Enhancement of Drug Dissolution of Erlotinib Tablets by Micronization Technique Using Pharmaceutical Experimental Design

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Lung cancer is the second most frequent cancer and among the top cause of death worldwide. Chemotherapy is the main therapeutic option for non-small-cell lung cancer (NSCLC), which accounts for the majority of all lung malignancies. The aim of the current work was to develop a tablet formulation having increased drug release profile to improve the bioavailability in order to reduce the dose of the drug. In this present study, Erlotinib tablet was prepared using micronization technique which showed increase drug release profile. Film-coated tablets containing Erlotinib hydrochloride (150 mg) were prepared by dry granulation technique and coated using Opadry ready-mix. Tablets were characterized for Hardness, Friability, Potency and Drug release profile. Drug release was checked in 0.1 N HCL containing 0.5 % SLS and biorelevant dissolution media up to 60 minutes. Tablets of the selected batch were subjected to dissolution in biorelevant media and compare with reference product. The improvement in the drug release was observed in the biorelevant media in comparison with reference product. The in-vitro dissolution data demonstrated the potential of micronization technology to prepare tablets with improved bioavailability of the drug.

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1. INTRODUCTION

Lung cancer is the most frequent cancer and the leading cause of cancer fatalities. Chemotherapy is the primary therapeutic option for non-small-cell lung cancer (NSCLC), which accounts for the majority of lung cancers [1-2].

Erlotinib is an anticancer medicine that inhibits the tyrosine kinase of the epidermal growth factor receptor (EGFR). It is used to treat non-small cell lung cancer (NSCLC) and pancreatic cancer. Erlotinib’s solubility is pH dependent, having a low solubility at neutral pH and a higher solubility at pH less than 5. It is classified as a class II drug by the Biopharmaceutical Classification System (BCS), which means it has a low solubility and a high permeability. It is absorbed in the GI tract and reaches its maximal concentration in the blood after 1.4 hours. Erlotinib has a daily dose of 150 mg for NSCLC. In healthy subjects, absolute bioavailability (BA) was found to be only 59 percent [3-5].

Erlotinib suppresses signaling pathways such as cell proliferation, metastasis, and angiogenesis. Folliculitis, diarrhoea, dry skin, and lethargy are all common adverse effects of EGFR TKIs. However, some adverse effects may worsen, and new symptoms may appear after months or years of medication. This could lead to dose reductions or even the premature discontinuation of effective treatment. Long-term side effects in individuals treated with erlotinib for lung adenocarcinoma with an EGFR activating mutation. Due to the good tumour response to this EGFR TKI patients and their treating physicians were highly motivated to continue treatment. As a result, early and ongoing side effects like folliculitis and diarrhoea were deemed tolerable. Skin toxicity remained in all cases. Many patients may receive reduce dose because of these side effects [6-9].

The size of drug particles affects their oral bioavailability because smaller particles have more surface area, which increases their dissolution. The solubility of the active pharmaceutical ingredient is proportional to the size of the drug particle. As the particle size decreases, the surface area to volume ratio increases. Because of the larger surface area, there is greater interaction with the solvent, which results in a higher solubility. Particle size reduction is a cost-effective, reproducible, and commercially feasible approach for increasing solubility. Micronization is a conventional technique for the particle size reduction. Micronization enhances the rate of drug dissolution by increasing the surface area of the drug, but it does not increase equilibrium solubility. The rate of dissolution of these pharmaceuticals is improved by reducing the particle size of these drugs, which results in an increase in surface area. Milling techniques employing a jet mill are used to micronize pharmaceuticals. The micronization techniques are applied to various poorly soluble drugs for improving their absorption, and as a result to increase their bioavailability [10-12].

For the drug products meant for oral administration, particle size of drugs and components are very important and can affect the manufacturing processing, solubility and in vivo bioavailability. Numerous drugs that have been developed for pharmaceutical administration purpose have low aqueous solubility and are categorized in class II and IV of the biopharmaceutical classification system. One of the limiting parameters for achieving excellent bioavailability is the dissolution rate. Particle size reduction, which increases surface area, is a promising strategy for improving dissolution rate and, as a result, bioavailability of poorly water-soluble medicines can be improved [12-13]. The aim of the study was to use micronization techniques to reduce particle size and accelerate the rate of Erlotinib dissolution from the tablet dosage form. Tablet formulation prepared by co-sifting of functional excipients and micronized erlotinib hydrochloride was analysed for drug dissolution in bio-relevant media and compared with available reference drug.

2. MATERIALS AND METHODS

2.1 Materials

Erlotinib Hydrochloride, Lactose monohydrate (DFE Pharma, Netherlands), Microcrystalline Cellulose (FMC International, Ireland), Sodium Lauryl Sulphate (BASF, Germany), Sodium Starch Glycollate (Roquette Freres, France), Magnesium stearate (Avantor, USA), Opadry White (Colorcon Asia Pvt. Ltd., India)

2.2 Formulation of Tablets

The milling of drug substance was done by using Air Jet Mill (Promas Engineering, Mumbai).
Milling performed at air pressure 3-4 kg/cm². The particle size of milled material was checked with laser diffraction technique (Table 1). The tablets were manufactured using dry granulation technique.

Table 1. Particle size of drug substance

|       |       |
|-------|-------|
| d(0.5)| 5 to 10 µ |
| d(0.9)| 15 to 20 µ |

Micronized erlotinib hydrochloride was further used to prepare tablet using lactose monohydrate, microcrystalline cellulose as diluent, sodium starch glycolate as disintegrant, sodium lauryl sulphate as surfactant and magnesium stearate as lubricant. The quantity of all the excipients are mention in the Table 2. Excipients were sieved through #40, co-sifting and mixing of dry excipients with erlotinib hydrochloride was done twice to ensure proper mixing of functional excipients with drug substance. Dry mix powder was subjected to prepare slugs/flakes, which were than broken in to granules with using 1.5 mm screen and milled granules mixed with extra granular disintegrant, further lubrication was done using magnesium stearate. The mix was compressed using 10.3 mm Round punches on a 12-station single rotary compression machine (Rimek Mini Press, Ahmedabad, India). Uncoated tablets were than coated using aqueous based Opadry white ready mix up to weight build-up of approximately 5.0 % in ganscoater (Ganscoater GAC, Gansons, Mumbai, India).

2.3 Optimization of the Tablet Formulation

Statistically designed experiments (Table 3) using a 2-factor, 2-level factorial design (Design Expert® Software (Version 13.0.5.0, Stat-Ease Inc., Minneapolis, MN) were performed to study the effect of two factors i.e concentration of SLS (X1) and concentration of SSG (X2) on the in-vitro dissolution and disintegration time of tablets.

Table 2. Composition of erlotinib tablet formulation

| Ingredients                              | Quantity (mg/Tablet) |
|------------------------------------------|----------------------|
| Erlotinib (equivalent to Erlotinib hydrochloride) | 150                  |
| Lactose Monohydrate                      | 104.00               |
| Microcrystalline Cellulose               | 127.06               |
| Sodium Starch Glycolate (SSG)            | 45.00                |
| Sodium Lauryl Sulphate (SLS)             | 4.50                 |
| Magnesium Stearate                       | 5.50                 |
| Core tablet weight                       | 450.00               |
| Coated Tablet weight                     | 472.50               |

Table 3. Composition of the tablet batches as per factorial design

| Ingredients                              | Quantity (mg/Tablet) |
|------------------------------------------|----------------------|
| Erlotinib (equivalent to Erlotinib hydrochloride) | T1 150 | T2 150 | T3 150 | T4 150 | T5 150 |
| Lactose Monohydrate                      | 104.00               |
| Microcrystalline Cellulose               | 127.06               |
| Sodium Starch Glycolate (SSG)            | 45.00                |
| Sodium Lauryl Sulphate (SLS)             | 4.50                 |
| Magnesium Stearate                       | 5.50                 |
| Core tablet weight                       | 450.00               |
| Coated Tablet weight                     | 472.50               |

2.4 Tablet Characterization

- Flow property of Granules: The bulk density, tap density, and Hausner ratio of the granules were all measured using following equation [14-15].
The compressibility index and Hausner ratio are calculated using measured values for bulk density ($\rho_{\text{bulk}}$) and tapped density ($\rho_{\text{tapped}}$) as follows:

\[
\text{Compressibility Index} = 100 \times \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \tag{1}
\]

\[
\text{Hausner Ratio} = \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \tag{2}
\]

- **Weight Variation:** The test for weight uniformity was carried out by weighing 20 tablets at random using weighing balance (Mettler Toledo, AG 204) and noting the average weight and standard deviation was determined [16-17].

- **Thickness:** The micrometer caliper was used to measure the thickness of ten pre-weighted tablets from each batch, and the average thickness and standard deviation was determined [16-17].

- **Friability:** The USP 35 monograph on tablet friability was used to determine tablet friability. Twenty tablets ($W1$) were weighed and placed in a friabilator, which was rotated at 25 rpm for four minutes. After removing the fines ($W2$), the tablets were reweighed and the friability was evaluated using the formula below.

\[
\% \text{ Friability} = \frac{W1 - W2}{W1} \times 100 \tag{3}
\]

- **Hardness:** The hardness of 10 tablets from each batch with known weight and thickness was evaluated using a hardness tester (Dr Schleuniger, 5Y). The average hardness, standard deviation, and relative standard variation were all calculated and reported [18-19].

- **Disintegration Time:** The test was carried out using a USP disintegration test apparatus (M/s Electrolab Tablet Disintegration Tester ED, 2 AL, India). A tablet was inserted in each of the six tubes of the basket during the test, the basket was immersed in water using a mechanical device, and the temperature was maintained at $37\pm2^{\circ}C$ [19-22].

- **In-vitro dissolution study:** Dissolution of tablets was conducted in USP type II apparatus (Electrolab, India). In-vitro dissolution was performed using the USP Apparatus II (Paddle) at $37\pm0.5^{\circ}C$ and at 50 RPM. The samples were withdrawn up to 60 minutes. For preparation of 0.1N HCl dissolution media, 5 ml of hydrochloric acid was dissolved in water and 5 gm of SLS was added to make the volume to 1000 ml. Sample were analysed using HPLC and the percentage drug dissolved was calculated. Similarly, the 500 ml of biorelevant Fasting state simulated gastric fluid (FaSSGF) was utilised for dissolution study of the optimised batch [23-26].

3. RESULTS AND DISCUSSION

A total of five formulations (Table 4) of erlotinib tablets with different ratio of disintegrant and surfactant levels were prepared using factorial design using two factors – concentration of SLS (X1), the concentration of SSG (X2) at two levels. The results demonstrated that batch with mid value of SLS concentration and SSG concentration showed good dissolution characteristics and disintegration time. The extent of in vitro drug release was determined by performing multiple linear regression analysis using Design Expert Software version 13.0.5.0. The 3D response surface plot (Fig. 1) and contour plot (Fig. 2) were developed to study the effects of variables on the disintegration of the drug graphically.

The tablet's were formulated using Erlotinib Hydrochloride as active pharmaceutical agent, Lactose monohydrate and Microcrystalline Cellulose as fillers, Sodium Lauryl Sulphate as surfactant, Sodium Starch Glycolate (SSG) as disintegrant and Magnesium stearate was added to enhance the powder flow. As a result, there was a consistent flow from the hopper to the die. It facilitates the ejection of tablets from the die cavity by reducing inter-particle friction, by preventing tablet material from adhering to machine components such as punches and dies. Excipients were sieved through #40. The co-sifting and mixing of dry excipients with erlotinib hydrochloride was done twice to ensure proper mixing of functional excipients with drug substance. Dry mix powder was subjected to prepare flakes. Flakes were than broken in to granules with using 1.5 mm screen and milled granules mixed with extra granular disintegrant in blender for further lubrication was done using magnesium stearate. The granules were characterize for the flow property (Table 5), which have shown passable flow characteristics. The particle size of granules has been shown in Table 6 and Fig. 3, respectively.
Table 4. Independent variables and dependent variables of erlotinib tablets

| Batch No | X1 (SLS Conc.) | X2 (SSG Conc) | Y1 (Disintegration time) | Y2 (Percent dissolution in 60 min) |
|----------|---------------|---------------|--------------------------|-------------------------------------|
| T1       | -1            | -1            | 6 min                    | 83%                                 |
| T2       | +1            | -1            | 6 min                    | 84%                                 |
| T3       | -1            | +1            | 3 min                    | 92%                                 |
| T4       | +1            | +1            | 3 min                    | 94%                                 |
| T5       | 0             | 0             | 4 min                    | 93%                                 |

Fig. 1. 3D response surface plot

Fig. 2. Contour plot
**Table 5. Flow characteristics of granules**

| Characteristics     | T1          | T2          | T3          | T4          | T5          |
|---------------------|-------------|-------------|-------------|-------------|-------------|
| **Bulk density**    | 0.58 gm/cc  | 0.57 gm/cc  | 0.60 gm/cc  | 0.61 gm/cc  | 0.60 gm/cc  |
| **Taped density**   | 0.77 gm/cc  | 0.76 gm/cc  | 0.78 gm/cc  | 0.80 gm/cc  | 0.78 gm/cc  |
| **Carr Index**      | 25          | 25          | 23          | 24          | 23          |
| **Hausner ratio**   | 1.33        | 1.33        | 1.30        | 1.31        | 1.30        |

**Table 6. Particle size of the granules**

| % Retained | T1  | T2  | T3  | T4  | T5  |
|------------|-----|-----|-----|-----|-----|
| # 40       | 50  | 53  | 58  | 55  | 52  |
| #60        | 59  | 68  | 61  | 67  | 65  |
| #80        | 75  | 84  | 83  | 82  | 80  |

**Fig. 3. Size analysis of granules**

**3.1 Tablet Characteristics**

The mix was compressed using 10.3 mm Round punches on a 12-station single rotary compression machine (Rimek Mini Press, Ahmedabad, India). All the tablets were characterized for weight variation test, hardness, thickness, disintegration and dissolution test. All of the formulations disintegrated quickly and were well within official limits. By introducing discs into 900ml purified water at 37±2°C in water, the disintegration time of six tablets was measured. It shows that the drug is fully available for dissolution and absorption from the GIT.

**Table 7. Tablet characteristics**

| Characteristics     | T1          | T2          | T3          | T4          | T5          |
|---------------------|-------------|-------------|-------------|-------------|-------------|
| **Weight**          | 450 mg +3%  | 450 mg +3%  | 450 mg +3%  | 450 mg +3%  | 450 mg +3%  |
| **Hardness**        | 7 - 12 kp   | 8 - 11 kp   | 8 - 12 kp   | 7 - 12 kp   | 8 - 12 kp   |
| **Thickness**       | 4.8 - 5.0 mm| 4.7 - 5.0 mm| 4.9 - 5.2 mm| 4.7 - 5.0 mm| 4.9 - 5.1 mm|
| **Disintegration time** | 6 min     | 6 min    | 3 min     | 3 min     | 4 min     |
| **Friability**      | 0.5 %       | 0.5 %      | 0.4 %      | 0.6 %      | 0.4 %      |
3.2 Dissolution Study

The optimised batch was selected for the *in-vitro* drug release study using USP Dissolution Apparatus II. The *in-vitro* dissolution of optimised batch (T5) was compared with marketed formulation (as reference) using 0.1N HCl with 0.5% HCL and biorelevant Fasting state simulated gastric fluid (FaSSGF) (Figs. 4 and 5 illustrates the *in-vitro* release of T5 in 0.1N HCl and biorelevant medium. There was no significant difference in the dissolution behaviour of optimised formulation with reference formulation in 0.1 N HCl. However, a marked difference in the dissolution was observed in biorelevant media, which demonstrates the enhancement of dissolution of the erlotinib tablets.

4. CONCLUSION

The granules made using micronized API exhibited flow properties suitable to carry out compression. The *in-vitro* dissolution results revealed that biorelevant media is reflecting discriminating behaviour for the same formulation. The outcome of this study clearly indicates that a stable oral tablets of erlotinib can be developed using varying concentration of SSG and SLS, resulting in improved dissolution characteristics. This outcome of the study indicates the application of micronization technique in enhanced dissolution, which may further leads to increased oral bioavailability. Furthermore, *in-vivo* studies could give a better understanding of the results observed in.

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Fig. 4. *In-vitro* dissolution of optimised formation (T5) and marketed formulation in 0.1 N HCl

Fig. 5. *In-vitro* dissolution of optimised formation (T5) and marketed formulation in Biorelevant media
present investigation and targeted applications of tablets.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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