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Formulation, Optimization and Evaluation of Osimertinib Tablets

Ramesh K*

Associate Professor, Department of Pharmaceutics, Nova College of Pharmacy, Andhra Pradesh, India

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ABSTRACT

Osimertinib mesylate is a kinase inhibitor, indicated for the treatment of patients 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 non-small cell lung cancer (NSCLC). Solubility of Osimertinib is known to be affected by pH, it belongs to BCS class-III molecule.

The present work attempted to study the impact of particle size of API, concentrations of disintegrant (L-HPC) on in vitro dissolution profiles of Osimertinib from tablet dosage form in comparison to in vitro drug release profiles of corresponding Innovator product in US market.

From the scientific discussion of Innovator product in EU market, and to improve 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 has shown similar physical (hardness, disintegration time) and in vitro drug release profiles to that of Innovator product.

Keywords: Osimertinib mesylate; Particle size; Disintegrant; Dissolution profile

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INTRODUCTION

Osimertinib mesylate is a kinase inhibitor, indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC). The brand name of the

Innovator product in US and EU market is TAGRISSO® (Osimertinib) 40 mg and 80 mg film coated tablets [1,2]. The Innovator of the product is AstraZeneca, 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 one 80 mg tablet once daily taken orally with or without a meal [1,2]. Approximately, 80-90% of lung cancer comprise non-small cell lung cancer (NSCLC) [3].

In the present study, it was planned to study the effect of particle size of API and concentrations of disintegrant (L-HPC) on *in-vitro* dissolution 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. To improve the flow properties of blend for compression, dry granulation method (by Roller compaction) was adopted [4]. Formulation was done with input API having PSD of 3 different d_{90} values/and 3 different concentrations of L-HPC with same quantitative composition 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.

The obtained results suggested that the film coated test product (3.7-4.3% w/w weight build-up) with input API having particle size below 10 µ showing similar hardness and dissolution profiles to that of Innovator product. The dissolution media 500 ml of pH 4.5 Acetate buffer at 25 rpm is found to be showing more discriminating dissolution media.

MATERIALS AND METHODS

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 8.4 µ, 65.6 µ and 135.2 µ) was gifted by Natco Pharmaceuticals, Hyderabad, India. Mannitol (Pearlitol 200SD) and Low-substituted Hydroxypropyl cellulose (LH-31) were gifted by Signet, Microcrystalline cellulose (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 IH was gifted by Colorcon Pvt Ltd, Goa, India. All other solvents used were of analytical grade. 3 M 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 present study, input API with 3 different particle size was evaluated, *i.e.,* d_{90} of 8.4 µ, 65.6 µ and 135.2 µ. 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 with d_{90} of 135.2 µ) 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 0.45 µ membrane filter. The standard solution of drug substance was prepared in all media and water (the concentration of the standard solution should be such that at that concentration/level 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 [6] and physical characterization of Osimertinib mesylate, 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 build-up).

From the product label and Physical characterization of Tagrisso® (Osimertinib) film coated tablets 80 mg, the following parameters has been set as a target parameters for the test product (Table 1).

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	14.6 × 7.34 mm and Oblong shape	14.5 × 7.3 mm and Oblong (core tablets)/14.62 ×

	and shape	(film coated tablets)	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 8.4 µ, 65.6 µ and 135.2 µ, 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), pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer at 25 rpm (Tables 2 and 3).

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 (d90)	**8.4 µ**	**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	132	132
4	Low-substituted hydroxyl propyl cellulose (LH-31)	25	25	25
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	20	20
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 (d90)	**65.6 µ**	**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	119.5	107
4	Low-substituted hydroxyl propyl cellulose (LH-31)	25	25	25
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
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	20	20
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 2 mm 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 1-2 rpm 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 2 mm screen at medium speed.
7. The extra granular material Low-substituted hydroxyl propyl cellulose (LH-31), if present was sifted through #40 mesh. Sodium stearyl fumarate was sifted through #60 mesh.
8. The granules and fines of step no. 6, and sifted material Low-substituted hydroxyl propyl cellulose of step no.7 (if present) were blended together manually in a poly bag for 5 min.
9. The blend of step no.8 and sifted material Sodium stearyl fumarate of step no.7 were blended together manually in a poly bag for 3 min.
10. The lubricated blend of step no. 9 was compressed with 14.5 × 7.3 mm Oblong shape, biconcave punches, embossed with "OSM" on one side and "80" on the other side.
11. 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.
12. 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. Film coating was continued till to get a weight gain of 4.0% w/w (3.7-4.3% w/w) of core tablet weight. Then the coated tablets were dried for 15 min at a bed temperature of 40°C-45°C after getting weight gain in the range of 3.7-4.3% w/w.

Assay of Tablets (by UV Method)

Preparation of standard solution: Accurately weighed qty (25.0 mg) of Osimertinib mesylate was transferred into 100 mL volumetric flask, to which 75 ml of pH 3 Potassium dihydrogen phosphate buffer and Acetonitrile (1:1 ratio) was added and subjected to sonication for 15 min (bath temperature maintained between 20 ºC and 25 ºC). Later the volume was made up to 100 ml with 1:1 ratio of pH 3 Potassium dihydrogen phosphate buffer and Acetonitrile. From this 5.0 ml of the solution was transferred to 25 mL volumetric flask, diluted with pH 3 Potassium dihydrogen phosphate 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 210 nm. From which standard graph was drawn.

Preparation of test sample solution: 10 No's of film coated tablets were taken in a mortar and crushed into fine powder and weight equivalent to 50.0 mg of Osimertinib was transferred to 100 ml volumetric flask, to which 75 ml of pH 3 Potassium dihydrogen phosphate buffer and Acetonitrile (1:1 ratio) was added and subjected to sonication

for 30 min (bath temperature was maintained between 20 ºC and 25 ºC). Later the volume was made up to 100 ml with 1:1 ratio of pH 3 Potassium dihydrogen phosphate buffer and Acetonitrile followed by centrifugation at 3000 rpm for 10 min. From this 5.0 ml of the solution was transferred to 50 mL of volumetric flask, diluted with pH 3 Potassium dihydrogen phosphate buffer and Acetonitrile (1:1 ratio) and mixed well. The absorbance of the solution checked at wavelength of 210 nm. From the standard graph, the content of active ingredient 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).

pH 4.5 Acetate buffer: 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 acetic acid (23.2 ml of Glacial acetic acid was transferred 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 2 N Glacial acetic acid solution.

pH 6.8 Phosphate buffer: Accurately weighed quantity of 68.05 g of Potassium dihydrogen phosphate was dissolved in 8,000 ml of Purified water. To which 1,120 ml of 0.2 M Sodium hydroxide 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 pH of the solution 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 (bath temperature was maintained between 20°C and 25°C). Later the volume was made up to 50 ml with dissolution media and mixed well. From this 5.0 ml of the solution was transferred to 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 of the different concentration of drug solution was recorded in 0.1 cm cell on a UV Spectrophotometer at 270 nm, 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 the drug substance is more soluble, the *in vitro* drug release profiles for test product of 5 formulations and its corresponding 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 10 µ 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 recorded in 0.1 cm cell on a UV Spectrophotometer at 270 nm, using the dissolution media as blank. The cumulative percentage drug release was calculated (Table 4).

Table 4. *In-Vitro* dissolution conditions

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

RESULTS AND DISCUSSION

Physical Characterization of Osimertinib mesylate API of Different Particle Size

The Physical characterization of csimertinib mesylate API of different particle size is given in Table 5.

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

Physical Parameter	**API with d90 of 8.4 µ**	**API with d90 of 65.6 µ**	**API with d90 of 135.2 µ**
Bulk Density (g/ml)	0.212	0.284	0.42
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 Osimertinib mesylate was determined in different medias covering pH range of 1-6.8. The results are tabulated in below given in Table 6.

Table 6. Solubility studies of Osimertinib mesylate over pH range of 1 to 6.8

S.No.	**pH range from 1.0-6.8**	**Solubility (mg/ml)** **d90 of 135.2 µ**
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	pH 4.5 Acetate buffer	8.6 ± 0.15
4	pH 6.8 Phosphate buffer	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 the results are presented in the Tables 7-9.

Table 7. Physical characterization of final blend

Parameters	B.No				
	OSM-F003	OSM-F005	OSM-F006	OSM-F007	OSM-F008
Bulk Density (g/ml)	0.562	0.54	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	1.3	1.37	1.28	1.27

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

Parameters	Batch No.				
	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

Parameters	Batch. No					
	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 film coated tablets of above 5 formulations is presented in the below given Table 10. The assay of test products was 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® 80 mg	Osimertinib Tablets 80 mg				
		OSM-	OSM-F005	OSM-F006	OSM-F007	OSM-F008
0	0	0	0	0	0	0
5	20.3 ± 17.2	17.8 ±	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 pH 4.5 Acetate buffer at 25 rpm

Time (min)	Tagrisso® 80 mg 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 pH 6.8 Phosphate buffer at 25 rpm

Time (min)	Tagrisso® 80 mg 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	94.6 ± 1.4	97.8 ± 0.8	99.4 ± 0.9	90.4 ± 0.7	98.4 ± 0.6	98.4 ± 0.3

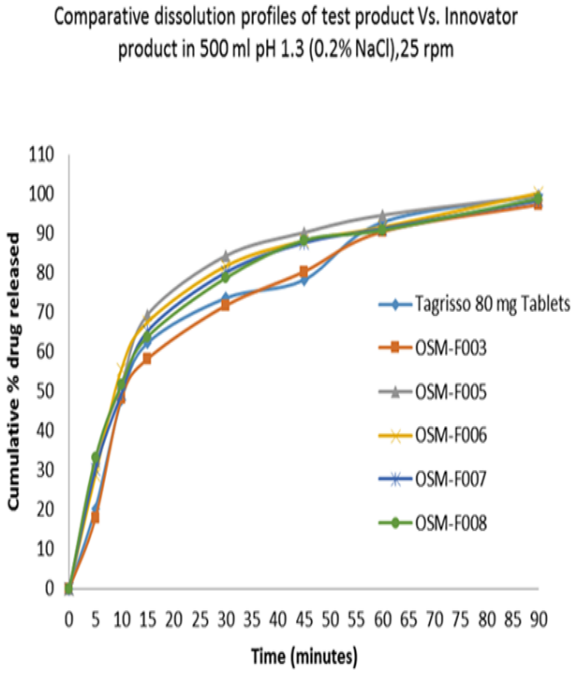

Figure 1. Graphical representation for comparative *in vitro* dissolution profiles in 500 ml of pH 1.3 (0.2% NaCl) at 25 rpm

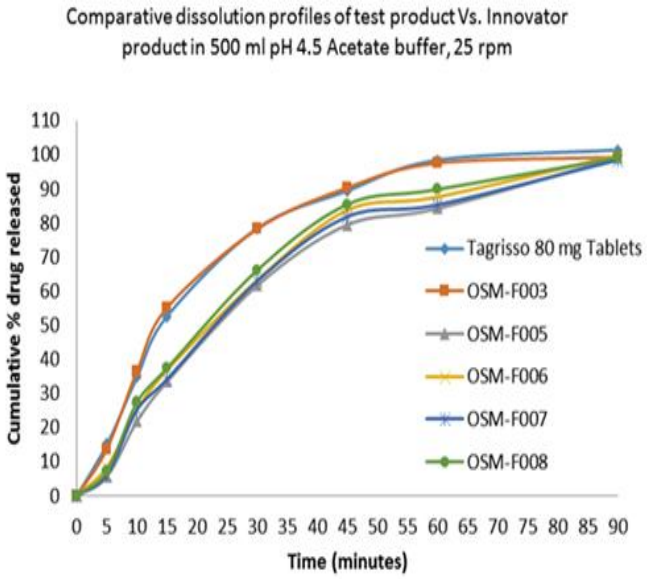

Figure 2. Graphical representation for comparative *in vitro* dissolution profiles in 500 ml of pH 4.5 Acetate buffer at 25 rpm

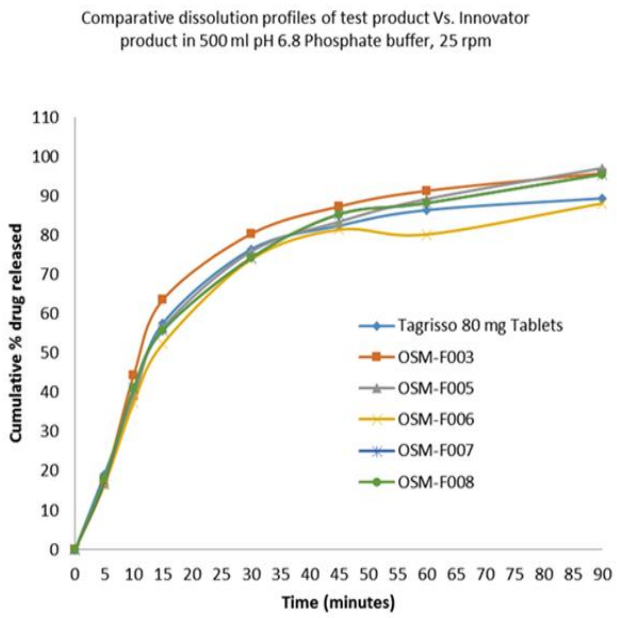

Figure 3. Graphical representation for comparative *in vitro* dissolution profiles in 500 ml of pH 6.8 phosphate buffer at 25 rpm

From the physical parameters of film coated tablets, the hardness and disintegration time of test product (B.No: OSM-F003, where particle size of API: d_{90} of 8.4 µ) was found to be similar to that of Innovator product.

From the comparative *in vitro* dissolution profiles, it was evident that the drug release from the test product with API having particle size d_{90} of 65.6 µ and 135.2 µ was found to be on higher side in pH 1.3 (0.2% NaCl) as compared to that of dissolution profile of Innovator product (Figure 1 and Table 11), whereas in pH 4.5 Acetate buffer the drug release was found to be on lower side (Figure 2 and Table 12).

From the drug release profiles of the 5 batches in 500 ml of pH 6.8 Phosphate buffer, it was observed that there was no significant difference in the drugs release and found to be comparable to that of drug release of Innovator product (Figure 3 and Table 13).

The drug release from the 5 batches of the test product with API having particle size d_{90} of 8.4 µ and 135.2 µ was found to be on higher side in pH 1.3 (0.2% NaCl) as compared to that of dissolution profile of Innovator product, whereas in pH 4.5 Acetate buffer the drug release was found to be on lower side and less than 90% release at the end of 60 min.

From the drug release from the test product with 3 different concentrations of L-HPC, it was observed that there was no appreciable increase in the drug release with increase concentrations of L-HPC and there is no appreciable change in disintegration time also.

SUMMARY AND CONCLUSION

From the scientefic discussion of Tagrisso® film coated tablets 80 mg and 40 mg, Europe and considering the flow properties of Osimertinib mesylate with d_{90} of 8.4 µ, 65.6 µ and 135.2 µ, 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), pH 4.5 Acetate buffer and pH 6.8 Phosphate

buffer was studied. The weight build-up of the maraked innovator product was found to be 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 disintegration time of test product (B.No: OSM-F003, where particle size of API, d_{90} of 8.4 µ) was found to be similar to that of Innovator product. The hardness and disintegration time 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. The drug release from the test product was slightly increasing with increase of particle size of API and concentration of L-HPC.

From the dissolution profiles in 500 ml of pH 4.5 Acetate buffer at 25 rpm, the drug release from B.No: OSM-F003 was found to be similar to that of Innovator product. The drug release from the test product with 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 pH 6.8 Phosphate buffer 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 at pH 6.8 Phosphate buffer.

From the drug release from the test product with 3 different concentrations of L-HPC, it was observed that there was no appreciable increase in the drug release with increase concentrations of L-HPC and there is no appreciable change in disintegration time 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 disintegration time 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 10 µ (preferably in the range of 4-9 µ) and 500 ml of pH 4.5 Acetate buffer is a discriminatory dissolution media for this product to get a similar dissolution profiles, hardness and disintegration time 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.

REFERENCES

[1]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf

[2]. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5e81b4a7-b971-45e1-9c31- 29cea8c87ce7

[3]. RL Keith; YE Miller. Nat Rev Clin Oncol. **2013**, 10, 334-343.

[4]. T Freeman; HV Bey; M Hanish; K Brockbank; B Armstrong. *Asian J Pharma Sci*. **2016**, 11, 516-527.

[5]. 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]. D Sonam, PA Kulkarni; VS Kashikar; B Jitendra; T Manoj. *J Pharm Pharm Sci*. **2013**, 2(4), 68-73.