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FEASIBILITY AND PROCESS OPTIMIZATION TRIALS FOR PREPARATION OF MINI-TABLETS OF ESOMEPRAZOLE BY DIRECT COMPRESSION TECHNIQUE

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ABSTRACT

In recent years the prominence of mini-tablets dosage forms continuously increasing. Mini-tablets are tiny solid oral dosage forms having diameters ≤ 3mm. They are like subunits of conventional tablets with same manufacturing process but only alteration is application of multi-tips tooling. These are patient friendly drug delivery system for patients having swallowing difficulties along with lesser inter-intra individual variability and reduced dose dumping risk. Simplicity and reproducibility of direct compression technique gives uniformity in dosage units compare to conventional granules and pellets manufacturing. The objective of this study is to evaluate feasibility by simple and easy direct compression process as well as process optimization of esomeprazole mini-tablets manufacturing with respect to different levels of drug loading, selection of excipients based on their particle size, particle size distribution and flow characteristics along with modification in conventional excipient addition steps.

Keywords: Multi-tips tooling, Dose flexibility, Drug loading optimization, Excipient selection, Particle size distribution, Reproducibility

INTRODUCTION:

Mini-tablets are advanced solid oral dosage forms having diameter ≤ 3 mm and extensive application area. For ease of use, they are usually filled in capsules or they can be compressed into larger tablets or packed into sachets. Mini tablets are produced in a robust and reproducible way with multiple tooling using rotary tablet compression machines. Thus, manufacturing process of mini-tablets are simple and easy. Main advantage is their miniature size which is helpful for patients having swallowing difficulties leads to higher patient compliance **[1,** Error! Reference source not found.**]**.

Two types of orally controlled release drug delivery systems **[**Error! Reference source not found.-Error! Reference source not found.**]**

- Single unit dosage forms (Tablets, Capsules)
- Multi-unit dosage forms (Granules, Pellets, Mini-tablets)

Mini-tablets are more beneficial compare to… **[**Error! Reference source not found.**]**

- Conventional dosage forms due to miniature size - higher surface area - faster gastric emptying)
- Other multi-unit dosage forms due to easy production techniques

Convenience of multi-tip punches… **[**Error! Reference source not found.**, [6]]**

- Higher productivity (Higher output in short period of time)
- Not require special equipments for manufacturing, only altered tooling is required.
- Overall cost is low.

Table 1: Comparison of single unit dosage forms and multi-unit dosage forms

Single Units Dosage Forms	Multi-Units Dosage Forms
Gastric emptying with high variability and it is highly dependent on presence or absence of food	Gastric emptying is more predictable and less dependent on presence or absence of food
Showing intra & inter individual variability in absorption rate	Not showing intra & inter individual variability in absorption rate
Higher risk of overdose and local irritation	Lower risk of overdose and local irritation
Simple technology	Complicated technology

Figure 1: Mini-tablets and size comparison of mini-tablets with respect to size 0 capsule

Importance of mini-tablets dosage form [Error! Reference source not found.**,** Error! Reference source not found.**-**Error! Reference source not found.**]**

- Mini-tablets are very tiny tablets compared to conventional tablets having diameter ≤ 3 mm.
- Patient-friendly drug delivery system for targeted populations because they offer better swallowing and flexible dosing.
- Combining various release kinetics, doses and active compounds in only one system which decreases dosing frequency and/or polypharmacy therapy problems
- Easy and reproducible manufacturing compare to granules and pellets. It can be compressed using conventional tablet press using especially designed multi-tip punches.
- Dimensional (shape and size) uniformity responsible for trouble free coating.
- Lower inter-intra individual variability. (Due to small size)
- Reduced dose dumping risk.
- Extensive dispersability throught gastrointestinal tract is responsible for consistent drug release kinetics and lower local irritation.
- Higher drug loading efficiency.

Advantages over pellets **[**Error! Reference source not found.**,** Error! Reference source not found.**]**

- Pellets are spherical structures which are manufactured by 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 absence of solvents in manufacturing process.
- Simplicity in manufacturing methods gives uniform dosage units so batch to batch variability is lower.

Advantages over granules **[**Error! Reference source not found.**,** Error! Reference source not found.**]**

- Mini tablets have a smooth surface, stable surface area and high mechanical resistance compared to granules. It can be easily coated 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 at the final step of the acid secretory pathway and thus reduces basal and stimulated gastric acid secretion irrespective of stimulus **[[16], [17]]**. It is widely used in the treatment of dyspepsia, peptic ulcer disease, gastro esophageal reflux disease (GERD) and zollinger-ellison syndrome. It having higher potency in acid inhibition than other PPIs which are the drugs of choice in the treatment of gastroesophageal reflux diseases (GERD). The superior clinical efficacy of esomeprazole, compared with omeprazole and the R-isomer, is due to its higher systemic bio-availability **[[18], [19]]**.

Primary studies have shown that Esomeprazole accomplishes better and more sustained acid control than Omeprazole, 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…

- Rapid degradation in gastric acid
- BCS class III drug (High water solubility and low permeability)
- Short biological half-life of around 1-1.5 hr
- It shows wide inter and intra-individual variability in the bioavailability (50-90%) due to its low permeability

The problem of drug degradation in acidic media can be overcome by coating the dosage form with enteric coating agents. Enteric coated dosage forms, once arrive in the intestinal environment, offer improved absorption.

But in case of enteric coated dosage forms premature drug release in the stomach potentially results in the degradation of the

drug or may cause irritation of the gastric mucosa. This can be reduced with coated multi-unit dosage forms like mini tablets because of a more rapid transit time compared to enteric coated single unit conventional tablets **[[16]]**.

Multiple unit dosage forms disperse in gastro-intestinal tract more homogeneously than the single unit dosage forms which leads to decreasing inter and intra-individual variability of absorption.

We can conclude that 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.

Mini-tablet formulation will increase the systemic bioavailability of drug due to…

- Small size ⟶ Higher surface area ⟶ Higher dissolution
- Small size ⟶ Faster gastric emptying rate ⟶ Less residence time in gastric media ⟶ Less degradation of drug.

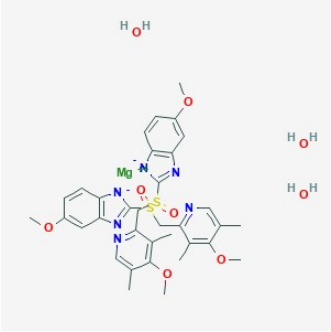


Figure 2: Esomeprazole magnesium trihydrate (Reference: PubChem) [[22]]

MATERIAL AND METHODS:

Materials: Esomeprazole magnesium trihydrate (Raks Pharma Pvt. Ltd.), Microcrystalline cellulose - Avicel PH-101, Avicel PH-102 and Avicel PH-200 (FMC BioPolymer), Lactose monohydrate - Spray dried fast flo-316 (Foremost) and FlowLac 100 (Meggle-pharma), Crospovidone (Kollidon CL, BASF and Polyplasdone XL-10, Ashland), Aerosil (Evonik), Magnesium stearate – Ligamed MF-2V (Peter Greven). All materials used were of pharmaceutical grade.

Methods: Esomeprazole is cohesive in nature so in most of research works formulation containing esomeprazole is manufactured by either wet granulation technique or by drug layering on pellets by fluid bed technology. But in this research work manufacturing of esomeprazole mini-tablets is done by direct compression to make the process simple and easily reproducible. So, compressibility and flow of lubricated blend are critical quality attributes.

Drug substance particle size is 166µ (Less than 250µ) so excipients selected based on their particle size in such way to get suitable PSD (Particle size distribution) for formulation. Drug substance flow property evaluation is mentioned in **Table 2**.

Blend PSD and flow properties plays crucial role during mini-tablet compression process.

- 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: 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) for 4 weeks.

Flow property evaluation of drug substance: Drug substance was evaluated for bulk density, tapped density, carr's index, hausner ratio and ring shear test to generate data regarding flow properties.

Excipients selection, excipient grade selection: Excipient selection was carried out based on literature search, prior experience, drug-excipient compatibility study, physico-chemical evaluation as well as placebo trials.

Formulation optimization trials (3.00 mm mini-tablets): Prototype trials were carried out by direct compression technique to finalize drug loading with respect to flow properties evaluation.

Dispense all required materials accurately. Co-sifting of API, MCC, lactose, crospovidone and aerosil through 30# sieve and blend it for 10 minutes at 25 RPM in conta blender. Sifting of magnesium stearate through 60# sieve and blending with above blend for 5 minutes at 25 RPM in conta blender. Compression of above blend with 3.0 mm multi-tip tooling to check the feasibility of mini-tablet formulation of esomeprazole mg trihydrate.

Compression parameters: Cadmach compression machine (CMD4-16-MT) [B&D tooling], Tooling – 3.00 mm multi-tip punch, round, standard concave, Upper punch – plain, Lower punch – plain, Gravity feeder, Target thickness will be set around 3.00 mm so due to near spherical shape it will be beneficial for uniformity in coating process.

Figure 3: Multi-tips tooling

Chemical analysis of drug product

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).

- Esomeprazole dose is 20 mg per day, so as per dose 8 uncoated mini-tablets filled into size 0 capsule and subjected for the chemical analysis.

Assay (Uncoated mini-tablets in size 0 capsule)

- Randomly sample out 10 capsules (80 mini-tablets) and crushed into fine powder in a mortar. Weighed a quantity of powdered mini-tablets containing 20 mg of Esomeprazole to 100 ml volumetric flask, add 20 ml of 0.1 M Sodium hydroxide, mix with aid of ultrasound and dilute to volume with 0.1 M Sodium Hydroxide. Centrifuge for 5 minutes and dilute 5.0 ml of the clear supernatant liquid to 50.0 ml with the

phosphate buffer pH 6.8. The resultant solution is then analyzed by using UV Spectrophotometer at λmax 302.0 nm.

Dissolution (Uncoated mini-tablets in size 0 capsule) (Dissolution condition selection as per USP monograph of esomeprazole magnesium DR capsules)

- Prepared delayed release tablets were evaluated for their integrity in the physiological environment of stomach and small intestine. This study was carried out using USP dissolution test apparatus type-II. The tablets were tested for drug release in 0.1N HCl (900 ml) for first 2 h as average gastric emptying time is 2 hours, then dissolution media was replaced with 6.8 pH phosphate buffer (900 ml) for 1 h. At the end of respective time periods, each sample of 10 ml were taken at specified intervals (i.e. 5, 10, 15, 30, 45, 60 minutes) and analyzed for Esomeprazole content at 302 nm using UV spectrophotometer (Shimadzu UV-1600).

RESULT AND DISCUSSION

Drug-excipient compatibility study:

- Physical observation – No color change or no lump formation in any vial.

All excipients were found compatible with drug substance.

Flow property evaluation of drug substance: As per below table we can conclude that drug substance having poor flow as well as cohesive nature. So other excipients were selected in such way that final lubricated blend having desired flow properties.

Formulation optimization trials (3.00 mm mini-tablets): IPQC parameters of lubricated blend, compressed mini-tablets and physical observations during compression were mentioned in below **Table 9** to finalize API loading.

API loading was finalized 10%, because

- In case of 5% API loading the number of mini-tablets will be higher,
- In case of 15% and 20% API loading flow of blend is poor which may result in weight variation at high turret speed.

Tiny bulges observed on surface of mini-tablets in every batch which will be further investigated. From literature review, it is concluded that if the particle size of crospovidone is higher than it may leads to tiny bulges formation on tablet surface due to wicking action at controlled room temperature and humidity level. Different grades of crospovidone evaluated by two placebo trials to check presence of tiny bulges on surface of mini-tablets **(Table 11)**.

From placebo trials it was concluded that polyplasdone XL-10 is better choice to obtain smooth surface of mini-tablets. So, in further trials disintegrant will be polyplasdone XL-10 **(Table 12)**.

Chemical analysis of drug product

Spectrophotometric estimation of esomeprazole (Figure 4)

Chemical analysis of Batch F02 – 10% API loading

Among executed four batches for optimization of API loading, batch F02 was selected for chemical analysis **(Table 14)**.

- Assay values are within limit. (As per USP monograph of esomeprazole magnesium DR capsules: each capsule contains an amount of esomeprazole magnesium equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of esomeprazole.)
- AV value is 15.9 which is out of limit which shows content uniformity is not there.
- % RSD is very high which also shows variation in drug distribution from unit to unit is very high.
- Some units show incomplete drug release and some units shows more than 100% drug release at recovery point (Paddle RPM 150)
- To improve blend uniformity, co-milling step will be added in manufacturing process.

Further trials will be carried out with below consideration…

To improve drug distribution…

- Co-milling of blend from 610µ screen
- Increase number of rotations for blending

API is very cohesive in nature so to improve the flow; API will be premixed with aerosil and then this premix will be blend with other excipients.

Few trials with new excipient directly compressible starch (Startab-DC starch 1500) instead of lactose fast flo-316 to improve the flow of blend.

Polyplasdone XL-10 will be used instead of Kollion-CL to resolve tiny bulges formation on mint-tablet surface **(Table 15)**.

Based on optimization trials it was concluded that formulation having startab instead of lactose monohydrate shows better flow properties. Beaker study (Purified water) was performed to see disintegration pattern of mini-tablets containing startab. In both cases, disintegration observed within 1 minutes with burst effect, which is satisfactory. But in case of 61.50% startab, disintegration is faster compared to 41.50% startab **(Table 16)**.

Based on chemical analysis it can be conclude that with addition of co-milling step will results into better content uniformity of dosage forms **(Table 17)**.

Assay value and AV value of each batch were well within the limits. %RSD of each batch were also satisfactory. Dissolution profiles of formulation containing startab are faster compare to formulation containing lactose monohydrate due to swelling nature of starch which helps to fasten the disintegration of dosage units.

Table 2: 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

Excipients selection, excipient grade selection:

Table 3: Selection of excipients [[21]]

Sr. No.	Excipients	Role	Reason for selection
1	Microcrystalline cellulose	Diluent	Water insoluble material, having good compressibility
2	Lactose monohydrate	Diluent	Water soluble material, having good flow
3	Hypromellose	Binder	Low viscosity dry binder
4	Crospovidone	Disintegrant	❑ Higher disintegration power compare to other super-disintegrants ❑ Non-ionic in nature
5	Colloidal silicon dioxide	Glidant	❑ API is cohesive in nature so to reduce sticking of API ❑ To improve the flow
6	Magnesium stearate	Lubricant	API is cohesive in nature so to reduce sticking of tablet with tooling during compression.

Table 4: Excipient selection (Grade selection) [[21]]

Sr. No.	Excipients	Reason for selection
1	Avicel PH-102 (Microcrystalline cellulose)	Avicel PH-101 FFC value – 4.4 (D50 value - 50µ) – Too small particle size Avicel PH-102 FFC value – 6.3 (D50 value - 100µ) Avicel PH-200 FFC value – 8.4 (D50 value - 200µ) – Higher particle size
2	Spray dried fast flo-316 (Lactose monohydrate)	Flowlac-100 FFC value - 7.5 (D50 value - 126µ) Fast flo-316 FFC value - 16 (D50 value - 85µ) – Higher flow
3	Methocel E5 premium LV (Hypromellose)	Low viscosity grade, Dry form binder
4	Polyplasdone XL-10 (Crospovidone)	Polyplasdone XL-10 (Ashland) ((D50 value 25-40µ) Polyplasdone XL (Ashland) ((D50 value 110-140µ)
5	Colloidal silicone dioxide (Aerosil 200 Pharma)	Specific surface area 200m^2/g – Good glidant property – Most common glidant
6	Ligamed MF-2-V (Magnesium stearate)	D90 value 25µ - Most common lubricant

Table 5: Avicel-PH grades comparison [[21]]

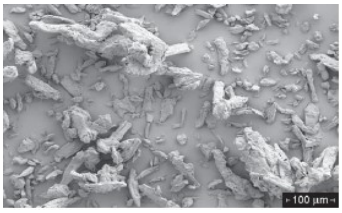
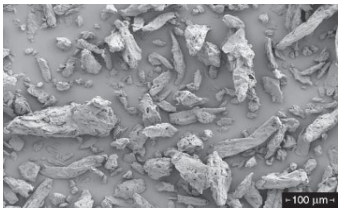
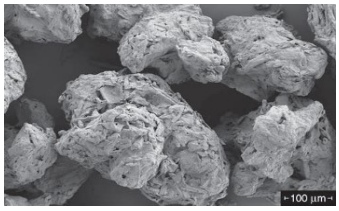
Diluents	Avicel PH-101	Avicel PH-102	Avicel PH-200
Morphology	Angular road like shape	Angular road like shape	Near to spherical shape
Flow properties	Poor	Medium	Good
Magnification	200X	200X	200X
			

Table 6: Lactose monohydrate grades comparison [[21]]

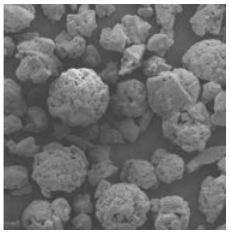
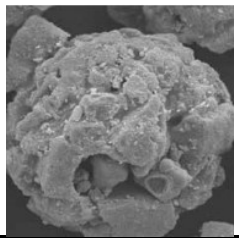
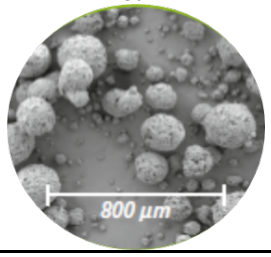
Diluents	Lactose monohydrate – Fast flo-316		Lactose monohydrate – Flowlac-100
Morphology	Spherical shape		Spherical shape
Flow properties	Excellent		Good
Magnification	150X	600X	150X
			

Table 7: Diluent selection - placebo blends to evaluate flow properties of different grades of diluents

Blend details	MCC (Avicel PH-102) + Lactose (Fast Flo-316)	MCC (Avicel PH-102) + FlowLac 100	MCC (Avicel PH-200) + Lactose (Fast Flo-316)	MCC (Avicel PH-200) + FlowLac 100
Ingredient	% w/w	% w/w	% w/w	% w/w
MCC	44	44	44	44
Lactose	44	44	44	44
Methocel E5 premium LV	5	5	5	5
Polyplasdone XL-10	5	5	5	5
Aerosil 200	1	1	1	1
Magnesium Stearate	1	1	1	1
Total	100	100	100	100
Bulk Density (g/mL)	0.44	0.43	0.45	0.45
Tapped Density (g/mL)	0.58	0.58	0.59	0.57
Compressibility Index (%)	24.14 (Passable)	25.86 (Passable)	23.73 (Passable)	21.05 (Passable)
Hausner Ratio	1.32 (Passable)	1.35 (Passable)	1.31 (Passable)	1.27 (Passable)
Angle of Repose (°)	28.07 (Excellent)	30.1 (Excellent to Good)	27.45 (Excellent)	26.01 (Excellent)
Flowability Index (Flodex)	66.67 (Medium)	58.82 (Medium)	125 (Good)	66.67 (Medium)

- Avicel PH-200 containing blend having better flow properties but for mini-tablet Avicel PH-102 is more suitable due to particle size (D50 value – 100)
- Compare to Flowlac-100, Fast flo-316 containing blend shows better flow properties

Table 8: Disintegrant selection [[21]]

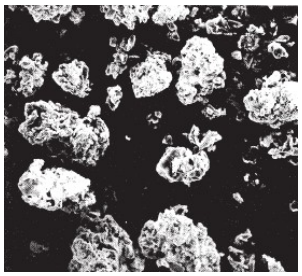
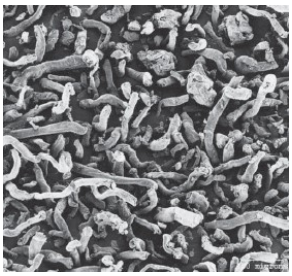
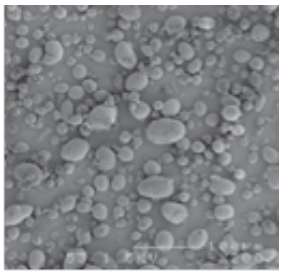
Disintegrants	Crospovidone	Croscarmellose sodium	Sodium starch glycolate
Mechanism	Wicking action	2D Swelling action	3D Swelling action
Morphology	Fine rough particles	Thread like particles	Granular shape particle
Ionic nature	Non-ionic	Anionic	Anionic
Magnification	400X	100X	200X
			
Disintegration	Powerful disintegrant	Compare to crospovidone slow disintegration property	

Table 9: Feasibility trials to evaluate API loading

Batch number	F01	F02	F03	F04
API loading	5%	10%	15%	20%
Ingredients	% w/w	% w/w	% w/w	% w/w
Esomeprazole mg trihydrate	5.00	10.00	15.00	20.00
MCC (Avicel PH-102)	44.00	41.50	39.00	36.50
Lactose monohydrate (Fast flo-316)	44.00	41.50	39.00	36.50
Crospovidone (Kollidon CL)	5.00	5.00	5.00	5.00
Aerosil 200	1.00	1.00	1.00	1.00
Magnesium stearate	1.00	1.00	1.00	1.00
Total	100.00	100.00	100.00	100.00
IPQC parameters of lubricated blend				
FFC value	36 (Free flowing)	8.2 (Easy flowing)	5.2 (Easy flow)	3.8 (Cohesive)
IPQC parameters of mini-tablets				
Weight (mg)	25.05 (24.70-25.30)	25.03 (24.40-25.50)	25.05 (24.30-25.70)	25.01 (24.20-25.80)
Thickness (mm)	3.00 (2.95-3.05)	3.13 (3.10-3.16)	3.23 (3.20-3.26)	3.29 (3.27-3.33)
Diameter (mm)	3.00 (2.99-3.01)	3.00 (2.99-3.01)	3.00 (2.99-3.01)	3.00 (2.99-3.01)
Hardness (N)	47 (42-51)	47 (42-54)	48 (44-55)	47 (40-52)
Disintegration time (Min:sec) [#40 screen)	00:45	00:50	01:05	01:12
Friability at 100 revolutions	0.15	0.14	0.14	0.13
at 200 revolutions	0.48	0.46	0.45	0.46
at 300 revolutions	0.75	0.74	0.73	0.73
Visual observations	Free flowing blend	Comparatively good flow	Poor flow of blend	Poor flow of blend
	No sticking of blend on tooling and turret	No sticking of blend on tooling and turret	Sticking of blend on tooling and turret	Sticking of blend on tooling and turret
	Easy die filling	Easy die filling	Easy die filling	Easy die filling
	No weight variation	No weight variation	No weight variation	No weight variation
	No tip breakage	No tip breakage	No tip breakage	No tip breakage
	Smooth surface of mini-tablets	Smooth surface of mini-tablets	Rough surface of mini-tablets	Rough surface of mini-tablets
	Tiny bulges observed on tablet surface	Tiny bulges observed on tablet surface	Tiny bulges observed on tablet surface	Tiny bulges observed on tablet surface

Table 10: Visual observations of feasibility trials to evaluate API loading

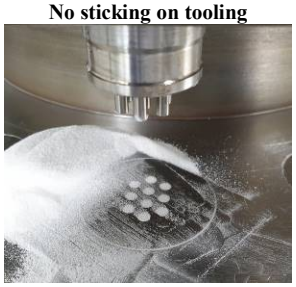
5% API loading	10% API loading	15% API loading	20% API loading
 No sticking on tooling	 No sticking on tooling	 Sticking on tooling	 Sticking on tooling
 Complete die filling			 Stcking on turret

Table 11: Crospovidone grades comparison [21]

Crospovidone grades (Information from vendor COA)	Kollidon CL	Polyplasdone XL	Polyplasdone XL-10
Manufacturer	BASF	Ashland	Ashland
Particle size (µ)	D50 = 110-130	D10 = 35 (15-60) D50 = 124 (65-175) D90 = 328 (270-385)	D10 = 10 (8-12) D50 = 25 (20-30) D90 = 57 (35-85)
Peroxide value (ppm) (Limit is less than 400)	45	31	87 (Peroxide impurities leads to oxidation of API)
% LOD (Max – 5)	1.8	2.8	3.8

Table 12: Placebo trials for the selection of crospovidone grade

Batch number	F05	F06
Ingredients	% w/w	% w/w
MCC (Avicel PH-102)	46.50	46.50
Lactose monohydrate (Fast flo-316)	46.50	46.50
Crospovidone (Kollidon CL)	5.00	-
Crospovidone (Polyplasdone XL-10)	-	5.00
Aerosil 200	1.00	1.00
Magnesium stearate	1.00	1.00
Total	100.00	100.00
IPQC parameters of mini-tablets		
Weight (mg)	25.05 (24.50 – 26.00)	25.30 (24.70-25.80)
Thickness (mm)	3.00 (2.95-3.05)	2.99 (2.93-3.01)
Diameter (mm)	3.00 (2.99-3.01)	3.00 (2.99-3.01)
Hardness (N)	45 (42-51)	46 (44-49)
Disintegration time (Min:sec) [#40 screen)	00:40	00:47
Visual observations	Tiny bulges observed	No tiny bulges

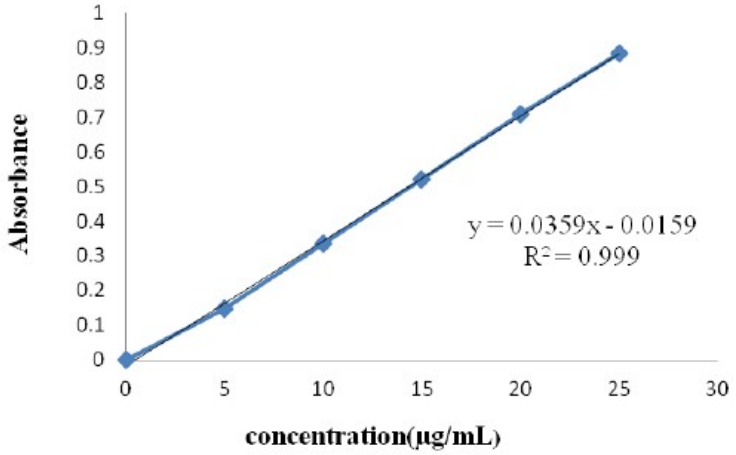


Figure 4: Spectrophotometric estimation of esomeprazole

Table 13: 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

Table 14: Chemical analysis of batch F02

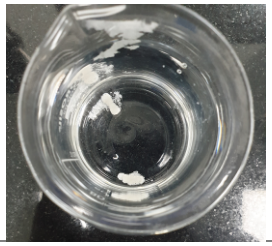
Assay	Set-1 = 96.4% and Set-2 = 103.2% (Average = 99.8%)									
Content uniformity	Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Avg.	SD	%RSD	AV value	
	90.5	92.5	97.5	103.2	100.2	100.8	6.6	6.6	15.9	
	Unit-6	Unit-7	Unit-8	Unit-9	Unit-10					
	104.1	105.6	95.6	107.8	110.5					
Dissolution Condition	USP type - II (Paddle), 100rpm, pH 6.8 phosphate buffer, 900ml									
Time Point (Minutes)	Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	Avg.	%RSD	Min	Max
5	8	37	5	18	7	22	16.2	11.16	5	37
10	19	55	16	30	22	35	29.5	13.10	16	55
15	34	80	32	46	40	58	48.3	16.55	32	80
30	68	95	65	90	82	95	82.5	12.15	65	95
45	88	96	87	90	95	106	93.7	6.45	87	106
60 (Recovery Point)	93	96	87	90	101	106	95.5	6.45	87	106

Table 15: Flow property evaluation and comparison of Lactose monohydrate (Fast flo-316) and Startab (DC starch 1500)

Parameters	Lactose monohydrate (Fast flo-316)	Startab (DC starch 1500)
Bulk density (g/mL)	0.56	0.59
Tapped density (g/mL)	0.70	0.70
Carr's index (%)	19.72 (Fair)	15.69 (Good)
Hausner ratio	1.25 (Fair)	1.19 (Fair)
FFC value	16 (Free flowing)	38 (Free flowing)
% LOD	0.42	8.25

Table 16: Optimization trials

Batch number	F07	F08	F09
Batch details	Trial with addition of API-Aerosil premix step, co-milling step and polyplasdone XL-10 instead of Kollidon CL.	Trial with addition of API-Aerosil premix step, co-milling step, polyplasdone XL-10 instead of Kollidon CL and Startab instead of lactose monohydrate	Trial with addition of API-Aerosil premix step, co-milling step, polyplasdone XL-10 instead of Kollidon CL and Startab instead of lactose monohydrate
Ingredients	% w/w	% w/w	% w/w
Esomeprazole mg trihydrate	10.00	10.00	10.00
MCC (Avicel PH-102)	41.50	41.50	21.50
Lactose monohydrate (Fast flo-316)	41.50	-	-
Startab (DC starch 1500)	-	41.50	61.50
Crospovidone (Polyplasdone XL-10)	5.00	5.00	5.00
Aerosil 200	1.00	1.00	1.00
Magnesium stearate	1.00	1.00	1.00
Total	100.00	100.00	100.00
IPQC parameters of lubricated blend			
FFC value	9.8 (Easy flowing)	15 (Free flowing)	15 (Free flowing)
IPQC parameters of mini-tablets			
Weight (mg)	25.07 (24.50-25.70)	25.18 (23.70-26.30)	25.78 (24.50-27.40)
Thickness (mm)	3.13 (3.11-3.15)	3.00 (2.90-3.10)	3.02 (2.95-3.10)
Diameter (mm)	3.00 (2.99-3.01)	3.00 (2.99-3.01)	3.00 (2.99-3.01)
Hardness (N)	46 (43-50)	38 (32-47)	39 (33-49)
Disintegration time (Min:sec) [#40 screen)	00:55	01:50	01:30
Friability at 100 revolutions	0.15	0.14	0.15
at 200 revolutions	0.45	0.43	0.44
at 300 revolutions	0.76	0.75	0.77
Visual observations	Comparatively good flow	Comparatively excellent flow	Comparatively excellent flow
	No sticking of blend on tooling and turret	No sticking of blend on tooling and turret	No sticking of blend on tooling and turret
	Easy die filling	Easy die filling	Easy die filling
	No weight variation	No weight variation	No weight variation
	No tip breakage	No tip breakage	No tip breakage
	Smooth surface of mini-tablets	Smooth surface of mini-tablets	Smooth surface of mini-tablets
	No tiny bulges on mini-tablet surface	No tiny bulges on mini-tablet surface	No tiny bulges on mini-tablet surface
Beaker study (With purified water)	-	Comparatively slower disintegration than F09	Comparatively faster disintegration than F08



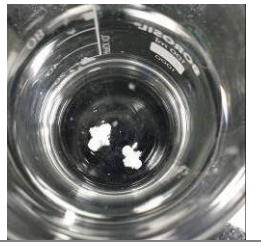


Table 17: Chemical analysis of batch F07, F08 and F09

Batch number		F07		F08		F09
Assay		99.8		100.5		99.2
Content uniformity	Units	%Drug content	Units	%Drug content	Units	%Drug content
	Unit-1	98.5	Unit-1	101.2	Unit-1	97.8
	Unit-2	101.5	Unit-2	96.8	Unit-2	99.4
	Unit-3	97.5	Unit-3	96.5	Unit-3	100.1
	Unit-4	102.4	Unit-4	103.4	Unit-4	98.2
	Unit-5	101.5	Unit-5	102.4	Unit-5	97.8
	Unit-6	103.1	Unit-6	102.5	Unit-6	103.1
	Unit-7	97.5	Unit-7	101.2	Unit-7	102.4
	Unit-8	99.0	Unit-8	98.5	Unit-8	97.5
	Unit-9	101.2	Unit-9	103.2	Unit-9	99.5
	Unit-10	103.4	Unit-10	104.5	Unit-10	98.6
	Average	100.6	Average	101.0	Average	99.4
	SD	2.2	SD	2.8	SD	1.9
	%RSD	2.2	%RSD	2.8	%RSD	2.0
	AV value	5.4	AV value	6.8	AV value	4.7
Dissolution Condition		USP type - II (Paddle), 100rpm, pH 6.8 phosphate buffer, 900ml				
Time Point (Minutes)	% Drug release	% RSD	% Drug release	% RSD	% Drug release	% RSD
5	16	8.5	23	7.1	28	5.8
10	24	7.7	50	6.4	61	7.8
15	46	8.1	85	4.5	88	5.5
30	82	7.2	96	4.0	97	2.1
45	98	2.0	99	1.4	99	1.4
60 (Recovery Point)	99	1.4	99	1.4	100	1.1

CONCLUSION

From feasibility and process optimization trials it is conclude that mini-tablets of poorly flowable drug substance like esomeprazole can be manufactured with using selected excipient having desired particle size and particle size distribution, incorporating proper excipient addition steps and combining beneficial unit operations like co-milling along with blending process to improve drug substance distribution with easy and simple direct compression technique instead of going for wet granulation and dry granulation technique. Reduced number of manufacturing steps is also critical factor for commercial manufacturing as well as drug product stability point of view.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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