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Development of Oral Tablet Formulation Containing Erlotinib: Randomly Methylated-β-cyclodextrin Inclusion Complex Using Direct Compression Method

Direkt Basım Yöntemi Kullanılarak Erlotinib: Randomize Metillenmiş-β-siklodekstrin İnklüzyon Kompleksi Içeren Oral Tablet Formülasyonu Geliştirilmesi

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ABSTRACT
INTRODUCTION: Erlotinib (ERL) is an tyrosine kinase inhibitor that has been used for metastatic non-small cell lung cancer (NSCLC). However, low aqueous solubility limits absorption and oral bioavailability hence complexation is applied to overcome these drawbacks. The aim of this study was to design and characterize oral tablet formulation containing ERL: randomly methylated-ß-cyclodextrin cyclodextrin (RAMEB CD) inclusion complex in order to enhance solubility and oral bioavailability for ERL.
METHODS: An inclusion complex was prepared with RAMEB CD using co-lyophilization technique. Physicochemical studies was performed by X-ray diffractometry (XRD) and Fourier-transform infrared spectroscopy (FT-IR). Tablet formulation of ERL: RAMEB CD inclusion complex were prepared using direct compression technique. Tablet characteristics like hardness, diameter, thickness, friability, weight variability, disintegration and dissolution were evaluated. Also, flow properties of powder were determined.
RESULTS: The characterization studies suggested that stable complexes between ERL and RAMEB were obtained with co-lyophilization method. Accordingly, tablet formulation using inclusion complex of ERL and RAMEB CD with drug dose equivalent to 25 mg was prepared using direct compression technique. Physical properties of the powder mixture were studied (Angle of repose (°): 34.27±1.78; flow time: 2.2 ± 0.4; Hausner ratio (HR): 1.05 ± 0.02; compressibility index: 14.27±1.55). Moisture content (%) was found as 0.27 ± 0.05. The thickness, diameter and hardness values were 3.92±0.05 mm, 11.3±0.06 mm and 81.38±2.27 N, respectively. Friability value was 0.27%. In uniformity of weight test, the average weight was 404.57 ± 1.6 mg, with less than 5% deviation for randomly selected 20 tablets. The disintegration time was found to be less than 15 min. Dissolution study showed that solubility of erlotinib was importantly increased by complexation with randomly methylated-ß-cyclodextrin. 99% drug was released from tablet formulation at 60 min.

DISCUSSION AND CONCLUSION: These results concluded that a new tablet formulation of ERL: RAMEB CD inclusion complex could be an alternative approach for achieving better dissolution and oral bioavailability in NSCLC treatment.
Keywords: erlotinib, inclusion complex, direct compression, dissolution
ÖZ
GİRİŞ ve AMAÇ: Erlotinib (ERL) metastatik küçük hücreli akciğer kanserinde kullanılan tirozin kinaz inhibitörüdür. Bununla birlikte, düşük suda çözünürlüğü absorpsiyonunu ve oral biyoyararlanımını sınırlamaktadır. Bu nedenle bu sakıncaların üstesinden gelmek için kompleksleşme yöntemi kullanılmaktadır. Çalışmanın amacı Erlotinib'in çözünürlüğünü ve oral biyoyararlanımını artırmak için Erlotinib: randomize metillenmiş ß-siklodekstrin (RAMEB CD) inklüzyon kompleksi içeren oral tablet formülasyonu geliştirilmesi ve karakterizasyonudur.
YÖNTEM ve GEREÇLER: RAMEB siklodekstrin içeren inklüzyon kompleksi ko-liyofilizasyon yöntemi ile hazırlanmıştır. X-ray difraktometresi ve Fourier-transform infrared spectroskopisi (FT-IR) kullanılarak fizikokimyasal karakterizasyon yapılmıştır. Direkt basım yöntemi ile ERL: RAMEB siklodekstrin inklüzyon kompleksi içeren tablet formülasyonu hazırlanmıştır. Sertlik, çap, kalınlık, kırılganlık, ağırlık değişkenliği, dağılma ve dissolüsyon testleri ile tablet karakteristikleri değerlendirilmiştir. Tozun akış özellikleri tayin edilmiştir.
BULGULAR: Bulgular: Karakterizasyon çalışmaları ko-liyofilizasyon tekniği ile ERL ve RAMEB arasında stabil kompleks elde edildiğini göstermiştir. Buna göre, direkt basım yöntemi ile 25 mg ilaç dozuna eşdeğer olacak şekilde ERL ve RAMEB inklüzyon kompleksi kullanılarak tablet formülasyonu hazırlanmıştır. Toz karışımının fiziksel özellikleri çalışılmıştır (Yığın açısı (°): 34.27±1.78; akış süresi: 2.2 ± 0.4; Hausner oranı (HR): 1.05 ± 0.02; basılabilirlik indeksi: 14.27±1.55). Nem içeriği %0.27 ± 0.05 bulunmuştur. Kalınlık, çap ve sertlik değerleri sırasıyla 3.92±0.05 mm, 11.3±0.06 mm and 81.38±2.27 N. Kırılganlık değeri %0.27'dir. Ağırlık sapması testinde; ortalama tablet ağırlığı 404.57 ± 1.6 mg olup rastgele seçilen 20 tablet için sapma %5'ten küçüktür. Dağılma zamanı 15 dakikadan az bulunmuştur. Dissolüsyon çalışması randomize metil-beta-siklodekstrin ile kompleksleşme ile erlotinibin suda çözünürlüğünün önemli ölçüde arttığını göstermiştir. 60 dakika sonunda ilacın %99'u salınmıştır.
TARTIŞMA ve SONUÇ: Elde edilen veriler ile ERL: RAMEB CD inklüzyon kompleksi içeren yeni tablet formülasyonunun daha iyi çözünme ve oral biyoyararlanım elde etmek için NSCLC tedavisinde alternatif bir yaklaşım olabileceği sonucuna varılmıştır.
Anahtar Kelimeler: erlotinib, inklüzyon kompleksi, direkt basım, dissolüsyon

Introduction

Erlotinib (ERL) is a selective protein-tyrosine kinase inhibitor, which is located in epidermal growth factor receptor (EGFR) and shows anticancer efficacy in EGFR-overexpressed tumors such as non-small cell lung cancer (NSCLC) and pancreatic cancer [1]. Erlotinib is commercially manufactured as a film-coated tablet (Tarceva®), which is approved by the EMA and FDA.

Erlotinib is a weak base and low aqueous solubility (0.4 mg/mL at pH 2). Due to low solubility, the dissolution rate is a limiting step resulting in limited absorption and low bioavailability. In oral administration, the peak plasma concentration of erlotinib is reached after approximately 4 h, with 60% bioavailability and 44% plasma concentration shown to act on tumor [2]. Also, ERL has a wide range of adverse effect profiles like diarrhea, rash, renal failure, thrombocytopenia, and neutropenia [3, 4]. Hence, novel formulations are needed to enhance its efficacy and safety. Different approaches like solid dispersion, polymorphism, size reduction, and complexation, have been reported as suitable techniques to increase

solubility [5, 6]. Also, a self-emulsifying formulation [7], a reverse micelle-loaded lipid nanocarrier formulation [8], and a sulfobutyl-ether-*β*-cyclodextrin complex formation [9] were studied in relation to improving the bioavailability of ERL.

Recently, cyclodextrin complexation has been studied to increase the solubility and bioavailability of hydrophobic drugs. Cyclodextrins (CDs) are cyclic oligosaccharides comprise of 6 glucopyranose units bound via α-(1, 4) bonds. α, β- and γ-CDs are natural CDs, with 6, 7, and 8 glucose units, respectively [10]. Cyclodextrins contain a hydrophilic outer surface related to aqueous solubility and a lipophilic cavity capable of forming inclusion complexes with several molecules. This structure impacts the physicochemical properties of encapsulated drugs, increasing their solubility, dissolution, and bioavailability [11–13]. Otherwise, the utilization of natural CDs as drug carriers is limited due to their low solubility. Different modified CD derivatives have been used to enhance aqueous solubility [9, 14–16]. Among the modified CDs, we studied the complexation of erlotinib with randomly methylated ß-cyclodextrin (RAMEB CD), which has not been studied yet.

The purpose of this work was to develop and characterize a new tablet formulation containing the ERL: RAMEB CD inclusion complex for increasing dissolution and oral bioavailability of erlotinib. Also, flow properties and quality control parameters were evaluated.

Materials And Methods

Materials

Erlotinib Hydrochloride (Molecular weight: 429.9 g/mol, Hetero Labs, Telangana, India) was a kind gift from Nobel İlaç. Randomly methylated-ß-cyclodextrin (RAMEB CD) was a kind gift from Cyclolab (Budapest, Hungary). Acetone was purchased from Sigma-Aldrich (St. Louis, USA). Tween 80 was obtained from Merck-Schuchardt (Hohenbrunn, Germany). All other chemicals were of reagent grade and solvents were of HPLC grade. Lactose monohydrate and Avicel pH 102 was purchased from Sigma-Aldrich. Magnesium stearate was provided by Nitika Pharmaceuticals (Maharashtra, India). Sodium starch glycolate was purchased from Avebe (Foxhol, Netherlands).

Preparation of ERL: RAMEB CD Inclusion Complex

ERL: RAMEB CD inclusion complex was prepared by a lyophilization technique that could be demonstrated in another study (data not shown). Briefly, ERL (27.8 mg, 21 mM) was dissolved in acetone (3 mL) and then slowly added to RAMEB CD (82.1 mg, 21 mM) solution in water (3 mL) at a molar ratio of 1:1. The suspension was magnetically stirred at room temperature for 24 h. The organic solvent was evaporated under a rotavapor (IKA RV 10 basic, Germany), the obtained solution was frozen at −20 °C and was lyophilized at −80 °C under 0.1 mbar for 24 h to get white fluffy powder (Labconco Freezone 4.5 Plus, USA).

Characterization of ERL: RAMEB CD inclusion complex

Fourier-transform infrared (FT-IR) spectroscopy

Fourier-transform IR spectra of ERL, RAMEB CD, physical mixture (PM) and ERL: RAMEB CD inclusion complex were measured using Perkin Elmer BX Spectrum (USA) in the range of 4000–500 cm^{-1} at ambient temperature.

X-ray diffractometry (XRD)

The XRD patterns of ERL, RAMEB CD, PM and ERL: RAMEB CD inclusion complex were performed using a Multipurpose X-ray Diffraction Multipurpose Diffractometer (X'Pert Pro MPD, Malvern PANalytical, UK) with Cu Ka radiation powered at voltage 45 kV and current 40 mA. The diffraction angle (2θ) was between 3°–40° and the scanning rate was 2°/min.

Preparation of Tablet Formulation Containing ERL: RAMEB CD Inclusion Complex

Tablet formulations containing lyophilized ERL: RAMEB CD inclusion complex (equivalent to 25 mg erlotinib) are prepared by direct compression method using excipients shown in Table 1. Tablet formulations were manufactured based on commercial drug Tarceva® [17]. It contains 31% lactose monohydrate and 33% Avicel pH 102 as fillers, 8% sodium starch

glycolate as a super disintegrant, and 1% magnesium stearate as a lubricant. Using a roller mixer for 5 min, ERL: RAMEB CD inclusion complex was blended with lactose monohydrate and Avicel pH 102, respectively. Then, sodium starch glycolate was added into the mixture, progressively. Finally, the powder mixture was mixed with magnesium stearate. Tablet weight was adjusted to 400 mg and tablets were compressed using Erweka AR 400 (Heusenstamm, Germany) to manufacture oral tablet formulations containing ERL: RAMEB cyclodextrin complex.

Powder Flow Properties

The angle of repose (°):

The angle of repose was determined according to the fixed height funnel standing technique. A standard funnel was fixed, powder flowed during the orifice of a cone. The radius (r) of the base and height of powder mass (h) was measured, and was calculated using this formula;

$$\tan(\alpha) = \frac{height}{0.5xbase}$$

The flow time was evaluated with a standard funnel. The results were given as mean ± standard deviation (SD).

Hausner Ratio (HR) and Compressibility Index:

The Hausner ratio and compressibility index are two parameters that can be applied to predict the characteristics of a powder flow. The two indices are calculated as follows:

$$Hausner\ ratio = \frac{Vo}{Vf}$$

$$Compressibility\ index = 100x\frac{Vo - Vf}{Vo}$$

where V_0 = bulk volume; Vf = tapped volume of powder.

Bulk/tapped volume and density:

The bulk (V_0) and apparent volumes (V_{10},V_{500}, and V_{1250}) of powder mixture (50 g) were measured in a 100 mL cylindrical vessel. Because the difference between V_{500} and V_{1250} was less than 2 mL, V_{1250} is the tapped volume. Bulk and tapped densities were calculated as below:

$$Bulk\ density = \frac{m}{Vo}$$

$$Tapped\ density = \frac{m}{\mathrm{V1250}}$$

m: sample weight (g), V_0: the bulk volume (mL), V_{1250}: the tapped volume (mL)

Moisture content (%):

3 g of powder were heated at 102 °C (Ohaus MB45 Moisture Analyzer, Parsippany, USA) until the weight remained constant.

Quality Control Tests for Tablets Containing ERL: RAMEB CD Inclusion Complex

Hardness, Thickness and Diameter:

Hardness (n = 10), diameter (n = 20), and thickness (n = 20) of tablets were measured using a Pharma Test PTB 311E (Hainburg, Germany).

Friability:

Tablets (n = 20) were weighed, then placed in a friabilator (Pharma Test PTF 10E, Hainburg, Germany). After rotating at 100 cycles, the final weight of tablets was checked. The weight loss was calculated as a percent.

Uniformity of weight:

Tablets (n=20) were weighed and their average mass was calculated. Then, all tablets were weighed singly, and the deviation of individual masses from the average mass was calculated.

Disintegration test:

The disintegration of tablets was performed using Pharma test PTZ-S (Hainburg, Germany) in 1 L of purified water at 37 °C. Tablets were placed in cylindrical tubes of the system and, then the device started to move up-down automatically (n = 6).

Dissolution test:

The dissolution experiment was undertaken using the FDA dissolution methods database [18]. It was performed using a paddle (USP Apparatus 2) in 0.02% Tween 80 in 0.01 N HCl (1000 mL) at 75 rpm. Tablets containing ERL:RAMEB CD inclusion complex and ERL tablets (containing 25 mg erlotinib) were added to 1000 ml medium (Sotax Dissolution Testing Device, Switzerland). At the appropriate time (5, 10 15, 20, 30, 45, 60 min), 2 mL of aliquot was withdrawn and replaced with the same volume of fresh medium. All samples were filtered through a 0.45 μm filter. The filtrate was analyzed by an analytically validated HPLC method ($r^2 = 0.9992$). These methods consist of a Kromasil® reversed-phase C18 (250 x 4.6 mm) column, a mobile phase of ammonium acetate buffer (pH 4.): acetonitrile (65:35 v/v), injection volume: 20 μL and flow rate: 1 mL min^{-1}.

Results and Discussion

Characterization of ERL: RAMEB CD Inclusion Complex

ERL: RAMEB CD inclusion complex was prepared with lyophilization technique and characterized by XRD and FT-IR analysis.

It can be concluded that the lyophilization technique was preferable as solubility improvement is concerned. The complexation mechanism between drug and cyclodextrin may be van der Waal's and non-bonding forces. For demonstrating successful complexation phenomenon between ERL and RAMEB CD, the outcome of the screening ratio could be explained by the fact that the hydrophobic region of drug and cyclodextrin shows enough interactions at this ratio (1:1; ERL:cyclodextrin). Besides, stronger interaction between RAMEB and ERL could be based on lipophilic methyl groups on the RAMEB CD ring which have higher solubility and solubilization properties [19–20].

Figure 1 shows FT-IR spectra of erlotinib, RAMEB CD, PM and ERL: RAMEB CD inclusion complex. The spectrum of erlotinib displayed strong absorption bands at 3277 cm^{-1} (for CH_3, C-H stretching vibrations), 1634 cm^{-1} (for NH, secondary amine bending vibrations), 3277 cm^{-1} (for ≡C-H stretching vibrations), 1238 cm^{-1}, 1069 cm^{-1} (for phenyl ether group) and 1021 cm^{-1} (for aliphatic ether group), which has been reported Parthasaradhi et al [21]. The spectra of RAMEB are characterized by intense bands at 3300–3500 cm^{-1} (O-H stretching vibration), and 2800–3000 cm^{-1} (for –CH and -CH_2- groups) [22]. FT-IR spectrum of PM had superposition of the spectra of both ERL and RAMEB-CD. The physical mixture presented no shift of the absorption band at 3277 cm^{-1} and 1634 cm^{-1}. However, significant changes were observed in the center-frequencies (1634 cm^{-1} and 3277 cm^{-1}) widths of the characteristic absorption peaks of ERL, which validated the formation of inclusion complex of ERL: RAMEB (Figure 1). FT-IR data indicated the ERL-RAMEB interaction as a result of peak broadening and peak disappearance of the characteristic peak.

The XRD patterns of ERL, RAMEB CD, PM and ERL: RAMEB CD inclusion complex were given (Figure 2). The XRD pattern of erlotinib showed the presence of strong, sharp peaks at 5.66, 9.74, 11.32, 18.95, 22.78, 23.6, 24.24, 30.07 on 2θ, confirm crystalline nature of ERL. The XRD pattern of RAMEB CD displayed two broad peaks and many undefined, diffused peaks with low intensities, indicating the amorphous structure of cyclodextrin [23]. The PM has very few crystalline ERL peaks, but with decreased intensities and absence of sharp peaks. Contrarily, compared to the XRD patterns of ERL and RAMEB CD, the inclusion complex presented an amorphous state, due to both cyclodextrin structure and lyophilization [9]. The inclusion complex diffractometric profile has less intense RAMEB CD peaks and the absence of the ERL sharp characteristic peaks, thus suggesting that ERL is in an amorphous state. Hence, the reduction in crystallinity attributed to the ERL: RAMEB CD inclusion complex

suggests that ERL forms with CD inclusion complex in solid-state, demonstrating that new compounds are formed [24]. This was evidence for the absence of ERL crystalline particles, and the XRD patterns were in agreement with FT-IR results, indicating the formation of ERL: RAMEB CD inclusion complex.

The Flow Properties of Powder Mixture in Tablet Formulation

The powder mixture including drug-CD inclusion complex and excipients was prepared and established the flow properties, such as the angle of repose, compressibility index, Hausner ratio and moisture content. The angle of repose is a predictor for flow characteristics of all powder mixtures. In this study, the angle of repose was found as 34.27 ± 1.78. According to the United States Pharmacopeia (USP) specifications, the formulation exhibits good flow property. Hausner ratio and compressibility index were 1.05 ± 0.02 and 14.27 ± 1.55, respectively which suggest good flow properties according to United States Pharmacopeia 30 (USP 30) [25]. These results are accordant with the angle of repose of powder. The moisture content is an important parameter in the powder flow and manufacturing process. In our study, the moisture content (%) was found 0.27 ± 0.05%. This value is under the limit that helps binding drugs with excipients in the manufacturing process. The obtained data showed that powder displayed good flow properties and was favorable for the direct compression technique.

Quality-control Tests for Tablets Containing ERL: RAMEB CD Inclusion Complex

In this study, all of the tablets were manufactured with uniform appearance and appropriate physical characteristics. The thickness and diameter of tablets are between 3.92 ± 0.05 mm and 11.3 ± 0.06 mm, respectively. The very low variabilities in thickness and diameter showed that the operation and weighing of the powder mixture are appropriate during the manufacturing process. The hardness value was 81.38 ± 2.27 N for tablets containing ERL: RAMEB CD inclusion complex, showing that tablets had suitable crushing strength to resist abrasion.

Friability is a significant parameter that points out the tablet's capability to resist abrasion along with packaging, transport, and handling; compendial specification not more than 1% [26]. Friability value was 0.27% for tablet formulation containing ERL: RAMEB CD inclusion complex (Table 2). This data correlates the pharmacopeia criteria and shows that tablets probably have adequately high mechanical stress during the process, handling and transportation [27].

The uniformity of weight (or weight variation) of prepared tablets was evaluated by USP 30. The average weight of prepared tablets was found 404.57 ± 1.6 mg, with less than 5% deviation for 20 tablets, which meets the acceptability criteria of USP [28]. These results suggested that the powder mixture retained homogeneity during the preparation and manufacturing process.

For all tablets, the first important step towards drug dissolution is the breakdown of the tablets into granules or primary powder particles, a process known as disintegration. The disintegration time of tablet formulation containing ERL: RAMEB CD inclusion complex was compatible according to USP 30 where uncoated tablets have disintegration time standard value less than 15 minutes (Table 2).

Before performing dissolution test, the HPLC method was validated. The linearity of the calibration curves was established over the concentration range of 1–200 µg/mL with a correlation coefficient value is 0.9992 ± 0.01. The values (mean ± SE; n = 3) of the slope and intercept were 60.103 and 19.837, respectively. According to obtained data, the developed method showed acceptable linearity at the range 1–200 µg/mL for ERL. The LOD was found as 0.21 µg/mL and LOQ was 0.71 µg/mL with acceptable accuracy and precision. To determine the accuracy of analytical method, six series solution with three different concentration (0.5, 10 and 50 mg/ml) were prepared and HPLC analysis was done. ERL's

recovery and recoveries of X, SD and CV was calculated. Data are shown in Table 3. The recovery value was determined as 101.82% ± 3.7. Coefficient of variation must be below 2% in a study as reported in the requirements of the similarities and differences in FDA, ICH and USP's validation guideline. Coefficient of variations were found to be below 2% therefore was found suitable for relevant criteria. To determine the precision of analytical method, reproducibility and inter-day precision analysis were done. Data are shown in Table 4 and Table 5. Coefficient of variations were found to be below 2% therefore was found suitable for relevant criteria. The results indicated that the precision and accuracy of the method were sufficient.

Figure 3 represents dissolution profiles of erlotinib tablet and ERL: RAMEB CD tablet. The tablet containing inclusion complex showed 70.43% dissolved drug at 10 minutes; an approximately 2.5-fold increased drug dissolution in comparison to erlotinib (30.2%). At one hour, the tablet containing inclusion complex released 98.57%, while the erlotinib tablet dissolved 46.51%; an approximately two-fold increase in dissolution. This increase in dissolution may be related to the solubilization effect of cyclodextrin, and due to particle size reduction to the molecular level and formation of hydrogen bond in the complex [29].

The similarity factor (f_2) was used to compare the dissolution profiles. If *the* f_2 value is 50–100, the curves can be considered as similar [30]. f_2 obtained between the two dissolution curves of ERL and inclusion complex was 11, suggesting that release behaviors for inclusion complex differed from that for ERL. The significant improvement in the solubility and dissolution rates of the inclusion complex should be attributed to better aqueous solubility and solubilization properties of RAMEB CD and complexation [31,32]. These findings suggested that RAMEB CD was able to form a water□soluble inclusion complex with ERL and improved its dissolution rate. On the other hand, an improved dissolution rate and solubility of ERL could result in enhanced bioavailability and thus could possibly minimize the dose-limited side effects. The complexation with RAMEB CD poses great potential for improving the therapeutic and safety profile of erlotinib.

Conclusion

In this study, ERL: RAMEB CD inclusion complex was successfully developed and evaluated. The inclusion complex was characterized by XRD and FT-IR studies. Following, a novel tablet formulation was prepared using ERL: RAMEB CD inclusion complex by a direct compression method. The in vitro dissolution studies displayed the increased aqueous solubility and dissolution rate of the complex. Briefly, this study applies an effective method of CD complexation to get through the limited drug solubility and prepare an efficient oral dosage form to increase the efficacy of erlotinib with reduced adverse effects.

Conflict of interest

The authors state no conflict of interest.

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Components	Amount (mg)	Percent (%)
ERL-RAMEB complex	109	27
Lactose monohydrate	123	31
Avicel pH 102	132	33
Sodium starch glycolate	32	8
Magnesium stearate	4	1

Table 1. Components of tablet formulation containing ERL: RAMEB CD inclusion complex.

Parameter	Tablets containing ERL/RAMEB complex (mean ± SD)
Thickness (n = 20)	3.92 ± 0.05 mm
Diameter (n = 20)	11.3 ± 0.06 mm
Hardness (n = 10)	81.38 ± 2.27 N
Friability (n = 20)	0.27%
Uniformity of weight (n = 20)	404.57 ± 1.6 mg
Disintegration time (n = 6)	5 min

Table 2. The obtained results of quality control tests for tablets containing ERL: RAMEB CD inclusion complex

Sample Number	10 µg/mL % Recovery	50 µg/mL % Recovery	150 µg/mL % Recovery
1	9.87	50,59	150,07
2	10.19	51,85	154,55
3	9.75	51,95	156,66
4	9.8	50,28	154,92
5	9.82	51,21	155,7
6	9.84	49,54	150,46
X	9,88	50.9	153.73
SD	0.18	0.94	2.78
CV	1.79	1.85	1.81

Table 3. Coefficient of variation and % recovery of erlotinib.

Sample	Concentration (µg/mL)	X	SD	CV
1	50.28	50.82	0.89	1.76
2	50.43			
3	50.26			
4	50.37			
5	51.04			
6	52.55			

Table 4. Repeatability results of erlotinib (n=6).

Sample	Concentration (µg/mL)	X	SD	CV
1	50,59	51.47	0.76	1.49
2	51,92			
3	51,91			

Table 5. Inter-day precision results of erlotinib (n=6).

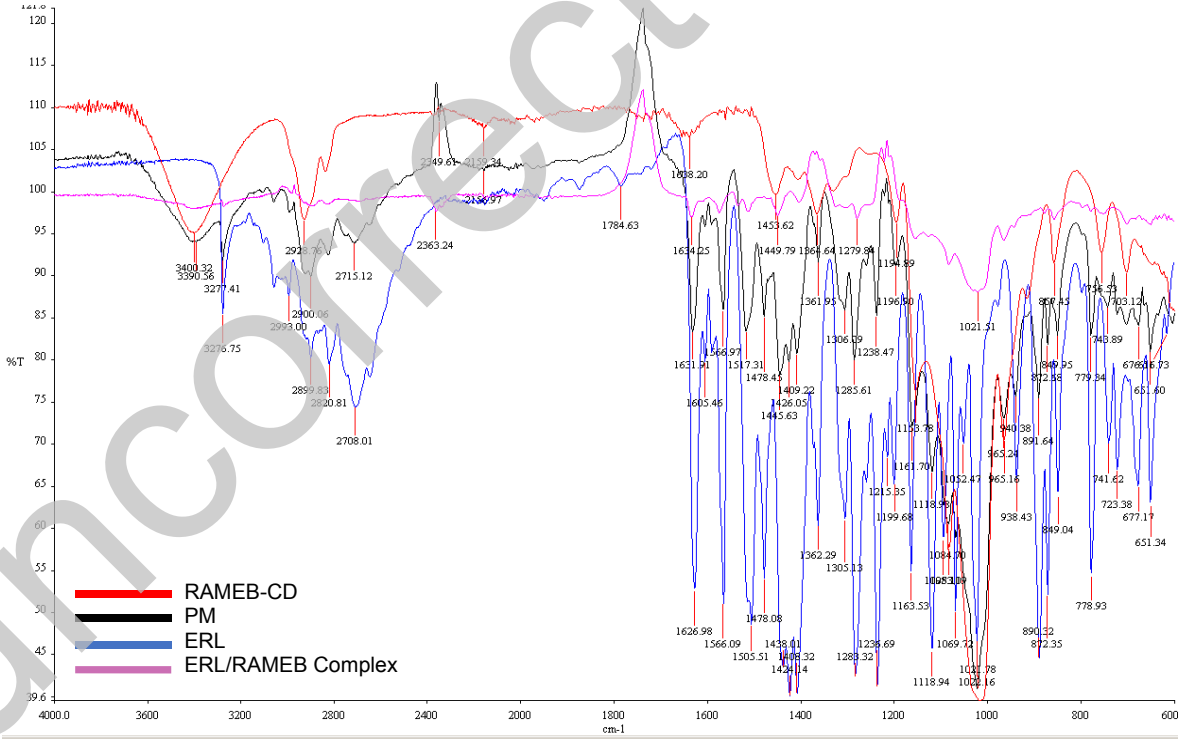

Figure 1. FT-IR spectra of ERL, RAMEB CD, PM, ERL: RAMEB CD inclusion complex.

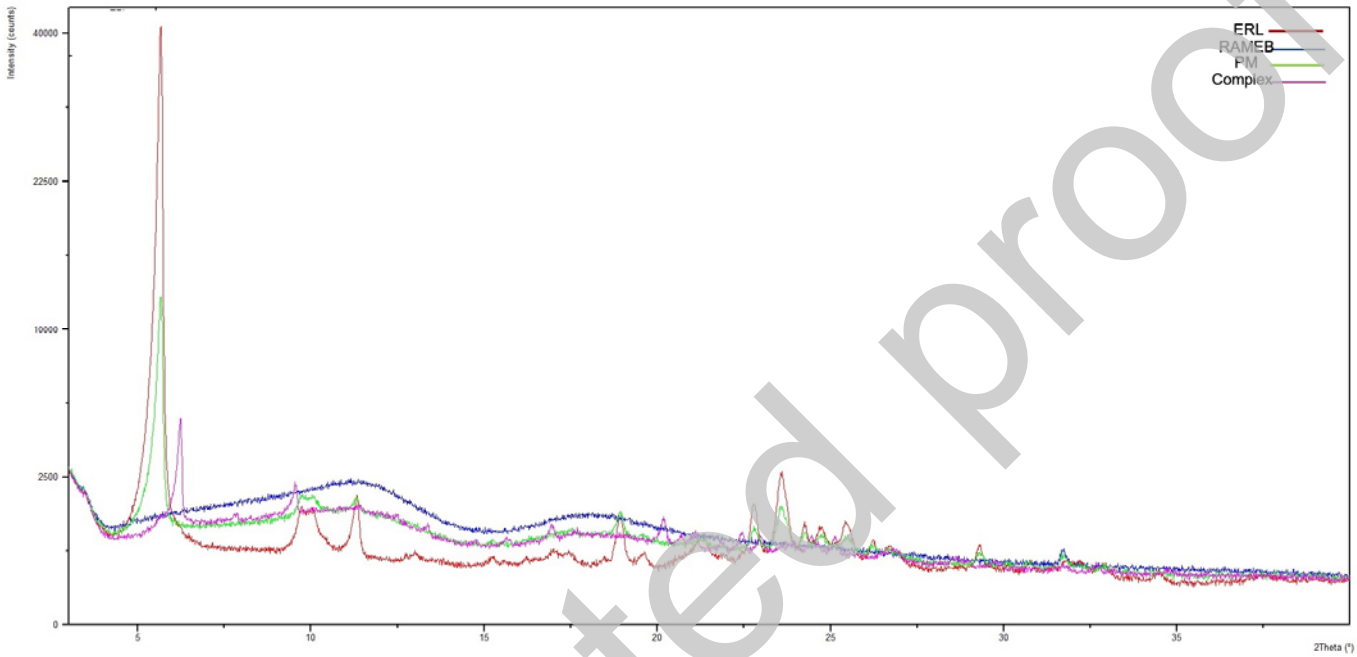

Figure 2. X-ray diffractometry patterns of ERL, RAMEB CD, PM, ERL: RAMEB CD inclusion complex.

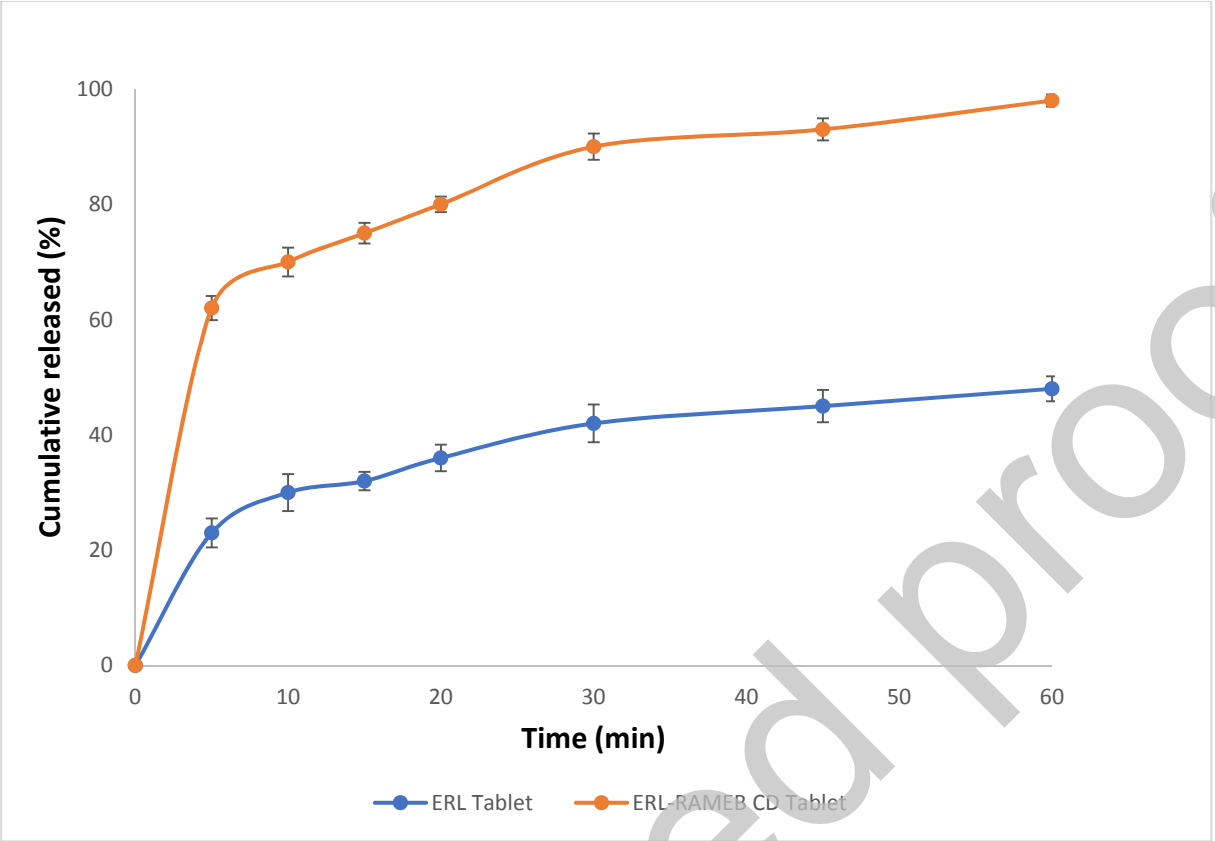

Figure 3. Dissolution profiles of erlotinib tablet and ERL: RAMEB CD tablet in 0.02% Tween 80 in 0.01 N HCl under sink conditions (n = 6, mean ± SD).