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ARTIFICIAL INTELLIGENCE EVALUATION OF RELEASE PROPERTIES OF TABLET FORMULATION CONTAINING FLURBIPROFEN

FLURBİPROFEN İÇEREN TABLET FORMÜLASYONUNUN SALIM ÖZELLİKLERİNİN YAPAY ZEKÂ İLE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: The aim of this study was to examine the behavior of two different modified release polymers at different concentrations in terms of their similarity to a commercial product in the market, and to perform optimization studies with these polymers using artificial intelligence to find the most suitable formulation.

Materials and Methods: Hydroxypropyl methyl cellulose K100M and sodium alginate polymers were compressed at three different concentrations with the same pressing force. Tests for tablet weights, tablet hardness, diameter/ thickness values and dissolution rate were conducted. The results were evaluated with Minitab19™.

Results: Tablet weights were found to be between 0.2142 mg±0.039 mg and 0.2974 mg±0.001 mg. Tablet thickness varied between 3.80 mm±0.00 mm and 5.00 mm±0.00 mm. Hardness values of formulations containing the 20 mg polymer could not be measured. For other polymer concentrations, they were between 22.6 N±10.11 N and 111.4 N±9.50 N. The dissolution results of formulations prepared with HPMC were lower than those of sodium alginate at the same concentration. The obtained data was evaluated with Minitab19™, which suggested a 41% sodium alginate concentration as the closest formulation to the reference product.

Conclusion: The advantages of artificial intelligence applications are not to be underestimated, and researchers are able to find and obtain results of experiments that they might not be able to conduct. In the light of all these findings, it would not be wrong to say that artificial intelligence will become even more preferable in the coming years.

Keywords: Flurbiprofen, modified release, artificial intelligence, Minitab, optimization

ÖZ

Amaç: Çalışmada iki farklı uzatılmış salım polimerinin farklı konsantrasyonlarda ki davranışının piyasada bulunan bir ticari ürüne benzerliği yönünden incelenmesi ve yapay zeka uygulaması olan Minitab19™ kullanılarak bu polimerlerle optimizasyon çalışması yapılması ve en uygun formülasyonun bulunması amaçlanmıştır.

Gereç ve Yöntem: Hidroksipropil metil selüloz K100 M ve sodyum aljinat polimerleri üç farklı konsantrasyonda, her tablette 20 mg, 60 mg ve 100 mg polimer içerecek şekilde aynı baskı kuvveti, 1000 psi'da basılmıştır ve basılan tabletlerin tablet ağırlıkları, sertlik testleri, çap/yükseklik değerleri ve çözünme hızı testleri gerçekleştirilmiştir. Orijinal ürüne benzer bir salım profili gösterecek bir formülasyon yapay zeka programı olan Minitab19™ ile sonuçlar değerlendirilmiş ve optimizasyon çalışması yapılmıştır.

Bulgular: Hazırlanan tabletlerin tablet ağırlıkları 0,2142 mg±0,039 mg ile 0,2974 mg±0,001 mg arasında bulunmuştur. Tablet çapları 3,80mm±0,00mm ile 5,00 mm±0,00 mm arasında değişkenlik göstermektedir. 20 mg polimer içeren formülasyonların tablet sertlik değerleri ölçülememişken, diğer polimer konsantrasyonları için 22,6 N±10,11 N ile 111,4 N±9,50 N arasında bulunmuştur. HPMC K100M ile hazırlanan formülasyonların çözünme hızı testi sonuçları aynı konsantrasyonda ki sodyum Aljinat sonuçlarına göre daha düşük bulunmuştur. Yapılan çalışmalar sonucunda elde edilen veriler Minitab19™ ile değerlendirilmiş ve yapay zeka programı %41 oranında sodyum aljinat konsantrasyonunu referans ürüne en yakın formülasyon olarak önermiştir.

Sonuç: Yapay zeka uygulamalarının sağladıkları avantajlar azımsanamayacak düzeydedir ve bilim insanlarının belki de deneme şansı olamayacak sonuçları datalar arasından bulup çıkartabilmektedirler. Tüm bu veriler ışığında önümüzdeki süreçlerde daha da tercih edilir hale geleceğini söylemek yanlış olmayacaktır.

Anahtar kelimeler: Flurbiprofen, modifiye salım, yapay zeka, Minitab, optimizasyon

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INTRODUCTION

Modified release (MR) formulations have been developed as an alternative option, since multiple drug administration and the need for repeated doses are a disadvantage in terms of patient compliance. Thus, the frequency of dosing and fluctuations in plasma levels are reduced and controlled (1). One of the groups of excipients used to develop a modified release formulation is hydrophilic polymers. By preparing matrix tablets with these polymers, it is possible to develop a formulation that will allow drug intake at the desired frequency (2). Among the polymers that can be used for this purpose are cross-linked hydrophilic polymers; sodium carboxymethylcellulose (CMC-Na), poly (ethylene glycol) (PEG), hyaluronic acid, hydrophilic matrices (such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC)), alginates, poly (hydroxyethyl methacrylate) or poly (HEMA) , and poly(vinyl alcohol) (PVA) (3). These polymers swell when they come into contact with water, and the drug begins to dissolve with the water that enters between the polymer chains that swell and move away (4). Although they show similar behavior in general, the specific behavior of each polymer differs.

HPMC is one of the most preferred polymers in modified release tablets (5). Likewise, another polymer used as a release retarder in modified release tablets is sodium alginate (6).

The disease groups in which modified-release drugs are most preferred are chronic diseases or painkillers that require the patient to take drugs several times a day (7). Flurbiprofen (FLB) is a Non-Steroidal pain reliever that is a derivative of phenyl propionic acid. Its solubility in water is low, therefore it shows low bioavailability. It can be used up to 400 mg per day (8). FLB is a pain-relieving agent preferred in acute musculoskeletal diseases with the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis signs and symptoms (9).

Today, artificial intelligence applications are used for a wide variety of formulation studies (10, 11). It has also been determined in different studies that it is very useful in the development of modified-release tablets and saves time, cost and labor (12, 13).

This study aimed to evaluate the release properties of different polymers with artificial intelligence in the development of a modified release tablet of low solubility FLB, which is preferred in the treatment of chronic pain, and to compare the health effects of different types of polymers and concentrations.

MATERIALS and METHOD

Flurbiprofen was gifted from Santa Farma İlaç San. A.Ş., Türkiye, and Pronatal pH 6160 (IMCD, Türkiye), hydroxypropyl methyl cellulose (HPMC) K100 M (Colorcon, ABD), magnesium sterate (Parteck LUB, Merck, Sweden) were also gifted. All other reagents were analytical grade.

Analytical method

The analyses of FLB tablets were performed using a UV spectrophotometer (Shimadzu UV-1280, Japan) at a wavelength of 248 nm (14). Accuracy, LOD and LOQ values were calculated.

Preparation of tablets

In order to evaluate the properties of HPMC and sodium alginate, 200 mg of FLB was kept constant in each formulation. Additionally, in order to compare the release properties of the polymers, the amounts of the lubricant Parteck LUB that was added to the formulation was also fixed at 3 mg in each formulation. The amount of polymer added for each tablet in the formulation and the formulation codes are given in Table 1.

Table 1: Formulation codes and polymer content ratios

Formulations	Polymer ratio		
	20 mg (-1)	60 mg (0)	100 mg (+1)
HPMC K100M	F1	F2	F3
Sodium alginate	F4	F5	F6

HPMC: Hydroxypropyl methylcellulose

The active substance and excipients were weighed precisely (Sartorius, France). The weighed powders were mixed in a cubic mixer (Aymes, Turkiye) for 10 minutes by adding FLB and polymers, then magnesium stearate for 5 minutes. The mixed powders were printed on a manual tablet pressing machine (Yener, Turkiye) with a 9.0 mm punch that has a pressing force of 1000 psi.

Physicochemical properties

Diameter, height, hardness and weight deviations of the tablets in each printed tablet formulation were checked (n=10). Mean and SD values were calculated. Diameter and height measurements were carried out with the help of a caliper (Werka, Switzerland), weight deviation control was made with a precision balance (Sartorius, France) and hardness test was done with Sotax HT (Switzerland).

Dissolution studies

Dissolution rate test of the pressed tablets in phosphate buffer (pH=6.8) was performed (Sotax AT7 Smart, Switzerland). 900 mL of dissolution medium was filled into each vessel and set to 37°C±0.5°C. After 30 min., 1h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h and 12 h, samples were taken and filtered through a 0.45 µm nylon filter (GVS, USA) in the Shimadzu UV-1280 spectrophotometer (Shimadzu, Japan) were analyzed (n=3, mean, SD).

Evaluation by artificial intelligence

Analysis results of the analyzed tablets were evaluated with Minitab19™ (Minitab Inc., USA) program, and the $p<0.05$ significance values of Pareto charts, R^2 and models were examined. In addition, an optimization study was carried out for the selection of the polymer and the concentration that would allow to obtain the physicochemical properties and the release profile closest to the reference product.

RESULTS

Analytical method

The correct equation of the analytical method developed

for the dissolution study of FLB tablets was calculated as y=0.0783x+0.0015 and R^2=0.9993. The LOD and LOQ values were 0.7485 µg/mL and 2.2684 µg/mL, respectively.

At the end of the study, an analytical method meeting the ICH Q2 (A) requirements and criteria was developed and used in FLB analysis studies.

Physicochemical properties

The data obtained at the end of the physicochemical test analyses are given in Table 2.

Table 2: Physicochemical test results of the tablets (n=10)

Formulation Code	Tablet Weight (g) (mean, ±SD)	Thickness (mm) (mean, ±SD)	Diameter (mm) (mean, ±SD)	Crushing Force (N) (mean, ±SD)
F1	0.2142±0.039	3.85±0.00	8.8±0.00	-
F2	0.2564±0.002	4.39±0.03	8.8±0.00	73.6±10.11
F3	0.2974±0.001	5.00±0.00	8.8±0.00	111.4±9.50
F4	0.2177±0.002	3.80±0.00	8.8±0.00	-
F5	0.2551±0.002	4.30±0.00	8.8±0.00	22.6±10.11
F6	0.2953±0.001	4.80±0.00	8.8±0.00	32.0±5.44

SD: Standard deviation

Dissolution studies

The findings of the reference product and formulation studies as a result of the dissolution rate test performed in pH 6.8 phosphate buffer are given in Figure 1.

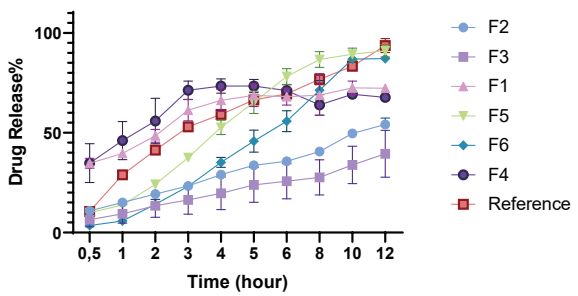

Figure 1: Formulation studies and dissolution rate data graph of reference product

Evaluation by artificial intelligence

The findings obtained as a result of evaluating the obtained data with Minitab19™ are given in Table 3.

These data of significance were also supported by Pareto Charts. Pareto charts are one of the methods used to determine the input that most influences the findings (15). Pareto graphs of these findings are given in Figure 2.

Matrix plots are used to see the relationships between several pairs of inputs and outputs at once. A matrix plot is an array of scatterplots. When you have many input and output variables a matrix of plot becomes very effective to see relationships among pairs of variables. In the Figure 3, the relationship of each input with each other can be seen with the matrix plot (Figure 3).

Table 3: Model R^2 values and p-value data of the outputs

	R^2 value (%)	Model p-value (<0.05)
Tablet weight	99.98	0.019
Crushing Force	99.57	0.099
Diss. 30 minutes	99.99	0.014
Diss. 1h	99.83	0.063
Diss. 2h	99.99	0.016
Diss. 3h	99.56	0.099
Diss. 4h	97.80	0.221
Diss. 5h	94.63	0.341
Diss. 6h	89.81	0.463
Diss. 8h	89.86	0.462
Diss. 10h	96.89	0.262
Diss. 12h	95.89	0.300

R^2: Coefficient of determination, Diss: Dissolution

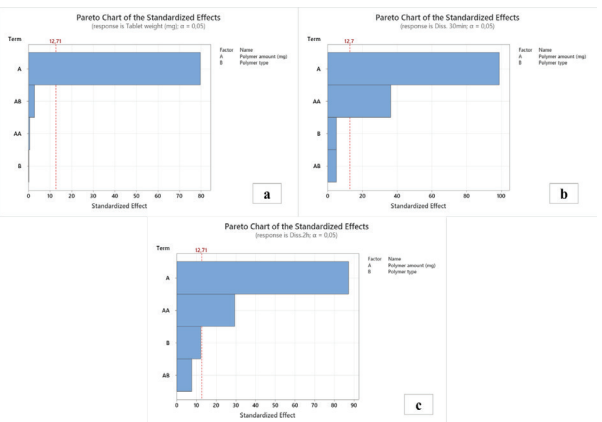

Figure 2: Pareto charts. a: Tablet weight; b: 30-minute dissolution; c: 2 hours dissolution

In the matrix plot, the effects of different polymer types and concentrations on the % release at different time points in the dissolution rate test are seen.

After all these evaluations, an optimization study was carried out and Minitab19™ recommended to prepare a formulation using 41% sodium alginate as the most suitable option. Dissolution rate test findings of the prepared formulation are given in Figure 4.

In the developed optimum formulation, the R^2 value for zero order release kinetics was 0.9836, and 0.9342 for the reference product.

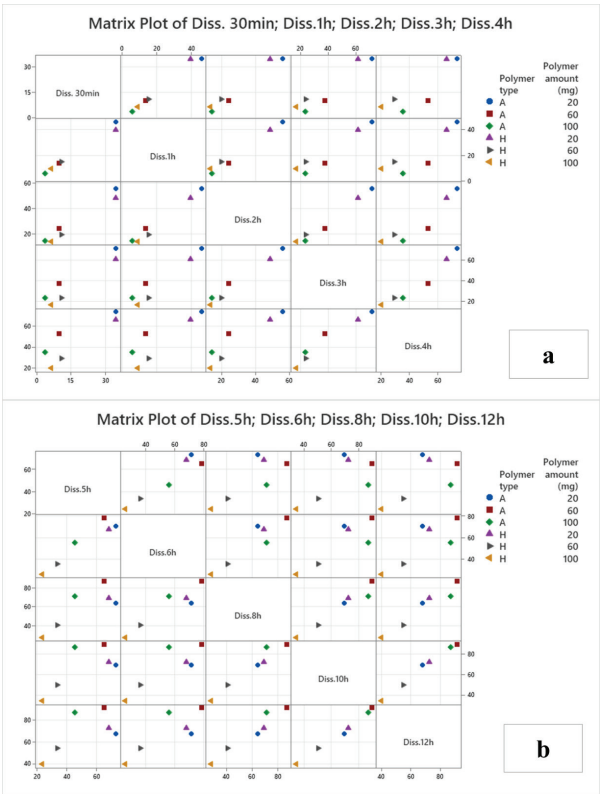

Figure 3: Matrix plot graph. a: Dissolution 30 min to 4h; b: Dissolution 5h to 12h.

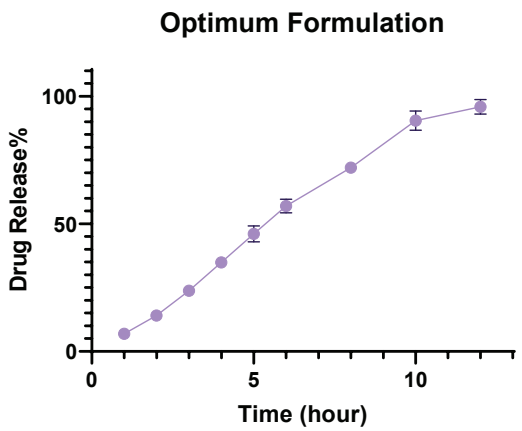

Figure 4: Dissolution rate data graph of the Optimum Formulation and reference product

DISCUSSION

As a result of the physicochemical tests, the tablet weight and thickness value increased due to the increased polymer amount, but there was no change in the tablet diameter despite the different weights with different polymers. The crushing force (N) values increased in proportion with the increase in the amount of polymer in the tablets, but the tablet properties of the two polymers differ at the same hardness values. In the formulations, polymer concentrations varied while the FLB and lubricant ratios were kept constant. The strength of tablets prepared with 20 mgs of polymer were found to be insufficient after tablet compression and thus could not provide sufficient compressibility of the tablet. In addition, the thickness values of the tablets prepared with HPMC K100M were higher than the thickness values of the tablets containing sodium alginate. However, this is not due to the looser binding of the tablet granules because the hardness test results of the tablets are also greater for formulations containing HPMC K100M. This finding is thought to be due to the different powder properties of the two polymers. Further evaluations were made on Minitab19™.

It is a known fact that different polymers and their different concentrations affect drug release and a parallel result was obtained from the findings we obtained (16). When the two polymers were compared, it was observed that HPMC further reduced the release rate with increasing concentration compared to sodium alginate. The viscosity value of HPMC K100M (Colorcon, USA) used here is approximately 100,000 cp at 20 rpm, although it gives different results when measured at different speed and rpm for its 2% solution (17). The viscosity value given for sodium alginate was determined as approximately 1000-1500 mPa for its 1% solution (18). It is possible to say that these differences obtained in the dissolution profile depend on the polymer viscosities.

After the evaluation by artificial intelligence program Minitab$^{19™}$, the R^2 value being above 85% means that the interaction of the inputs and the outputs in the models is highly significant. In addition, p-values below 0.05 indicate the usefulness of the models (19). In the study, it is shown that the R^2 values of all models were found to be high and that it was beneficial. Tablet weight, p-value results of 30-minute dissolution and 2 hours dissolution were found below 0.05, and it was revealed that the polymer type and concentration were effective especially at these points.

According to the Pareto charts, it has been found that the amount of polymer used in the input formulation has the most effect on the output.

It is seen that the optimum formulation for a matrix structured formulation shows a more favorable release kinetics (20). Artificial intelligence was used in formulation optimization in an alternative formulation study of the market product by comparing HPMC and sodium alginate, two different polymers that are used quite frequently, and a similar dissolution rate to the reference product was obtained, in which an ammonium methacrylate copolymer mixture was used as the polymer (9).

The mean crushing force of the formulation was found to be 44 N. When all these findings are evaluated, the closest ratio to the original product is the previously untested 41% sodium alginate value. When the general values are examined, HPMC has a slower release rate, sodium alginate has a faster release, and the release rate in formulations prepared with sodium alginate has shown a more similar profile to the reference product.

CONCLUSION

Interest in artificial intelligence applications is increasing day by day and these algorithms are used for many different purposes. In this study, artificial intelligence was used in formulation optimization studies and a value that was not studied as a formulation was proposed by the program. As can be seen, these applications provide data to researchers, who cannot obtain said data by conducting experiments one-by-one with their estimations, thus saving time. In addition to that, they also help reduce expenses, as the cost advantages they bring are at a level that cannot be ignored.

In this study, a formulation that provides similar release characteristics to the market product containing FLB was developed. The polymer ratio at the concentration recommended by artificial intelligence was not one of the ratios that were originally tested in the experimental design. The program successfully evaluated the dataset, filtered it and suggested the most appropriate ratio.

Ethics Committee Approval: Authors declared that ethics committee approval is not required for this study.

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Author Contributions: Conception/Design of Study- B.M., Y.S.Ç.; Data Acquisition- Y.S.Ç., B.M.; Data Analysis/Interpretation- B.M., Y.S.Ç.; Drafting Manuscript- B.M., Y.S.Ç; Critical Revision of Manuscript- B.M., Y.S.Ç; Final Approval and Accountability- B.M., Y.S.Ç.; Material and Technical Support- B.M., Y.S.Ç.; Supervision- B.M., Y.S.Ç.

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