

A NEW APPROACH FOR THE ESTIMATION OF DRUG RELEASE FROM
ETHYL CELLULOSE GRANULES

ETİL SELÜLOZ İLE HAZIRLANAN GRANÜLLERDEN İLAÇ SALIMININ TAHMİN
EDİLMESİ İÇİN YENİ BİR YAKLAŞIM

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In this study, ethyl cellulose granules containing oxolamine citrate as the model drug were prepared at different drug-polymer ratios. To estimate the release of oxolamine citrate from granules and to be able to optimize the formulation, simple linear regression equations were generated in the form of $y=mx+n$. First, the relationships between drug contents and drug releases were investigated for each dissolution time with regression analysis. The slope and intercept values of these regression equations were then examined as a function of time. Thus, two equations including slope and intercept values were obtained. Finally, a general equation was obtained using the slope and intercept equations. The predicted results from the general equation were confirmed with the observed ones and a good correlation was obtained. In addition, the general equation was then validated successfully for three different formulations.

Bu çalışmada model madde olarak oksolamin sitrat içeren granüller, etil selüloz kullanılarak değişik ilaç-polimer oranlarında hazırlandı. Granüllerden ilacın salımını tahmin etmek için ve formülasyon optimizasyonu amacıyla $y=mx+n$ şeklinde basit regresyon denklemleri oluşturuldu. İlk olarak, her bir dissolusyon zamanı için ilaç salımları ve formülasyonlardaki ilaç içerikleri arasındaki ilişkiler regresyon analizi ile incelendi. Bu regresyon denklemlerinin eğim ve kesişim değerleri zamanın bir fonksiyonu olarak incelendi. Eğim ve kesişim değerlerini içeren iki denklem elde edildi. Bu iki denklem kullanılarak daha sonra genel bir denklem elde edildi. Genel denklem uygulanarak tahmin edilen salım sonuçları, gözlenen değerler ile karşılaştırıldı ve iyi bir korelasyon gözlemlendi. Ayrıca, elde edilen bu genel denklem üç farklı formülasyon üzerinde de başarıyla valide edildi.

Keywords: Granules; Formulation optimization; Regression equation; Drug release; Oxolamine citrate

Anahtar Kelimeler: Granüle; Formülasyon optimizasyonu; Regresyon denklemi; İlaç salımı; Oksolamin sitrat

Introduction

To prolong a drug action and to avoid excessive drug concentrations in plasma and tissues, controlled-release dosage forms have been used extensively (1). For this purpose, granules as multiparticulate oral dosage forms are nowadays a common choice when a sustained-release profile is required. These dosage forms are distributed widely throughout the gastrointestinal tract leading to reduction in local side-effects and the risk of dose dumping (2-3). In the development of granules, shape is an important character-

istic that must be optimized. Perfectly rounded spheres are desired for good pellet quality and regulating drug release (4).

In the recent years, optimization techniques were more widely used in the pharmaceutical industry for estimating drug release. There are many methods used for optimization. Once experimental data are collected and relationships generated by regression analysis, the formulator is able to select the best formulation. The results of an optimization study, especially the graphic output, can enable for product improvement (5-8).

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The aim of this study was to propose a new approach for the development of an equation to estimate drug release. For this purpose, Sustained-release oxolamine citrate (OXC) granules were prepared and the release studies carried out. The release results were examined by simple linear regression equations and an equation was estimated therefrom. The equation was successfully confirmed and then validated with the repeated *in vitro* release studies on these different formulations.

Materials and Methods

The preparation of granules

The granules were prepared at 1:1, 1:2 and 1:3 polymer-drug ratios. For this purpose, OXC (as a water-soluble model drug) and ethyl cellulose (as a water-insoluble polymer) were mixed in a mortar thoroughly. This mixture was wetted with ethyl alcohol sufficiently and filled into a syringe. The soft mass was passed through the syringe by pressing and dried in an oven at 40°C for 3-4 hours and then cut as small beads. For the assay procedure, calculated amounts of the granules were dissolved in 5 mL of ethyl alcohol and the volume was adjusted to 100 mL with distilled water. The absorbances were measured at 240 nm against the blank without drug. Each determination was carried out in triplicate.

In vitro release studies

Release tests were carried out in 900 mL of distilled water at 37±0.5°C. The granules, containing 20 mg of OXC, were placed in a special basket (40 mesh) with a cap to prevent the samples from floating. Rotating paddle method was applied at 50 rpm. At certain times up to seven hours, five mL aliquots were withdrawn and were spectrophotometrically assayed directly after filtration and returned to the dissolution beakers. Each determination was carried out in triplicate.

Mathematical evaluations

For this purpose the following procedures were carried on (9,10):

- i- The release profiles were plotted against time.
- ii- For each dissolution time, the logarithms of drug release (y) against different drug contents (x) were investigated. As a result of this investigation, it has been assumed that the relationship is in the form of;

$$y = mx + n + e$$

where m and n are slope and intercept respectively and e is the usual error term.

- iii- The slopes were plotted against time and a linear relationship between these two variables was observed and this relationship was estimated.
- iv- Similar manipulations were performed for intercept values. The intercepts against the square root of time were plotted and it was observed that this relationship was also linear. An estimated linear equation was also found for this purpose.
- v- The estimated equations obtained at stages (iii) and (iv) were put together for the general equation given at stage (ii).

Results and Discussion

Effect of formulation variables on the release results

The length of the prepared granules were in the range of 1.8-2.5 mm and the diameter was about 1.5 mm. Smooth cylindrical granules were obtained with the applied technique. The drug contents were found to be 46.4%, 66.1% and 73.1% for 1:1, 1:2 and 1:3 polymer-drug ratios, respectively. It was observed that the release rate increased as the drug content increased as the drug content increased. The release rate from the granules was found to be proportional to the square root of time as explained for matrix systems previously (11). The release plots belonging to these formulations are given in Fig.1.

Mathematical evaluations of the release results

When the release results were examined, it was observed that there were linear relationships as explained in (ii). The regression analyses performed for each dissolution time ranging from 0.5 to 7 hours showed that all the slopes were statistically significant ($p < 0.001$). The plots and the regression equations of these relationships are shown in Fig.2.

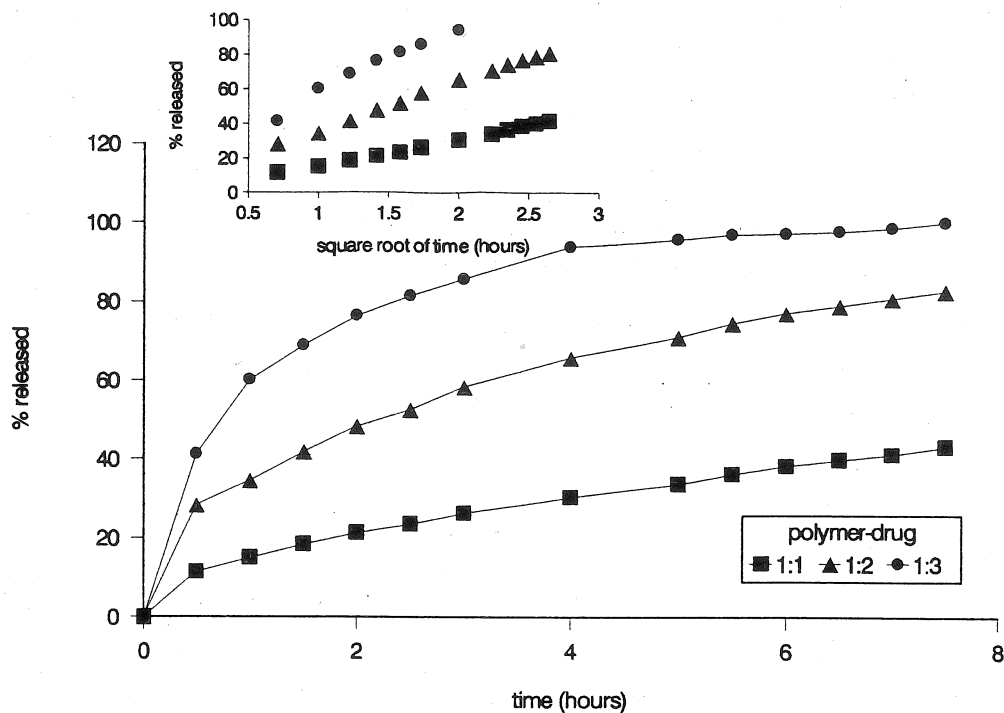


Fig.1. The release profiles of OXC obtained from three different formulations
 (Insert: The release of drug as a function of square root of time)

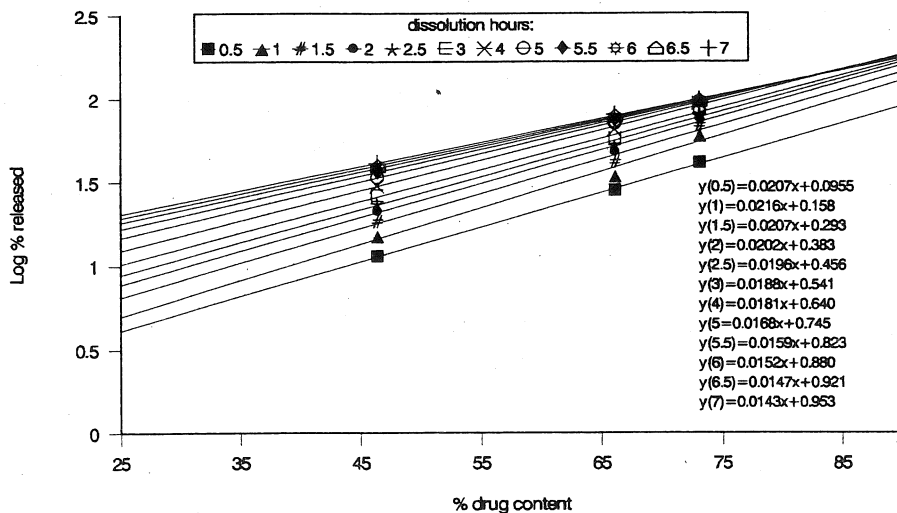


Fig.2 . The correlations between the logarithms of the drug release and drug contents for all the studied dissolution times

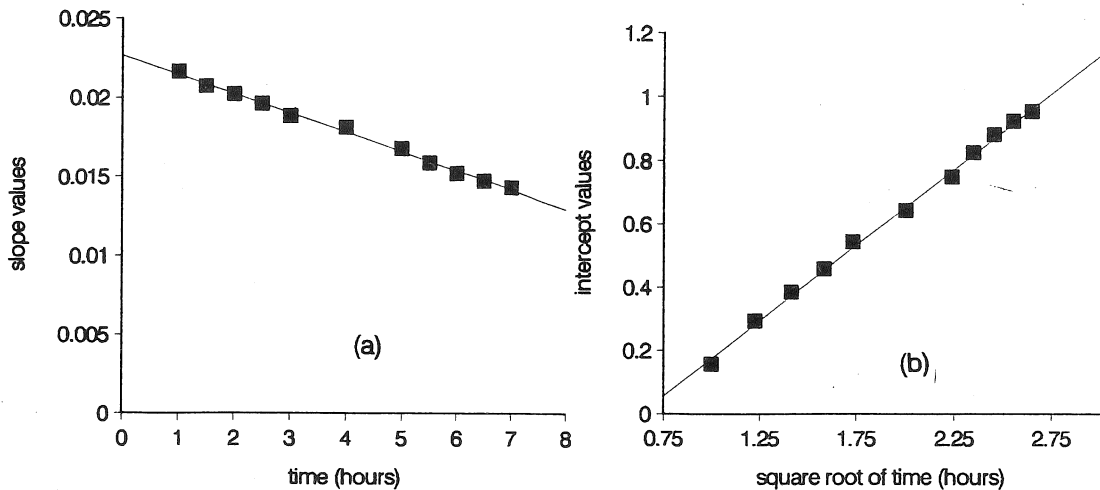


Fig.3. The plots of the correlation of slope (a) and intercept (b) values as a function of time

Each regression equation was reexamined considering the slope and intercept values as explained in (iii) and (iv). The slope and intercept values for 0.5 hour were excluded since there was a lag time for penetration of water to the granules. Fig.3-a shows the linear relationship between the slope values and time ($F=2084, p<0.001$).

The equation of this relationship is:

$$\text{Slope} = -0.00121 \text{ time} + 0.0226 \quad (\text{Eq.1.})$$

After regression analysis, similar linear relationship between the intercept values and square root of time was

found ($F=4010, p<0.001$). The plot of this relationship is shown in Fig 3-b and the equation is;

$$\text{Intercept} = 0.477 \sqrt{\text{time}} - 0.301 \quad (\text{Eq.2})$$

Thus, all the regression equations shown in Fig.2 were reduced to one equation as a function of time for slope and intercept values, separately. These Eq.1 and Eq.2 were put together in the general equation of $y = mx + n$. Finally, the equation was estimated as follows;

$$\text{Log}\% \text{released} = (-0.00121 \text{ time} + 0.0226) \text{ drug content} + 0.477 \sqrt{\text{time}} - 0.301 \quad (\text{Eq.3})$$

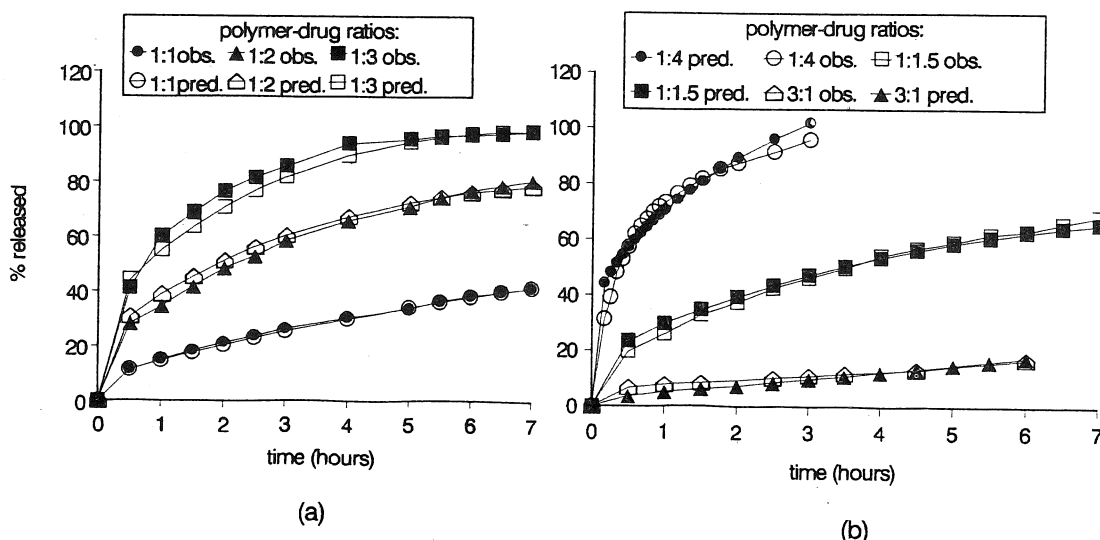


Fig.4. The confirmation (a) and validation (b) of the general equation

To confirm this equation, the predicted OXC releases were calculated for each time and each formulation by applying Eq.3. All the observed and the predicted results were very close to each other as shown in Fig.4-a. The relationship between the observed and the predicted release results were found to be significant ($F=4233$, $p<0.001$) with the regression coefficient of 99.2% *Validation of the regression equation*

For this purpose, three formulations other than the previously examined drug contents were also prepared at 1:4, 1:1.5 and 3:1 polymer-drug ratios and drug contents were found as 78.2%, 60.6% and 24.9% respectively. After triplicate release studies, the simulated release profiles were compared with the predicted ones by using Eq.3. An excellent conformity was observed as depicted in Fig.4-b. The results were found to be statistically significant ($F=2235$, $p<0.001$) with the regression coefficient of 98.3%.

As the conclusion, development of an equation has an important advantage to optimize a formulation in pharmaceutical industry. It was shown that an investigator can develop an equation by applying simple linear regression equations logically. In this study, the number of the formulations may seem to be limited. It would certainly be more useful to carry on for more formulations. However, our primary aim was to propose a new approach to obtain such an equation for the estimation of drug release. Although three formulations were studied primarily, the release of drug as a function of drug content and time could be predicted very

well. As a result, we propose that these simple linear regression approaches can be used successfully in designing drug-polymer ratios during the formulation stages of the experiments.

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