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PREPARATION OF DICLOFENAC SODIUM MATRIX TABLETS BY USING HYDROXYETHYLCELLULOSE POLYMER

HİDROKSİETİLSELÜLOZ POLİMERİ KULLANILARAK DİKLOFENAK SODYUM MATRİKS TABLETLERİNİN HAZIRLANMASI

ÜMİT GÖNÜLLÜ

Deparment of Pharmaceutical Technology, Faculty of Pharmacy, University of Istanbul, 34452-Istanbul TURKEY

Diclofenac sodium (DS) matrix tablets were prepared with 20% and 30% hydroxyethylcellulose as polymer material by using direct compression technique. In order to prevent the irritant effect of DS to the stomach, tablets were coated with Eudragit L100. Results obtained from in vitro dissolution tests were compared with sustained release preparations marketed in Turkey and conventional tablet forms. No significant difference for release time and amount of active substance was observed between Formula A and Formula B prepared with 20% and 30% polymer respectively. Results of in vitro dissolution tests have shown similarities with sustained release preparation marketed in Turkey(Formula C).

Polimer madde olarak %20 ve %30 oranlarında hidroksietilselüloz kullanılarak diklofenak sodyum (DS) matriks tabletleri direkt basım tekniği ile hazırlandı. Tabletler DS'un mideye olan iritan tesirini önlemek amacı ile Eudragit L 100 ile kaplandı. İn vitro dissolüsyon testleri yapılarak sonuçlar geciktirilmiş serbestleşme yapan piyasa preparatları ve konvansiyonel tablet formları ile karşılaştırıldı. Polimerin %20 ve %30 oranlarında kullanılması ile hazırlanan Formül A ve Formül B arasında etken maddenin serbestleşme zamanı ve miktarı bakımından farklılık görülmedi. İn vitro dissolüsyon test sonuçları geciktirilmiş serbestleşme yapan piyasa preparatı (Formül C) ile benzerlik gösterdi.

Keywords: *Diclofenac sodium; Matrix tablet; Hydroxyethylcellulose*

Anahtar Kelimeler: *Diklofenak sodyum; Matriks tablet; Hidroksietilselüloz*

Introduction

Diclofenac sodium (DS) is a nonsteroidal anti-inflammatory and analgesic drug with a chemical structure of sodium[2-(2,6-dichloroanilino)phenyl] acetate. It has been used in the long-term symptomatic treatment of rheumatoid arthritis and osteoarthritis. The usual dose by mouth is 75 to 150 mg daily in divided doses. Sustained release matrix tablets containing 100 mg DS is used once a day (1,2). In DS matrix tablet formulations, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), ethyl cellulose(EC), polyvinylpyrolidone (PVP), polyvinyl alcohol (PVA), Eudragit, xanthan gum, sodium alginate and polyacrylamide have been used as polymers(3-12). Determination of DS has been made by using gas-liquid chromatography, combination of gas-mass chromatographic, high-performance liquid chromatographic and spetroscopic methods(13-17). In Turkish market, DS dosage forms are present as 25 and 50 mg tablets, 100 mg retard tablet, 75 mg/3 ml injectable and 25,50,100 mg suppositories. In this study, DS matrix tablets were prepared by using hydroxyethylcellulose as polymer and tablets were coated with Eudragit L 100 in order to provide resistancy to the stomach. Results obtained from dissolution tests(18) of DS matrix tablets were compared with those of commercial sustained release and conventional tablet forms.

Materials

Diclofenac sodium (99.6%)(Fako), microcrystalline cellulose (Avicel pH 101) (Merck), magnesium stearate (Merck), hydroxyethylcellulose (Natrosol 250 HHX-PHARM), Eudragit L 100 (Röhm Pharma, Weitesstadt), dibutylphthalate (Select Chemie, USA), isopropanol(J.T.Baker), talc (Prever, Italy), sodiumdihydrogen phosphate (Merck), potassium dihydrogen phosphate (Merck).

Spectrophotometer (UV-1601 UV-Visible Spectrophotometer-Shimadzu), dissolution apparatus (Dissolution Tester DT 6E) (Aymes), tablet machine (Korsch, Schmersal, Germany), pH-meter (Schott Gerate),mechanical shaker (Mini-Shaker B. Braun), compass (Digimatic Micrometer Mitutoyo 0-25 mm 0.001 mm), tablet hardness measurement apparatus (Tablet Tester 6D Schleuniger), friability test apparatus (Aymes), mesh (BS 410: 1976 0.3 mm Prüfsieb), quuantative filter paper (S&S 589), Wurster apparatus (Aymes), balance (Libror AEX-120G Shimadzu).

Methods

Determination of diclofenac sodium: Stock solution of DS (0.02%) in distilled water was prepared and 0.01-0.6 ml were taken from the stoch and completed to 10 ml with distilled water. Absorbances of the solutions containing 2-12 mcg/ml were measured by using a spectrophotometer and plotted. Standard equation of DS was calculated therefrom.

Preparation of matrix tablets: DS was sieved through mesh, mixed with hydroxyethylcellulose (HEC), avicel and magnesium stearate in a glass bottle and pressed in a tablet machine having constent pressure. DS matrix tablet formulation with 20% (Formula A) and 30% HEC (Formula B) are shown in Table 1. Matrix tablets were coated with a film (7.5 g Eudragit L 100, 2.2 g dibutylphthalate and 3.75 g talc suspension in 130 g isopropanol) in a Wurster apparatus at 50°C.

Table 1. DS matrix tablet formulations with 20% (Formula A) and 30% HEC (Formula B)

Ingredient (mg)	Formula A	Formula B
Diclofenac sodium	100	100
Hydroxyethylcellulose	40	60
Avicel	56	36
Magnesium stearate	4	4

Controls performed on prepared tablets:

A-Determination of active ingredient: Tablets (n=6) were powdered in a mortar, transferred to a volumetric flask with distilled water, mixed in a mechanical shaker for 4 hrs and sufficient amount of distilled water was added to make 100 ml. This solution was filtered through a quantitative filter paper and aliquots of 0.1 ml were transferred to volumetric flasks and their volumes adjusted to 10 ml with distilled water. Absorbances were measured at 276 nm spectrophotometrically.

B- Physical measurements: Weight variations, diameter/height ratios and hardness tests were performed. For these 10 individual tablets were weighed, diameters and heights measured by a compass and hardnesses measured by hardness tester. Mean values and standard deviations of all tests were calculated. For friability, 10 tablets were weighed, subjected to friability test and reweighed to calculate the loss.

C- Resistance test in simulated gastric medium: Six uncoated and six film coated tablets were put into simulated gastric medium and tested in a horizontal disintegration test apparatus.

D- Dissolution rate tests: Matrix tablets prepared with 20% and 30% HEC (Formula A and B respectively), commercial retard film tablet (Formula C) and commercial retard micropellet capsule (Formula D) containing 100 mg DS, commercial drage (Formula E) and commercial film coated tablet (Formula F) containing 50 mg DS were subjected to dissolution test. Dissolution rate determination was performed by using rotating basket method at 50 rpm in 900 ml phosphate buffer (pH=6.8±0.05).

Results and Discussion

1. *Results of diclofenac sodium determination*:
   Equation of the standard curve:

   $y=0.0344x+0.004066$, $r^2=0.996$
   x=concentration (mcg/ml),
   y=absorbance, r^2=determination coefficient

2. *Control tests on tablets:*

a. Mean values ($\bar{x}$) and standard deviations (±SD) of active ingredient are given in Table 2.

Table 2. Results of mean values($\bar{x}$) and standard deviations (SD±) of active ingredient

DS Matrix tablets			
Formula A		Formula B	
$\bar{x}$ (mg)	(±)SD	$\bar{x}$ (mg)	(±)SD
101.65	1.0334	101.77	1.0625

b. Results of physical measurements on tablets are given in Table 3.

Table 3. Results of physical controls Performed on tablets

Control	Formulations	
	Formula A	Formula B
	$\bar{x}$ ± SD	$\bar{x}$ ± SD
Weight variation (mg)	201.95 2.02	203.77 1.64
Diameter/height	3.15 0.76	3.09 0.43
Hardness (kp)	11 1.12	10.42 0.70

Friability was found as 0.2% for Formulas A and B.

c. In determining the resistance of film layer to simulated gastric medium, it was observed that tablets without film coating disintegrated immediately, while coated tablets were found to be resistant to the gastric medium for 2 hours. Film coated tablets were then put into simulated intestinal medium and they retained their gel form during the test period.

d. Results of dissolution tests and dissolution profiles of formulations are shown in Tables 4a, 4b and Figures 1,2 respectively.

Table 4a. Results of dissolution tests for formulations containing 100 mg DS

%Released diclofenac sodium				
Time (hr)	Formula A	Formula B	Formula C	Formula D
1	17.69	17.11	17.12	14.50
2	22.62	22.92	20.59	27.27
3	28.43	27.85	23.79	32.50
4	32.20	30.18	28.45	37.43
5	35.69	36.27	33.67	42.08
6	44.40	43.24	36.85	45.56
7	45.27	43.82	38.89	49.34
8	46.72	45.85	40.34	61.24

Formula A-Matrix tablet containing 100 mg DS prepared with 20% HEC
Formula B-Matrix tablet containing 100 mg DS perpared with 30% HEC
Formula C-Commercial retard film tablet containing 100 mg DS
Formula D-Commercial retard micropellet capsul containing 100 mg DS

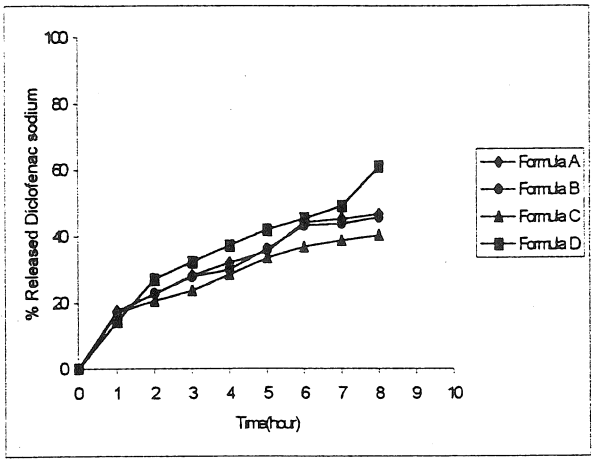

Fig.1. Dissolution profiles of Formulas A,B,C and D in phosphate buffer solution (pH 6.8±0.05)

Table 4b. Results of dissolution tests (Formulations containing 50 mg DS)

%Released diclofenac sodium		
Time(minute)	Formula E	Formula F
15	5	10.55
30	8.7	72.93
45	-	86.13
60	8.7	99.87
120	23.2	
180	58.04	
240	76.62	

Formulas E-Commercial drage containing 50 mg DS
Formulas F-Commercial film coated tablet containing 50 mg DS

e. Release rate kinetics of active ingredient in formulations are shown in Table 5.

It has been reported that in preparation of DS matrix tablets, HPMC, HPC, EC, PVP, PVA, Eudragit,

xanthan gum, sodium alginate and polyacrylamide were used. In matrix tablets prepared with HPMC having different viscosity grades, release of

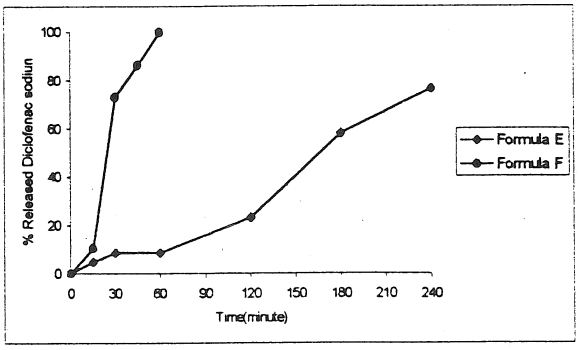

Fig.2. Dissolution profiles of Formulas E and F in phosphate buffer solution (pH=6.8±0.05)

DS was found to be retarded and it was stated that amount and viscosity grade of HPMC was important. In addition, in another study where four different types of HPMC were used, dissolution rate was found to be delayed with an increase in HPMC amount and decrease in particule size (3-5). With a matrix formulation prepared by using HPC, released amount of DS was found to give similar results when compared to market preparation containing same amount of DS(6). In DS matrix tablets containing PVP K 30 as a polymer, a nonlinear relation was defined between released amount of DS and PVP K 30 amount (8) whereas in another formulation, it has been reported that the best results were obtained with hydrolyzed PVA having a MW:60.000-80.000(9). It has been also stated that the release rate kinetics of DS in Eudragit and ethyl cellulose matrix tablet formulations were conforming to Higuchi(7).

DS matrix tablets prepared with 20 and 30% HEC by direct compression technique were subjected to *in vitro* dissolution test at pH=6.8±0.05 phosphate buffer according to USP. With formulation containing 20% HEC (Formula **A**), 46.72% DS was released in 8 hours, however with formulation containing 30% HEC (Formula **B**), the released amount was found to be 45.85% while for commercial sustained release preparation (Formula **C**) this value was 40.34% and with commercial retard micropellet capsule (Formula **D**) it was 61.24%. In this case, commercial sustained release preparation containing 100 mg DS (Formula **C**) and DS matrix tablets containing 20% (Formula A) and 30% (Formula **B**) HEC have shown similarities from released DS amount and release time point of view. According to these findings, it could be concluded that there was no need for 30% HEC since 20% HEC was enough for matrix tablet formulations. However Formula **D** which is a micropellet formulation containing 100 mg DS has released more active substance than the

Table 5. Release rate kinetics of active ingredient in formulations

Formulations	0 Order		1st Order		Higuchi		RRSBW	
	k_o	r^2	k_1	r^2	k_h	r^2	β	r^2
A	4.37	0.9711	0.13	0.9411	17.11	0.9765	0.59	0.9740
B	4.26	0.9715	0.13	0.9383	16.66	0.9776	0.59	0.9761
C	3.55	0.9786	0.12	0.9545	13.86	0.9805	0.52	0.9659
D	5.73	0.9604	0.16	0.8688	22.41	0.9674	0.76	0.9736
E	0.32	0.9504	0.01	0.9663	6.166	0.8736	1.17	0.8802
F	1.87	0.8468	0.04	0.7154	22.54	0.9080	2.80	0.9677

k_o=mg.h^{-1}, k_1=h^{-1}, k_h=mg.cm^{-2}.h$^{-0.5}$

other three formulations after 8 hours. Conventional tablets containing 50 mg DS have shown different dissolution rates than each other. Within 30minutes 8.7% DS was released from Formula **E** whereas this amount was found to be 72.93% for Formula **F**. 76.62% DS was released from Formula **E** after 4 hours but from Formula **F**, 99.87% DS was released after 1 hour. It could be considered that this situation could be due to variations of formulations.

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