.42	2.46	2.39	2.45	2.48	2.43	2.43
Diameter (mm)	2.00	2.00	2.00	2.01	1.99	1.99	1.98	1.99	2.00	2.01	2.00
Hardness (Newton)	33.00	38.00	38.00	37.00	37.00	34.00	33.00	35.00	35.00	37.00	35.70
Disintegration time	1 minute 25 seconds (#40 mesh screen)										
Friability (%)	100 rotations – 0.36%, 200 rotations – 0.98%, 300 rotations – 1.4%										
Visual observation	No sticking of blend on tooling, dusting is high on turret Smooth surface of mini-tablets Comparatively good flow										

Table 10: Barrier coating dispersion feasibility and composition evaluation trials

Batch number		F02	F03	F04	F05	F06
Sr. No.	Ingredient	Quantity (%w/w)				
1	Copovidone (Kollidon VA64)	40.0	NA	NA	NA	NA
2	Kollicoat IR	NA	35.0	NA	NA	NA
3	Kollicoat Protect	NA	NA	35.0	30.0	30.0
4	Talc (Luzenac Pharma M)	59.5	64.5	64.5	69.5	66.0
5	Magnesium stearate (Ligamed MF-2V)	NA	NA	NA	NA	3.5
6	Iron Oxide Yellow	0.5	0.5	0.5	0.5	0.5
7	Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Table 11: Results of barrier coating level optimization trials

Batch No.	F07	F08	F09	F10	F11	F12
Barrier coating level (% w/w of core)	5%	10%	15%	20%	25%	30%
Surface cover	Poor	Slightly Poor	Satisfactory	Satisfactory	Satisfactory	Satisfactory
Tablets damage or erosion test	Surface and edges erosion	Edge erosion	Slight edge erosion	No erosion	No erosion	No erosion
Disintegration time	2 min 10 sec	3 min 15 sec	5 min 20 sec	7 min 18 sec	10 min 5 sec	12 min 30 sec

Table 12: Enteric coating dispersion feasibility and composition evaluation trials along with visual observations

Batch number		F13	F14	F15	F16
Sr. No.	Ingredients	Quantity (%w/w)			
1	Eudragit L30D-55	78.74	77.22	71.68	76.92
2	Glyceryl monostearate (5% of polymer)	3.94	NA	NA	NA
3	Glyceryl monostearate (7.5% of polymer)	NA	5.79	5.38	5.77
4	Triethyl citrate (20% of polymer)	15.75	15.44	NA	15.38
5	Triethyl citrate (30% of polymer)	NA	NA	21.51	NA
6	Polysorbate 80 (2% of polymer)	1.57	1.54	1.43	NA
7	Polysorbate 80 (2.5% of polymer)	NA	NA	NA	1.92
8	Purified water (Q.S. to 20% w/w dispersion)	Q.S.	Q.S.	Q.S.	Q.S.
Total		100.00	100.00	100.00	100.00
Visual observations	Sticking tendency	High	Medium	Medium	Low
	Lump formation	High	Medium	Medium	Low
	Gun blocking	High	Medium	High	Low

Table 13: Enteric coating composition optimization – Eudragit L 30D-55 alone and in combination with Eudragit NE 30D 80% coating on 20% barrier coated mini-tablets

Batch number		F16*	F17
Sr. No.	Ingredients	Quantity (%w/w)	
1	Eudragit L 30D-55	76.92	70.33
2	Eudragit NE 30D	NA	7.04
3	Glyceryl monostearate (7.5% of polymer)	5.77	5.11
4	Triethyl citrate (20% of polymer)	15.38	15.82
5	Polysorbate 80 (2.5% of polymer)	1.92	1.71
6	Purified water (Q.S. to 20% w/w dispersion)	Q.S.	Q.S.
Total		100.00	100.00
Visual observations	Sticking tendency	Low	Low
	Lump formation	Low	Low
	Gun blocking	Low	Low

* Batch F16 mentioned here for compositional comparison with F17

Table 14: Enteric coated mini-tablets physical strength evaluation study

Batch number	F16	F17
Batch details	Only Eudragit L 30D-55	Eudragit L 30D-55 with Eudragit NE 30D in 9:1 ratio
Physical appearance after 500 rotations in tablet friabilator	Damage of coating layer observed in few mini-tablets	No damage of enteric coat in any mini-tablet

Figure 4: Enteric coated mini-tablets along with size 0 capsule

Table 15: Capsule size selection

API loading	API content per 25 mg mini tablet	No. of mini-tablets required for 20 mg dose	Conclusion
10 % w/w	2.50	8	Capsule size 1 was required to fill 8 mini-tablets (Uncoated) Capsule size 0 was required to fill 8 mini-tablets (Coated)

Table 16: Drug release profile of capsules containing different level of enteric coated mini-tablets

Batch number	F18		F19		F20		F21		F22		F23		F24	
Enteric coating level	20%		30%		40%		50%		60%		70%		80%	
Time (minutes)	% DR	% RSD	% DR	% RSD	% DR	% RSD	% DR	% RSD	% DR	% RSD	% DR	% RSD	% DR	% RSD
Acid stage														
120	24	20.0	19	21.8	14	16.5	11	12.0	6	13.6	3	21.7	1	100.0
Buffer stage														
5	Acid resistance test failed								15	8.6	14	9.2	16	8.3
10									29	7.0	30	6.2	31	7.0
15									43	6.5	43	5.4	44	4.7
30									87	3.9	88	2.0	89	2.4
45									99	1.1	99	0.6	99	0.5
60									99	0.5	100	0.5	100	0.4

Dissolution Conditions (N=6), Apparatus: USP II (Paddle), 100 rpm
Media: Acid Stage: 0.1 N HCl, 300 mL Buffer Stage: pH 6.8 phosphate buffer; 1000 mL
%DR = % Drug release, %RSD = % Relative standard deviation

Table 17: Confirmatory and fine tuning trials to finalize the optimal level of enteric coat

Batch number	F25		F26		F27	
Enteric coating level	53%		56%		60%	
Time (minutes)	%Drug Release	%RSD	%Drug Release	%RSD	%Drug Release	%RSD
Acid stage						
120	12	8.3	10	16.5	5	13.3
Buffer stage						
5	Acid resistance test failed (All units released more than 10% of drug substance in acid stage)		Average value was within limit but few units showed more than 10% drug release in acid stage		17	7.8
10					31	8.1
15					47	4.3
30					89	2.6
45					99	0.8
60					100	0.5

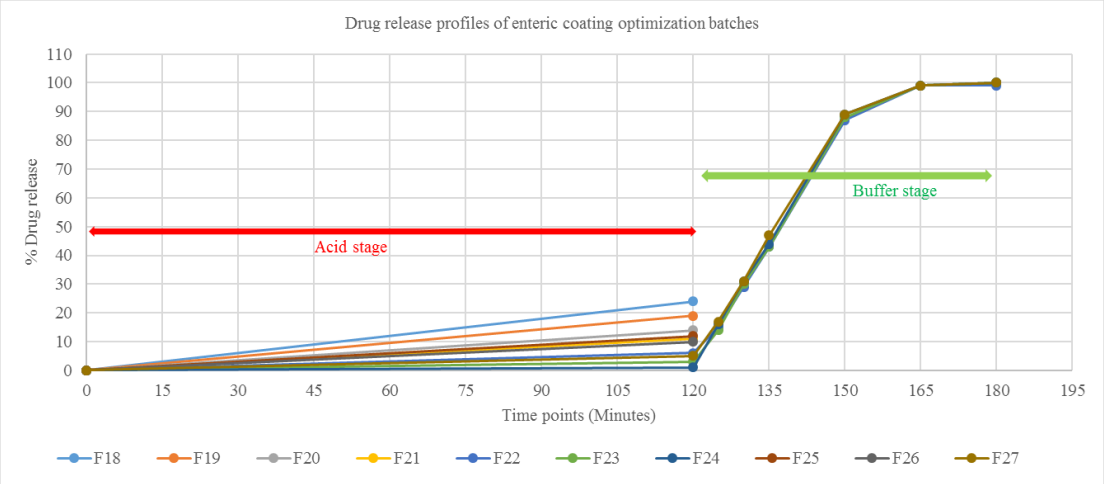

Figure 5: Drug release profiles of enteric coating optimization trials

Table 18: Composition of reproducible batch/confirmatory batch with finalized comosition

F28 (Confirmatory/Reproducible batch)				
Sr. no.	Ingredient	mg/mini-tablet	%w/w (of Total)	%w/w (Individual)
Mini-tablet core (Size - 3.0 mm)				
1	Esomeprazole mg trihydrate	2.50	5.21	10.00
2	MCC (Avicel PH-102)	5.38	11.20	21.50
3	Startab (DC starch 1500)	15.38	32.03	61.50
4	Crospovidone (Polyplasdone XL-10)	1.25	2.60	5.00
5	Aerosil 200	0.25	0.52	1.00
6	Magnesium stearate	0.25	0.52	1.00
	Total (Mini-tablet core)	25.00	NA	100.00
Barrier coating (20% level – 5mg weight per 25mg mini-tablet)				
1	Kollicoat protect	1.50	3.13	30.00
2	Talc (Luzenac Pharma M)	3.30	6.88	66.00
3	Magnesium stearate (Ligamed MF-2V)	0.20	0.42	4.00
4	Purified water* (q.s. to 10% w/w solid content)	Q.S.	Q.S.	Q.S.
	Total (Barrier coat)	5.00	NA	100.00
Enteric coating (60% level – 18mg weight per 30mg barrier coated mini-tablet)				
1	Eudragit L 30D-55	12.66	26.37	70.33
2	Eudragit NE 30 D	1.27	2.64	7.04
3	Glyceryl monostearate (7.5% of polymer)	0.92	1.92	5.11
4	Triethyl citrate (20% of polymer)	2.85	5.93	15.82
5	Polysorbate 80 (2.5% of polymer)	0.31	0.64	1.71
6	Purified water* (q.s. to 20% w/w dispersion)	Q.S.	Q.S.	Q.S.
	Total (Enteric coat)	18.00	NA	100.00
	Total	48.00	100.00	NA
* Not present in final product as it is evaporated during processing				

Table 19: Manufacturing process of reproducible batch/confirmatory batch with finalized composition

Sr. No.	Step	Procedure
1	Dispensing	Dispense all required materials accurately.
2	Co-sifting & blending	Co-sifting of API and aerosil through 30# sieve and blend it for 10 minute at 25 RPM in conta blender.
3	Co-sifting & blending	Co-sifting of MCC, startab and crospovidone (Polyplasdone XL-10) through 30# sieve and blend it with above API-aerosil premix for 10 minute at 25 RPM in conta blender.
4	Co-milling	Co-milling of above blend from 610µ screen in co-mil at 1000RPM.
5	Lubrication	Sifting of magnesium stearate through 60# sieve and blending with above blend for 5 minutes at 25 RPM in conta blender.
6	Compression	Compression of above lubricated blend with 3.0 mm multitip tooling.
7	Barrier coating	Coating as per optimized barrier coating composition in auto coater (275mm pan)
8	Enteric coating	Coating as per optimized enteric coating composition in auto coater (275mm pan)
9	Capsule filling	8 enteric coated mini-tablets filled into size 0 hard gelatin capsule shells
Finished dosage form subjected for physico-chemical analysis and stability study.		

Table 20: IPQC parameters of reproducible batch/confirmatory batch with finalized composition

Batch number	F01/F10/F27	F28
Batch details	Optimized batch	Reproducible batch
IPQC parameters of lubricated blend		
Bulk density (g/mL)	0.45	0.47
Tapped density (g/mL)	0.57	0.58
Carr's index (%)	19.70 (Fair)	18.97 (Fair)
Hausner ratio	1.25 (Fair)	1.23 (Fair)
FFC value	15 (Free flowing)	15 (Free flowing)
Flodex value	166 (Good)	166 (Good)
IPQC parameters of compressed mini-tablets		
Weight (mg) [n=10]	25.78 (24.50-27.40)	25.37 (24.50-26.50)
Thickness (mm) [n=10]	3.02 (2.95-3.10)	3.03 (2.95-3.12)
Diameter (mm) [n=10]	3.00 (2.99-3.01)	3.00 (2.99-3.01)
Hardness (Newton) [n=10]	40 (33-49)	42 (35-50)
Disintegration time (minute:sec) [n=6] (#40 mesh screen)	01:30	01:42
Friability (%) @ 300 revolution [target – NMT 1.0%	0.60	0.58
IPQC parameters of barrier coated mini-tablets		
Disintegration time (minute:sec) [n=6]	07:18	06:50
Assay of enteric coated tablets (as Esomeprazole mg. trihydrate)	99.80	100.4
No. of mini-tablets per capsules (as Esomeprazole mg. trihydrate)	8	8

Table 21: Drug release profile comparison of reproducible batch/confirmatory batch with optimized batch

Batch number	F27		F28	
Batch details	Optimized batch		Reproducible batch	
Time (minutes)	%Drug Release	%RSD	%Drug Release	%RSD
Acid stage				
120	5	13.3	4	16.5
Buffer stage				
5	17	7.8	19	16.6
10	31	8.1	34	6.8
15	47	4.3	49	5.1
30	89	2.6	89	2.1
45	99	0.8	99	0.4
60	100	0.5	100	0.5

Dissolution Conditions (N=6), Apparatus: USP II (Paddle), 100 rpm
Media: Acid Stage: 0.1 N HCl, 300 mL Buffer Stage: pH 6.8 phosphate buffer; 1000 mL

Stability study of reproducible batch/confirmatory batch:

Table 22: Stability data of reproducible batch/confirmatory batch

Batch number	F28			
Batch details	Reproducible batch			
Pack style	60cc, round, white HDPE bottle with child-resistant closure containing 1g desiccant (30 capsules per bottle)			
Stability condition	40°C±2°C/75%RH±5%RH (Accelerated condition)			
Time points	Initial		1 month	
Assay (%) [90%-110%]	100.4		99.8	
Single max. impurity (Omeprazole sulfone RRT-0.8)	BQL		0.06	
Total impurities (%) (Related substance)	BQL		0.06	
Time (minutes)	%Drug Release	%RSD	%Drug Release	%RSD
Acid stage [Not more than 10%]				
120	4	16.5	5	17.0
Buffer stage [NLT 75% (Q) in 30 minutes]				
5	19	16.6	17	16.5
10	34	6.8	32	9.9
15	49	5.1	46	4.4
30	89	2.1	88	2.6
45	99	0.4	98	0.7
60	100	0.5	99	0.0
Dissolution Conditions (N=6), Apparatus: USP II (Paddle), 100 rpm Media: Acid Stage: 0.1 N HCl, 300 mL Buffer Stage: pH 6.8 phosphate buffer; 1000 mL				

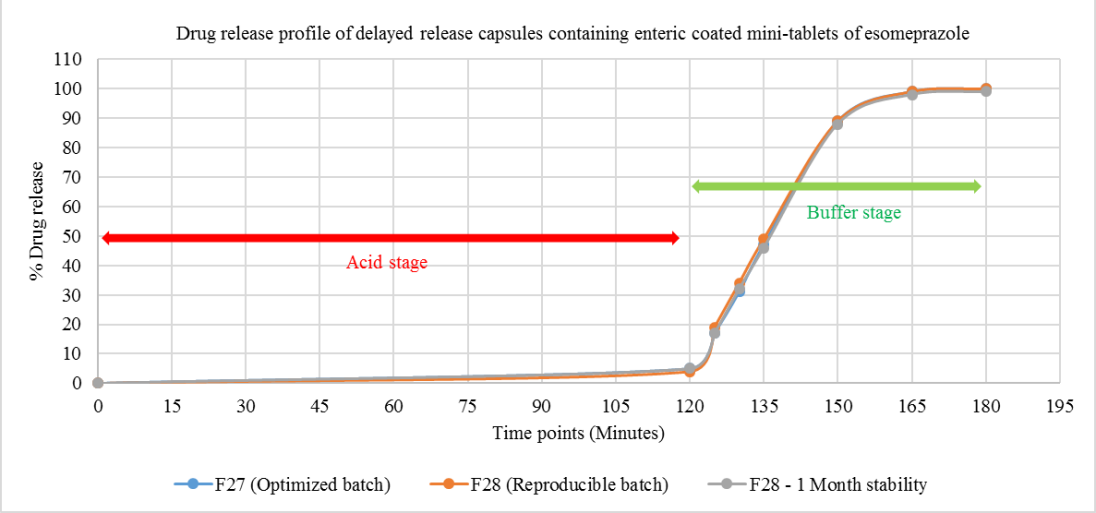

Figure 6: Drug release profile of delayed release capsule containing enteric coated mini-tablets of esomeprazole

CONCLUSION

All the physico-chemical characterization data of reproducible batch (F28) are similar to optimized batch (F01/F10/F27). Hence it can be concluded the developed formula and process are reproducible. Also based on stability data of reproducible batch at accelerated stability condition (40°C±2°C/75%RH±5%RH), it can be concluding that developed delayed release capsule formulation containing enteric coated mini-tablets is stable.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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