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Studies on Prolonged Release Matrix Tablet Formulations of Hydralazine Hydrochloride

A.Hadi Bilaç* and Dolunay Sarı Aydın

Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 26470 Eskişehir, Turkey

Abstract

The purpose of this study was to prepare prolonged release tablet formulations of hydralazine hydrochloride which has been used as an antihypertensive agent. To achieve this, carbomers (Carbopol® 834, 934, 940 and 1342) were used as polymer in different concentrations. Magnesium stearate was used as lubricant and direct compression method was applied for preparing tablets.

Tests on tablets prepared according to different formulations were carried out in respect of their content uniformity, diameter-height ratio, weight deviation, hardness, friability and *in vitro* dissolution rate of the drug. Spectrophotometric method was used for hydralazine hydrochloride assay, USP XXII basket method was performed for the *in vitro* dissolution studies and dissolution data were evaluated kinetically.

Key words : Hydralazine hydrochloride, prolonged release, matrix tablet, Carbopol®

Introduction

Hydralazine hydrochloride (Hyd.HCl) effects on veins directly as a dilatator is as an antihypertensive agent. By reducing periferic vein resistance, relaxing the plain muscles of arteriols and increasing the renal blood flow, it is preferred to the other hypertension agents. In addition, it reduces the resistance of veins in the kidneys thus providing blood flow at sufficient level during medical treatments.

Hyd.HCl is metabolized very rapidly with a half-life about 2-4 hours. Treatment starts with a dose of 40 mg which is given by 3-4 times in a day. Unless is used with a beta blocker such as propranolol, it causes tachicardy and palpitation. If the patient uses propranolol besides Hyd.HCl, the dose can be increased to100 mg and also according to the response the dose can be increased up to 200-400 mg daily (Martindale XXX, USP 1990, Rawlins 1977, Kayaalp 1988). Spectrophotometric and titrimetric methods have been used for the assay of Hyd.HCl (Chester *et.al.* 1979,Clarke E.G.C. 1981).

In recent years the use of polymers for the purpose of controlling the drug release has become an important subject. A wide range of polymers can be employed among which the group of acryllic acide derivatives, known officially as carbomers or by their commercial name Carbopol® were included (Perez-Marcos *et al.*1991, Malley *et. al.* 1987) prepared controlled release matrix tablet of sodium salicylate using Carbopol® 934. Their studies carried out with thin sheets of various concentrations of sodium salicylate pressed into Carbopol® matrix. (Şenel *et. al.*, 1991) studied the factors effecting the formulation of sustained release potassium chloride tablets. Polyvinylchloride and methylcellulose were used as matrix materials.

* *Corresponding author*

The in vitro release of lithium carbonate incorporated into polymethylmetacrylate, polyvinylchloride, hydrogenated vegetable oil and carbomer was studied by (Çiftçi *et al.*, 1990). The formulation containing 10%(w/w) carbomer showed sustained release profile comparable to that of the standard. Hydrogenated vegetable oil and Carbopol® have been used separately in the production of sustained release systems as insoluble and erodible matrices for oral administration. The release rate changes are explained on the bases of interaction between the gel and other matrix components in the presence of water (Malamataris and Ganderlon 1991).

In this study, prolonged release matrix tablet formulations of Hyd.HCl elaborated using the direct compression technique were prepared. To achieve this, Carbopols® 834, 934, 940,1342, were used as polymer in different concentrations (40-50%).

Materials and Methods

Hydralazine hydrochloride Ciba-Geigy Istanbul, Turkey; Carbopol® 834, 934, 940, 1342 Goodrich, USA; Magnesium stearate; E.Merck Germany.

Preparation of the tablets: Formulations were prepared by direct compression technique Magnesium stearate (5%) and Carbopol® (834, 934, 940 and 1342) in different concentrations (40-50%) were used as lubricant and polymer respectively. Tablets weighing 105 mg were compressed using by single punch tablet machine, according to the classical tabletting procedure. The formulation codes and contents are shown in Table 1.

Hydralazine hydrochloride content: A spectrophotometric method was used for the Hyd.HCl assay. 25 mg of Hyd.HCl was accurately weighed and dissolved in water and the volume was adjusted to 100 ml. Ten samples of 1-5.5 ml (0.5 ml intervals) were taken from this stock solution and diluted to 50 ml with water. Absorbances were measured spectrophotometrically at 305 nm against water. Regression equation and regression coefficients were calculated.

Table 1. Matrix tablet formulations of hydralazine hydrochloride

Contents	Tablet code							
	F1	F2	F3	F4	F5	F6	F7	F8
Hydralazine hydrochloride (mg)	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3
Carbopol® 834 (w/w %)	50	-	-	-	40	-	-	-
Carbopol® 1342 (w/w %)	-	50	-	-	-	40	-	-
Carbopol® 940 (w/w	-	-	50	-	-	-	40	-
Carbopol® 934 (w/w	-	-	-	50	-	-	-	40
Magnesium stearate(w/w %)	5	5	5	5	5	5	5	5

Crushing strength: Ten tablets were tested using Monsanto hardness apparatus.

Friability : Twenty tablets were weighed and rotated for 100 revolutions for 4 min in a Roche friabilator (TS 1).The tablets were then reweighed and the percentage of friability calculated.

Diameter-height ratio: This ratio was determined using a micrometer.

In vitro dissolution test: Dissolution tests were performed according to the basket method described in USP XXII (100rpm, 37 $C^{o} \pm 0.5$). Dissolution studies were carried out in 900 ml of simulated gastric (SGM) and intestinal medium (SIM) without enzymes for a period of 8 hours. The absorbances of the samples were measured spectrophotometerically at 305 nm against blank. The amounts of Hyd.HCl in the samples were calculated using the standard curve equation.

The dissolution data were evaluated kinetically according to zero order, first-order, Hixon-Crowell, RRSBW, Q square root of time and Higuchi equations. The release rate constants (k), and determination coefficients (r^2) were calculated by means of a computer program (Ağabeyoğlu 1984).

Results and Discussion

Content uniformity, friability, hardness, and diameter-height ratio results of tablets were in accordance with the pharmacopoeial limits (USP XXII). The results are presented in Table 2.

Table 2. Content uniformity, friability, hardness, and diameter-height ratio results of tablets (n= 10)

Parameters	Tablet code							
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8
Hydralazine hydrochloride(mg)	68.6	70.1	71.3	71.9	70.4	70.9	71.1	70.1
Tablet weight (mg)	104.08	105.02	105.42	105.42	104.52	98.87	98.69	98.68
Weight deviation (%)	± 2.32	± 1.44	± 1.06	± 1.90	± 0.58	±0.76	± 0.87	±0.73
Hardness (kg)	4.50	4.20	2.50	2.00	1.50	4.75	2.50	2.00
Friability (%)	0.08	0.29	0.08	0.21	0.22	0.16	0.06	0.26
Diameter-height ratio	5.06	5.06	4.90	4.76	5.06	4.90	5.06	4.90

Table 3. Dissolution results of formulations

Time	Released %							
(min)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
30	27.48	24.14	27.11	30.20	28.04	24.40	26.62	28.64
60	42.23	36.40	49.64	44.68	45.09	41.71	58.08	44.71
120	65.72	65.18	97.22	69.85	69.85	78.11	99.15	83.85
180	82.91	78.71	-	86.99	95.42	82.66	-	88.64
240	88.94	84.44	-	96.03	-	86.67	-	95.67
360	94.05	90.25	-	97.48	-	90.02	-	99.25
420	95.18	91.02	-	98.05	-	93.54	-	-
480	95.48	92.08	-	98.20	-	94.68	-	-

Released amount of Hyd.HCl from matrix tablets are shown in Table 3. According to the results, tablets prepared with 50% (w/w) Carbopol 1342 (F 2) were found to be the most suitable formulation for Hyd.HCl followed by 40% Carbopol® 1342 (F 6) and 50% Carbopol® 834 (F 1). Hence F2 was considered as the best formula to be kinetically evaluate using a computer program (Ağabeyoğlu, 1984) (Table 4). The highest determination

coefficient and the best linear relation were observed with F2 in respect to RRSBW kinetics (Fig 1).

When the branched polymer is in contact with synthetic gastric liquid, it turns into a gel, because of the liquid transfer into the polymer. On the other hand, release of the drug is observed, which does not follow the classical kinetic equation, as the release are partially controlled by diffusion.

This study showed that the release mechanism in a matrix system comprising an insoluble hydrophobic and hydrophilic gel-forming parts, depends greatly on the wettability of the added drug. Furthermore, with wettable and water soluble drug, the matrix swells and release is mainly achieved by diffusion due to dissolution of the gel formed.

Table 4 Kinetic assessment of release data for formulation F 2

Kinetic Models			
Hixon-Crowell (modified)	r^2	=	0.9294
	A	=	0.6465
	B	=	$1.0648.10^{-3}$
	AIC	=	-29.3803
	WSSD	=	0.0808
First order	r^2	=	0.9216
	Kr'	=	0.2798 h^{-1}
	AIC	=	-12.4224
	WSSD	=	0.4213
Zero order	r^2	=	0.7236
	Kro	=	4.5573 mg/h
	AIC	=	-0.4949
	WSSD	=	0.4946
RRSBW	r^2	=	0.9525
	$T_{\%63.2}$	=	128.0140 min.
	B	=	0.8014
	AIC	=	-32.8761
	WSSD	=	0.4191
Q square root of time	r^2	=	0.8344
	k	=	6.6410
	AIC	=	-19.1598
	WSSD	=	0.5369
Higuchi	r^2	=	0.9041
	Slope	=	1.4591

Özet

Bu çalışmanın amacı, antihipertansif ilaç olarak kullanılan hidralazin hidroklorür'ün uzatılmış etki gösteren matriks tabletini hazırlamaktır. Bunun için polimer olarak değişik konsantrasyonlarda karbomerler (Carbopols® 834, 934, 940 ve 1342), kaydırıcı olarak ise magnezyum stearat kullanılmış ve tabletler direkt basım tekniğine gore basılmıştır.

Tabletlerde etken madde, yükseklik- çap oranı, ağırlık sapması, ufalanma - aşınma kontrolü ve *in vitro* çözünme hızı tayinleri yapılmıştır. Etken madde miktar tayini spektrofotometrik yöntem ile, *in vitro* çözünme hızı testleri ise döner sepet yöntemi (USP XXII) ile yapılmış, zamana

karşı etken maddenin yüzde salım profilleri çizilmiş ve çözünme hızı sonuçları kinetik açıdan incelenmiştir.

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