INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION, OPTIMIZATION AND EVALUATION OF OSIMERTINIB TABLETS

Dr. K. Ramesh[1*], Dr.M.Ganesh[2], Dr. Suresh Kumar Packiriswamy[3], G.Sridhar[4]

[1]*Nova College of Pharmacy, Vegavaram, Jangareddygudem Mandal, West Godavari Dist, A P, India.*
[2]*St.Mary's College of Education, Sarpavaram, Kakinada, Andhra Pradesh, India.*
[3]*Nova College of Pharmacy, Vegavaram, Jangareddygudem Mandal, West Godavari Dist, Andhra Pradesh, India.*
[4]*Research Associate, Hetero Labs Ltd, Jeedimetla, Hyderabad.*

ARTICLE INFO

Article history
Received 08/03/2019
Available online
31/03/2019

Keywords
Osimertinib Mesylate,
Particle Size,
Disintegrant,
Dissolution Profile.

ABSTRACT

Osimertinib mesylate is a kinase inhibitor, prescribed for the treatment of patients, who are diagnosed with metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC). The Innovator of the product is AstraZeneca and its brand name in US and EU market is TAGRISSO® (Osimertinib) 40 mg and 80 mg film coated Tablets. The recommended dose is one 80 mg tablet once daily taken orally with or without a meal. Approximately, 80-90 % of lung cancer comprise NSCLC. Solubility of Osimertinib is known to be affected by pH, it belongs to BCS class-III molecule. The current work attempted to study the impact of both particle size of API and concentrations of disintegrant (L-HPC) on in vitro drug release profiles of Osimertinib from tablet dosage form in comparison to in vitro drug release profiles of corresponding Innovator product in US market. Based on the scientific discussion of TAGRISSO® in EU market, and to increase the flow properties of blend for compression into tablets, dry granulation method (by Roller compaction) was adopted. Assay and in vitro dissolution of the finished product was analysed by UV method. The obtained dissolution results suggested that 500 ml of pH 4.5 Acetate buffer at 25 rpm was found to be more discriminatory media than pH 6.8 Phosphate buffer and pH 1.3 (containing 0.2 % NaCl) and film coated tablets with input micronized API (<10µ) has shown similar physical characteristics (hardness, disintegration time) and in vitro drug release profiles to that of Innovator product.

Corresponding author
Dr. K. Ramesh
Professor,
Department of Pharmaceutics,
+91-9493014310
drkramesh09@gmail.com

*Please cite this article in press as **Dr. K. Ramesh** et al. Formulation, Optimization and Evaluation of Osimertinib Tablets. Indo American Journal of Pharmaceutical Research.2019:9(03).*

INTRODUCTION

Osimertinib mesylate is a kinase inhibitor, prescribed for the treatment of patients, who are diagnosed with metastatic EGFR T790M mutation positive NSCLC. The brand name and Innovator of the Innovator product in US and EU market is TAGRISSO® (Osimertinib) 40 mg and 80 mg film coated tablets [1,2] and AstraZeneca, respectively. It has been approved for marketing in US by FDA on 13th Nov, 2015 and in EU by EMEA on 1st Feb, 2016. The recommended dose is 80 mg tablet (only one) once daily taken orally with or without a meal [1,2]. Around 80-90% of lung cancer comprise NSCLC [3].

In the current study, the effect of particle size of API and concentrations of disintegrant (L-HPC) on *in-vitro* drug release profiles of Osimertinib from tablet dosage form in comparison to the drug release profiles of corresponding Innovator product in US, *i.e.,* Tagrisso® (Osimertinib) 80 mg film coated tablets was studied. Dry granulation method (by Roller compaction) was adopted [4] to enhance the flow properties of blend. Formulation trials were taken with input API having PSD of 3 different d_{90} values in one set of trials / and 3 different concentrations of L-HPC with same quantitative composition in another set of trials and evaluated for dissolution profiles in 3 different dissolution media and compared against the *in vitro* dissolution profiles of corresponding Innovator product. The hardness and disintegration time of the test product was found to be increased with reducing the particle size of input API.

From the physical characteristics and *In vitro* dissolution profiles of the test product, it was evident that the film coated tablets product (3.7 – 4.3 % w/w weight gain) with input API (d_{90} < 10 µ) showing similar hardness and dissolution profiles to that of Innovator product. The dissolution media 500 ml of Acetate buffer, pH 4.5 at 25 rpm is found to be showing more discriminating dissolution media.

MATERIALS

Tagrisso® (Osimertinib) 80 mg film coated tablets (30 No's – 1 carton) were obtained as gift samples from Mr. Janardhan, who is my M. Pharm classmate, currently working as Pharmacist in Pharmaceutical Consultant stores, New city, New York, USA (Manufactured and distributed by AstraZeneca, US). Osimertinib mesylate drug substance (with d90 of 8.4µ, 65.6µ and 135.2µ) was gifted by Natco Pharmaceuticals, Hyderabad, India. Mannitol (Pearlitol 200SD) and Low-substituted Hydroxypropyl cellulose (LH – 31) were gifted by Signet, Microcrystalline cellulose (grade Avicel PH 102) was gifted by FMC biopolymer. Sodium stearyl fumarate was gifter by MSN Laboratories Pvt.Ltd, Hyderabad (Supplier Rank Organic Chemicals Pvt. Ltd). Opadry II Yellow 85F520105 was gifted by Colorcon Pvt Ltd, Goa, India. All other solvents used were of analytical grade. 3M Nose masks purchased from Amazon.

METHODS

Dry granulation (by Roller compaction) was being chosen as a manufacturing process for manufacturing of blend to be compressed into tablets. The same qualitative composition (Tagrissso® 40 mg and 80 mg film coated tablets) was being chosen in the formulation of the test product. The in-*vitro* dissolution of the test product was evaluated by UV method.

Physical Characterization of Active Pharmaceutical Ingredient (API):

In the current study, input API with 3 different particle size was evaluated, *i.e.,* d_{90} of 8.4µ, 65.6µ and 135.2µ. It was checked for bulk density, tapped density (USP-II/1250 taps), from which Hausner ration and Compressibility index were calculated [5].

Bulk density = Weight / Bulk volume

Tapped density = Weight / Tapped volume

Compressibility index (%) = Tapped density - Bulk density / Tapped density

Hausner's ratio = Tapped density / Bulk density

The saturation Solubility studies of API:

The known quantity of Osimertinib mesylate (2 mg, coarser 135.2µ) was transferred to 100 ml of volumetric flask, to which 50 ml medium / solvent added and mixed well to dissolve API by means of sonication for 2-3 min. Then known excess qty of API added slowly under continuous swirling, if it dissolved until the medium / solvent shows resistance towards dissolving an API (Note: If an API does not dissolve completely even after 2-3 min of sonication, add an excess amount of API (Approx. 500 mg) and sonication for 30 min, maintain temperature of water in sonicator at 25 ºC). After completion of 30 min sonication, filter the solution through 0.45µ membrane filter. The standard solution of API was prepared in all media and water (at that concentration of the standard solution, the solubility of drug substance should be complete and should give an accurate response).
The content of API dissolved was estimated by UV method (note down the total amount of API being added).

Formulation of Osimertinib Tablets 80 mg by Dry granulation method using Roller compaction:

From the scientific discussion of Tagrisso® (Osimertinib) 40 mg and 80 mg film coated tablets in EU [6] and physical characterization of API, dry granulation (by Roller compaction) manufacturing process was being chosen [7] to improve the flow properties of blend to be compressed into tablets and followed by film coating (3.7 – 4.3 % w/w weight gain).
The following parameters has been set as a target parameters for the test product from the product label and Physical characterization of the Innovator product.

Table – 1: Target parameters for the development of the test product.

S.No	Attribute(s)	Innovator Product	Target parameters for the Test product
1.	Label claim	Each film coated tablet contains Osimertinib mesylate, which is equivalent to 80 mg of Osimertinib.	Each film coated tablet contains 95.4 mg of Osimertinib mesylate, which is equivalent to 80 mg of Osimertinib.
2.	Raw materials	Core portion: Mannitol, Microcrystalline cellulose, Low substituted - Hydroxypropyl cellulose, and Sodium stearyl fumarate.	Qualitative composition will be similar to that of Innovator product, but specific grades of each raw material and quantitative composition of Innovator product is not known.
		Film coating: Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Ferric oxide yellow, Ferric oxide red and Ferric oxide black.	Since it is not a functional coating, qualitatively it can be changed
3.	Dimension and shape	14.6 x 7.34 mm and Oblong shape (film coated tablets)	14.5 x 7.3 mm and Oblong (core tablets) / 14.62 x 7.41 mm and Oblong (film coated tablets)
4.	Thickness	5.40 – 5.45 mm	It will be changed w.r.t hardness
4.	Hardness	21.7 – 23 kp	20 – 23 kp (Film coated tablets)
5.	Disintegration time	4 min 10 sec – 4 min 45 sec	4 – 6 min (Film coated tablets)
6.	Manufacturing process	Dry granulation (by Roller compaction)	Dry granulation (by Roller compaction)
7.	Function of each excipient in test product	Mannitol - Diluent Microcrystalline cellulose – Diluent / Disintegrant Low substituted - Hydroxypropyl cellulose – Disintegrant Sodium stearyl fumarate - Lubricant Film coating - For aesthetic purpose	

From the scientific discussion of Tagrisso® 40 mg and 80 mg film coated tablets in Europe market and considering the flow properties of API with d_{90} of 8.4µ, 65.6µ and 135.2µ, it was decided to develop the product by dry granulation using roller compaction manufacturing process in order to improve the flow properties of blend to be compressed into tablets. From the label of the Innovator product, the same qualitative composition in core portion being chosen. The film coated tablets (4.0±0.3% w/w) were evaluated for *in vitro* dissolution profiles in 500 ml of 3 different dissolution mediums, *i.e.,* pH 1.3 (0.2% NaCl), Acetate buffer (pH 4.5) and Phosphate buffer (pH 6.8) at 25 rpm.

Table 2: Composition of Osimertinib Tablets 80 mg (Effect of particle size of API).

S.No	Composition	OSM-F003	OSM-F005	OSM-F006
	Particle size of API (d_{90}) →	8.4µ	65.6 µ	135.2 µ
I.	Intra-granular Ingredients			
1.	Osimertinib mesylate*	95.4	95.4	95.4
2.	Mannitol (Pearlitol SD200)#	232.6	232.6	232.6
3.	Microcrystalline cellulose (Avicel PH 102)	132.0	132.0	132.0
4.	Low-substituted hydroxyl propyl cellulose (LH-31)	25.0	25.0	25.0
5.	Sodium stearyl fumarate	7.5	7.5	7.5
II.	Extra granular ingredient			
6.	Sodium stearyl fumarate	7.5	7.5	7.5
Weight of uncoated tablet		500.0 mg	500.0 mg	500.0 mg
III.	Film coating (15% w/w solid content)			
7	Opadry II Yellow 85F520105**	20.0	20.0	20.0
8.	Purified water	113.3	113.3	113.3
Weight of film coated tablet		520.0 mg	520.0 mg	520.0 mg

Table 3: Composition of Osimertinib Tablets 80 mg (Effect of L-HPC).

S.No	Composition	OSM-F005	OSM-F007	OSM-F008
	Total concentration of L-HPC (w.r.t core) →	5.0% w/w	7.5% w/w	10.0% w/w
	Particle size of API (d_{90}) →	65.6µ	65.6 µ	65.6 µ
I.	Intra-granular Ingredients			
1.	Osimertinib mesylate*	95.4	95.4	95.4
2.	Mannitol (Pearlitol SD200) #	232.6	232.6	232.6
3.	Microcrystalline cellulose (Avicel PH 102)	132.0	119.5	107.0
4.	Low-substituted hydroxyl propyl cellulose (LH-31)	25.0	25.0	25.0
5.	Sodium stearyl fumarate	7.5	7.5	7.5
II.	Extra granular ingredient			
6.	Low-substituted hydroxyl propyl cellulose (LH-31)	---	12.5	25.0
7.	Sodium stearyl fumarate	7.5	7.5	7.5
Weight of uncoated tablet		500.0 mg	500.0 mg	500.0 mg
III.	Film coating (15% w/w solid content)			
8.	Opadry II Yellow 85F520105**	20.0	20.0	20.0
9.	Purified water@	113.3	113.3	113.3
Weight of film coated tablet		520.0 mg	520.0 mg	520.0 mg

*Qty of Osimertinib mesylate was based on 100% w/w Assay (on dried basis of Osimertinib mesylate).
Qty of Mannitol was adjusted to make the tablet weight remain constant based on Assay and % w/w Loss- on Drying of Osimertinib mesylate.
@ It will not be appears in the final product, except in traces.
**Film coating material calculated based on target weight build-up of 4 % w/w of core tablet weight, taken 30% extra qty considering manufacturing process losses during film coating.

Brief manufacturing process:

1. Osimertinib mesylate, Mannitol, Microcrystalline cellulose and Low-substituted hydroxpropyl cellulose were sifted together through #40 mesh.
2. Sodium stearyl fumarate was sifted through #60 mesh
3. The materials of step 1 and 2 blended together manually in a polybag for 5 min.
4. The blend of step 3 was subjected to compaction by using lab scale model roller compactor at roller force in the range of 2700 to 3000 LBF, Roller speed 2-3 rpm and Screw speed 25-27 rpm.
5. The flakes were milled by using rotary mill fitted with 2mm screen at medium speed, then formed granular mass was sifted through # 20 mesh. The #20 passed granules were checked for % of retained granules and % of passed fines over #60 mesh.
6. If % of retained granules over #60 mesh less than 55% w/w (range 55 – 60% w/w), fine portion (#60 mesh passed) was subjected to further cycling of roller compaction at roller force in the range of 2000 to 2500 LBF, Roller speed 1-2rpm and Screw speed 20-22 rpm. This step of process was repeated till to get % of retained granules over #60 mess in the range of 55 - 60% w/w. If the retained granules over #60 mesh more than 60% w/w, mill the coarser granules by using rotary mill fitted with 2mm screen at medium speed.
7. Low-substituted hydroxyl propyl cellulose (LH-31), if present was sifted through #40 mesh.
8. Sodium stearyl fumarate was sifted through #60 mesh.
9. The granules and fines of step no. 6, and sifted material of step no.7 (if present) were blended together manually in a poly bag for 5 min.
10. The blend of step no.8 and sifted material of step no.8 were blended together manually in a poly bag for 3 min.
11. The lubricated blend of step no. 10 was compressed with 14.5 x 7.3 mm Oblong shape, biconcave punches, embossed with "OSM" on one side and "80" on the other side.
12. Film coating suspension preparation: The required qty (considering 30% overages) of Opadry II Yellow 85F520105 was added in required quantity of Purified water (15% w/w solid content) under continuous stirring and stirred for about 45 min and coating suspension was continuously stirred whilst coating was under process.
13. The Core tablets of step no. 10 were loaded in a perforated coating pan and subjected to pre-warming at an inlet temperature of 55 °C – 60 °C. Then coating suspension was started spraying when the bed temperature reaches about 45°C. Then the coated tablets [target weight gain of 4.0 % w/w (3.7 – 4.3 % w/w] were dried for 15 min at a bed temperature of 40 °C – 45 °C.

Assay of Tablets (by UV method):

Preparation of standard solution:

Accurately weighed qty (25.0 mg) of API was transferred into 100 mL volumetric flask, to which 1:1 ratio of KH_2PO_4 buffer, pH 3 (75 ml) and Acetonitrile was added and subjected to sonication for 15 min (20 ºC - 25 ºC). Then the volume was made up to 100 ml with 1:1 ratio of KH_2PO_4 (pH 3) and Acetonitrile. From this 5.0 ml of the solution was added to 25 mL volumetric flask, diluted with pH 3 KH_2PO_4 buffer and Acetonitrile (1:1 ratio) and mixed well. In the same way, different concentrations of drug solutions were prepared, and the absorbance of the solution checked at wavelength of 210nm. From which standard graph was drawn.

Preparation of test sample solution:

10 No's of film coated tablets were taken and crushed into fine powder in a mortar and weight equivalent to 50.0 mg of Osimertinib was added to 100 ml volumetric flask, to which 1:1 ratio of 75 ml of KH_2PO_4 buffer (pH 3) and Acetonitrile was added and subjected to sonication for 30 min (20 ºC - 25 ºC). Then the volume was made up to 100 ml with 1:1 ratio of KH_2PO_4 buffer (pH 3) and Acetonitrile followed by centrifugation at 3000 rpm for 10 min. From this 5.0 ml of the solution was added to 50 mL of volumetric flask, diluted with pH 3 KH_2PO_4 buffer and Acetonitrile (1:1 ratio) and mixed well. The absorbance of the solution checked at wavelength of 210nm. From the standard graph, the content of API was estimated.

***In vitro* drug release studies**

Preparation of dissolution medium

pH 1.3 (0.2% NaCl):

Accurately weighed quantity of NaCl (10.0 g) was transferred into a beaker contain 5,000 ml of purified water and stirred well to dissolve. The pH of this solution was adjusted to 1.3±0.05 with diluted Hydrochloric acid (10 % v/v).

Acetate buffer, pH 4.5:

Accurately weighed quantity of 29.9 g of Sodium acetate trihydrate was dissolved in 8,000 ml of Purified water, to which 140 ml of 2 N Glacial CH_3COOH (23.2 ml of Glacial CH_3COOH was taken into a 200 ml of volumetric flask and diluted with Purified water and mixed well). Then diluted with Purified water to 10,000 mL, and mixed well. The pH of the solution was adjusted to 4.5±0.05 with 2N Glacial acetic acid solution.

Phosphate buffer, pH 6.8:

Exactly weighed quantity of 68.05 g of KH_2PO_4 was dissolved in 8,000 ml of Purified water. To which 1,120 ml of 0.2 M NaOH solution (16.0 g of NaOH pellets were taken in 2,000 ml of volumetric flask, to which 1,000 ml of Purified water added and mixed well. Then diluted to 2,000 ml with Purified water). The resulting solution was diluted to 10,000 ml with Purified water. Then the solution pH was adjusted to 6.8±0.05 with 0.2 M NaOH solution.

Preparation of Standard drug solution:

Accurately weighed qty (25.0 mg) of Osimertinib mesylate was transferred into 50 mL volumetric flask, to which 30 ml of dissolution medium was added and subjected to sonication for 15 min (20ºC - 25 ºC). Later the volume was made up to 50 ml with dissolution media and mixed well. From this 5.0 ml of the solution was taken in 25 mL of volumetric flask, diluted with dissolution media and mixed well. In the same way, different concentrations of drug solutions were prepared. The absorbance was recorded in 0.1 cm cell at 270 nm on a UV Spectrophotometer, using the dissolution media as blank. From the recorded absorbance, the standard graph was drawn.

Preparation of test product sample solution:

The parameters of the dissolution apparatus were set as mentioned in table 3. As API is more soluble, the *in vitro* drug release profiles for test product of 5 formulations and its Innovator product was evaluated in 500 ml at 25 rpm. The conditions and parameters of dissolution testing are presented in Table 3. One tablet each was placed into each of 6 dissolution vessels. From which 10 ml of sample solution was withdrawn through 10µ filters from each dissolution vessel at the end of specified time point. The aliquot was replaced with equal volume of dissolution media, which was maintained at 37±0.5 ºC. The absorbance of the test product solution was verified in 0.1 cm cell at 270 nm on a UV Spectrophotometer, using the dissolution media as blank. The accumulative percentage drug release was calculated.

Table 4: *In-Vitro* dissolution conditions.

Instrument	**Electro lab - USP type II (Paddle) Dissolution test apparatus**		
Dissolution medium	pH 1.3 (0.2% NaCl)	Acetate buffer, pH 4.5	Phosphate buffer, pH 6.8
Apparatus	USP type II (Paddle)	USP type II (Paddle)	USP type II (Paddle)
Temperature	37±0.5 °C	37±0.5 °C	37±0.5 °C
RPM	25	25	25
Volume	500 ml	500 ml	500 ml
Sampling intervals	5, 10, 15, 30,45, 60 and 90 min	-do -	-do-
Sample volume	10 ml withdrawn and exchanged with 10 ml of dissolution medium		

RESULTS AND DISCUSSION:

Physical Characterization of API of different particle size

Table 5: Physical characterization of Osimertinib mesylate of different particle size.

Physical Parameter	API with d_{90} of 8.4µ	API with d_{90} of 65.6µ	API with d_{90} of 135.2µ
Bulk Density (g/ml)	0.212	0.284	0.420
Tapped Density (g/ml)	0.284	0.402	0.612
Compressibility Index (%)	25.35	29.35	31.37
Hausner Ratio	1.34	1.42	1.46
Inference	The API with above 3 different particle size exhibits poor flow characteristics		

Solubility Studies of Osimertinib mesylate

The solubility of micronized API was determined in pH range of 1 – 6.8 and presented in below given Table 6.

Table 6: Solubility studies of API over pH range of 1 to 6.8.

S.No.		Solubility (mg/ml) n=3
	pH range from 1.0 – 6.8	d_{90} of 135.2µ
1.	0.1 N HCl (pH 1.2)	65.4±0.32
2.	pH 1.3 (with 0.2% NaCl)	36.2 ± 0.24
3.	Acetate buffer, pH 4.5	8.6 ± 0.15
4.	Phosphate buffer, pH 6.8	8.1±0.12
5.	Water	4.3±0.08

The solubility of drug substance is showing decreasing trend from pH 1.2 to pH 6.8.

The physical characterization of final (lubricated) blend, core tablets and coated tablets was done and presented in the below given tables.

Table 7: Physical characterization of final blend.

B.No → / Parameters ↓	OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
Bulk Density (g/ml)	0.562	0.540	0.524	0.552	0.548
Tapped Density (g/ml)	0.704	0.702	0.718	0.706	0.692
Compressibility Index (%)	20.17	23.08	27.02	21.81	21.49
Hausner Ratio	1.25	1.30	1.37	1.28	1.27

Table 8: Compression parameters of Osimertinib Tablets 80 mg, core tablets.

Batch. No → / Parameters ↓	OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
Tablet weight (mg)	496 -506	497 -508	498 -510	495 -507	492 -504
Hardness (kP)	13.5 – 15.8	13.0 – 14.5	13.0 – 15	13.5 – 14.5	13.8 – 15.2
Disintegration time	4 min 30 sec – 5 min	2 min 15 sec – 2 min 45 sec	1 min 45 sec – 2 min 15 sec	2 min 30 sec – 2 min 45 sec	2 min 10 sec – 2 min 30 sec
Friability (% w/w)	0.14 – 0.15	0.18 – 0.22	0.16 – 0.20	0.17 – 0.19	0.17 – 0.19

Table 9: Physical parameters of Osimertinib Tablets 80 mg, coated tablets.

Batch. No → / Parameters ↓	Tagrisso 80 mg tablets	OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
Tablet weight (mg)	516 - 532	518 – 526	519 – 527	519 – 527	517 – 525	519 – 527
Thickness (mm)	5.38 – 5.46	5.44 – 5.52	5.45 – 5.56	5.45 – 5.56	5.47 – 5.54	5.43 – 5.54
Hardness (kP)	21.6 – 22.9	20.1 – 21.4	17.0 – 18.2	17.0 – 18.2	17.2 – 18.4	16.8 – 18.0
Disintegration time	4 min 15 sec – 4 min 50 sec	4 min 30 sec – 5 min 15 sec	3 min 20 sec – 3 min 50 sec	2 min 45 sec – 3 min 20 sec	3 min 10 sec – 3 min 40 sec	3 min –3 min 30 sec

Assay of film coated tablets:
Assay of above 5 formulations is presented in the below given Table 10 and found to be in the range of 96% – 100%.

Table 10: Assay of Osimertinib Tablets 80 mg, coated tablets.

S.No.	Formulation, B.Nos	% Assay
1.	OSM-F003	97.4 ±0.6
2.	OSM-F005	98.3 ±1.2
3.	OSM-F006	97.2±1.4
4.	OSM-F007	98.1±0.9
5.	OSM-F008	96.6.4±1.6

***In Vitro* Dissolution Studies (**Mean±SD, n=3)

Table 11: Cumulative *in vitro* Dissolution Profiles in 500 ml of pH 1.3 (0.2% NaCl) at 25 rpm.

Time (min)	Tagrisso® 80mg tablets	Osimertinib Tablets 80 mg				
		OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
0	0	0	0	0	0	0
5	20.3±17.2	17.8±16.2	32.3±14.6	28.6±18.1	30.1±13.1	33.1±12.7
10	47.8±9.2	48.1±7.1	51.8±6.2	55.6±7.4	49.3±8.4	51.6±7.6
15	62.2±7.5	58.2±5.4	69.4±4.4	67.5±5.1	65.2±3.8	63.8±3.3
30	73.6±3.2	71.7±2.1	84.3±3.1	81.7±4.4	80.1±2.2	78.7±2.0
45	78.2±2.4	80.3±1.6	90.2±2.1	88.1±2.7	87.6±1.6	88.2±1.4
60	92.8±1.6	90.4±1.2	94.6±0.8	91.6±1.6	91.2±1.1	90.8±1.2
90	99.6±0.9	97.3±1.1	99.6±0.6	100.2±0.9	98.3±0.7	98.8±0.6
Infinity (at 200 rpm for 10 min)	101.4±0.3	99.4±0.7	100.6±0.4	101.4±0.3	100.2±0.5	100.7±0.4

Table 12: Cumulative i*n vitro* Dissolution Profiles in 500 ml of Acetate buffer, pH 4.5 at 25 rpm.

Time (min)	Tagrisso® 80mg tablets	Osimertinib Tablets 80 mg				
		OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
0	0	0	0	0	0	0
5	15.1±18.2	13.7±16.2	5.6±22.6	8.4±20.1	6.1±19.3	7.2±18.3
10	34.7±10.4	36.6±8.8	21.8±11.2	25.2±10.7	25.2±10.7	27.42±9.2
15	52.6±7.2	55.1±6.5	33.4±7.7	36.8±6.3	34.2±6.9	37.4±6.1
30	78.4±5.4	78.2±4.1	61.6±5.3	63.2±5.1	62.9±4.6	66.1±5.4
45	89.4±3.4	90.3±2.6	79.4±3.4	83.7±2.7	81.8±3.7	85.4±2.3
60	98.4±1.8	97.5±1.1	84.2±2.3	87.6±1.4	85.3±1.9	89.8±1.1
90	101.4±0.4	99.3±0.6	99.1±1.1	99.7±0.8	98.4±0.7	99.1±0.8

Table 13: Cumulative *in vitro* Dissolution Profiles in 500 ml of Phosphate buffer, pH 6.8 at 25 rpm.

Time (min)	Tagrisso® 80mg tablets	Osimertinib Tablets 80 mg				
		OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
0	0	0	0	0	0	0
5	19.1±24.6	17.4±18.1	16.8±16.2	16.4±17.7	17.3±15.1	18.2±14.4
10	38.7±13.3	44.4±11.2	39.2±9.8	37.4±10.3	41.1±8.3	41.1±8.1
15	57.6±9.2	63.6±7.1	56.4±6.6	52.4±7.0	55.8±6.2	55.8±6.5
30	76.4±8.3	80.3±5.2	75.8±4.4	73.8±4.9	74.2±4.1	74.2±3.6
45	82.4±6.6	87.3±2.8	83.4±2.7	81.4±2.4	85.3±2.3	85.3±2.0
60	86.4±5.4	91.3±1.7	89.2±1.5	80.2±1.3	88.2±1.1	88.2±0.9
90	89.4±2.7	95.8±1.3	97.1±1.5	88.1±1.0	95.5±1.0	95.5±0.6
Infinity (at 200 rpm for 10 min)	94.6±1.4	97.8±0.8	99.4±0.9	90.4±0.7	98.4±0.6	98.4±0.3

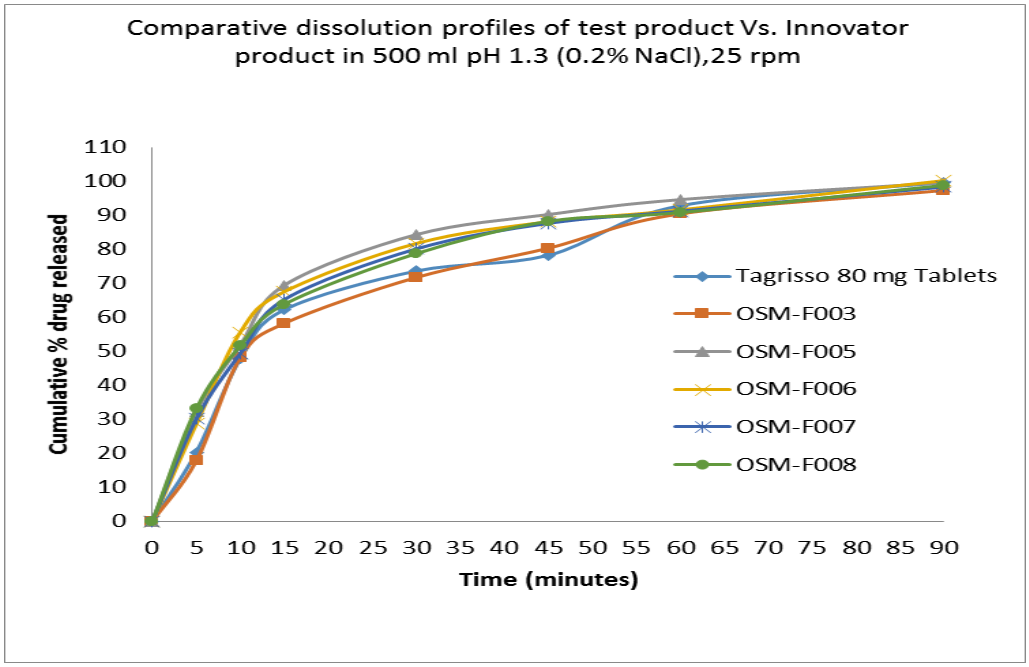

Figure 1: Graphical representation for comparative *in vitro* dissolution profiles in pH 1.3 (0.2% NaCl).

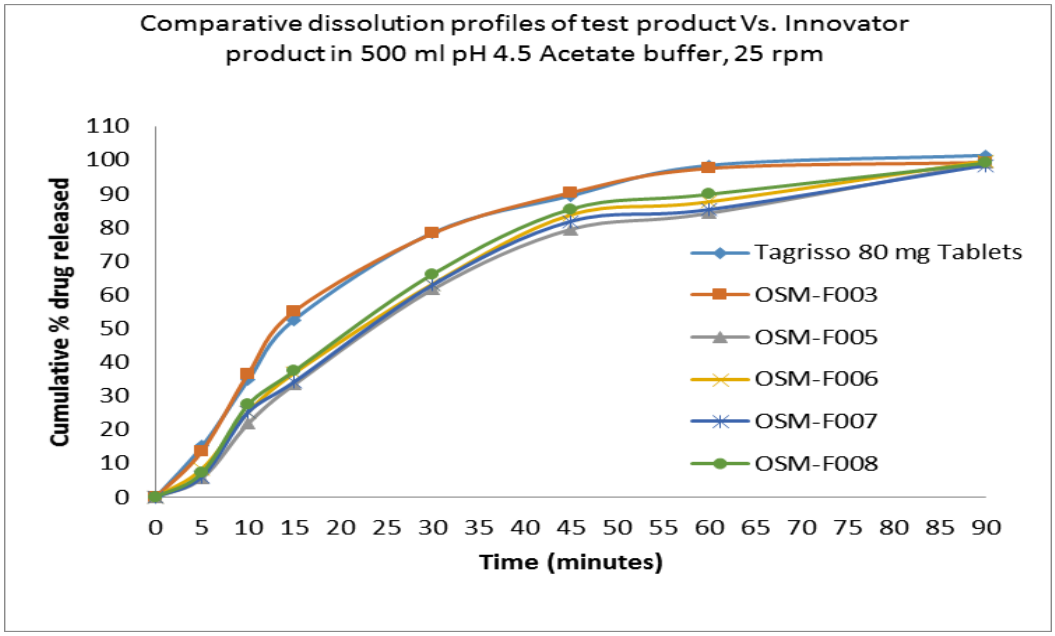

Figure 2: Graphical representation for comparative *in vitro* dissolution profiles in Acetate buffer, pH 4.5.

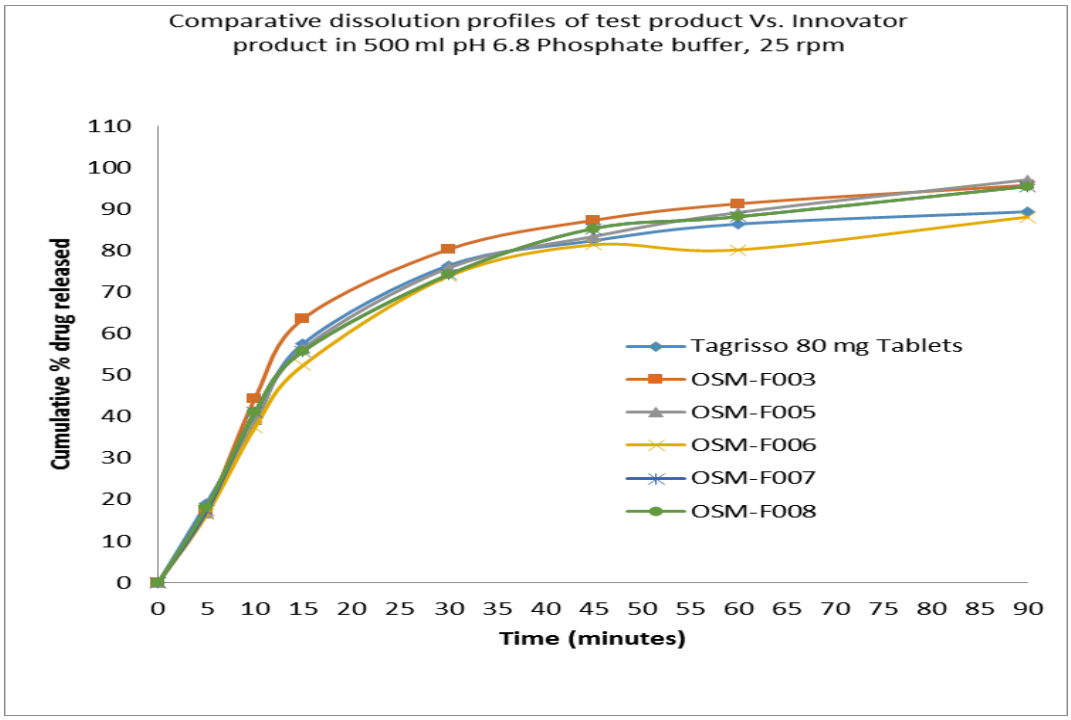

Figure 3: Graphical representation for comparative *in vitro* dissolution profiles in Phosphate buffer, pH 6.8.

CONCLUSION

From the Scientefic discussion of Tagrisso® film coated tablets 80 mg & 40 mg, Europe and considering the flow properties of Osimertinib mesylate with d_{90} of 8.4µ, 65.6µ and 135.2µ, the product was developed by dry granulation using roller compaction. In the present work, the effect of particle size of API with same concentration of L-HPC / and effect of concentration of disintegrant (L-HPC) with sampe particle size of API on *in-vitro* dissolution profile of the test product in 500 ml of pH 1.3 (0.2% NaCl), Acetate buffer, pH 4.5 and Phosphate buffer, pH 6.8 was studied. The maraked innovator product was found to be film coated at around 4% w/w of core tablets weight, hence it was decided to apply the same percentage of film coating in the test product.

From the physical parameters of coated tablets, the hardness and DT of test product (B.No: OSM-F003, where particle size of API, d_{90} of 8.4µ) was found to be comparable to that of Innovator product. The hardness and DT in remaining 4 batches were not matched to that of Innovator product.

From the dissolution profiles in 500 ml of pH 1.3 (0.2% NaCl), the drug release from B.No: OSM-F003 was found to be comparable to that of Innovator product and it was slightly increasing with increase of particle size of API and concentration of L-HPC.

From the dissolution profiles in 500 ml of Acetate buffer, pH 4.5 at 25 rpm, the drug release from B.No: OSM-F003 was found to be similar to that of Innovator product and increasing of particle size of API shown slower and less than 90% release at the end of 60 min as compared to that of Innovator product.

From the dissolution profiles in 500 ml of Phosphate buffer, pH 6.8 at 25 rpm, it was concluded that there was no effect of particle size of API on the drug release. Micronized particle gives slightly faster dissolution in this media.

It was observed with 3 different concentrations of L-HPC that there was no substantial increase in the drug release with increase concentrations of L-HPC and there is no appreciable change in DT also.

Considering the solubility of API, the median T_{max} of the marketed product (6 h – in the range of 3 – 24 h), the similar hardness and DT to that Innovator product, the comparative *in vitro* dissolution profiles of test product against marked Innovator product in US, it was concluded that micronized API with d_{90} less than 10µ (preferably in the range of 4 - 9µ) and 500 ml of Acetate buffer, pH 4.5 is a discriminatory dissolution media for this product to get a similar dissolution profiles, hardness and DT to that of Innovator product.

ACKNOWLEDGEMENTS

I got required qty of Osimertinib mesylate from Natco Pharmaceuticals, Hyderabad. I procured required raw materials from reputed excipient suppliers. I got 30 No's of Innovator samples from my friend Mr. Janardhan from USA.

ABBREVIATIONS

1.	epidermal growth factor receptor	EGFR
2.	non-small cell lung cancer	NSCLC
3.	United states of America	US / USA
4	Europe union / Europe	EU
5.	Bio pharmaceutical Classification system	BCS
6.	Active Pharmaceutical Ingredient	API
7.	Ultra violet – Visible	UV
8.	Food and Drug Administration	FDA
9.	European Medicines Evaluation Agency	EMEA
10.	milligram	mg
11.	Gram	g
12.	Low substituted Hydroxypropyl cellulose	L-HPC
13.	Micron / micro meter	µ
14.	90% of the particle	d_{90}
15.	Percentage	%
16	Weight / weight	w/w
17.	Revolution per minute	RPM
18.	millilitre	mL
19.	Numbers	No's / n
20.	Private Ltd	Pvt. Ltd
21.	United States Pharmacopeia	USP
22.	Minute	Min
23.	Degree centigrade	° C
24.	Approximately	Approx.
25.	milli meter	mm
26.	Kilo pond	kP
27.	With respect to	w.r.t
28.	Quantity	Qty
29.	Potassium dihydrogen phosphate	KH_2PO_4
30.	Acetic acid	CH_3COOH
31.	Sodium chloride	NaCl
32.	Sodium hydroxide	NaOH
33.	Hydrochloric acid	HCl
34.	Plus or minus	±
35.	Standard deviation	SD
36.	Pound – force / pound of force (LB is an abbreviation of the Latin word libra	Lbf or lb_f (1 lbf = 4.448 Newtons)

Conflict of Interest:

None

REFERENCES

1. Tagrisso Product label. Available from Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s011lbl.pdf
2. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5e81b4a7-b971-45e1-9c31-29cea8c87ce7
3. Keith R.L, Miller Y. E. Lung Cancer chemoprevention: Current status and future prospects. Nat Rev Clin Oncol. 2013; 10:334–343.
4. [Tim Freeman, Harmut Vom Bey, Michael Hanish, Katrina Brockbank, Brian Armstrong. The influence of roller compaction processing variables on the rheological properties of granules. Asian J Pharma Sci. 2016; 11:516–527.
5. USP<616>,https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/bulk_density.pdf.
6. https://www.ema.europa.eu/documents/assessment-report/tagrisso-epar-public-assessment-report_en.pdf
7. Dhumal Sonam, Kulkarni PA, Kashikar VS, Baweja Jitendra, Thottasseri Manoj. A Review: Roller Compaction for Tablet Dosage Form Development. Research and Reviews. J Pharm Pharm Sci. 2013; 2(4): 68-73.

5487847845**1190302**