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INVESTIGATIONS ON THE LIPOPHILIC MATRIX TABLETS OF VERAPAMIL HYDROCHLORIDE PREPARED WITH PRECIROL ATO 5*

PRESIROL ATO 5 İLE HAZIRLANMIŞ VERAPAMİL HİDROKLORÜR LİPOFİLİK MATRİKS TABLETLERİ ÜZERİNDE İNCELEMELER

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Verapamil HCl (VPH) is used in the control of supraventricular tachyarrhythmias, and in the management of classical or variant angina pectoris. Its usual oral dose is 40 to 120 mg three times daily. VPH is available as tablets, sustained release tablets and intravenous preparations. The aim of this study was to prepare the lipophilic matrix tablets in order to improve the poor flow property and prolong the release of VPH. Precirol ATO 5 (glycerol palmitostearate) was used as a lipophilic matrix agent. Compritol 888 ATO and lactose were chosen as lubricant and diluent respectively in the tablet formulations. Flow properties of each formulation were investigated. Spectrophotometric method was applied for the assay of VPH in tablets and the absorbances were measured at 278 nm. The effect of Precirol ATO 5 on the drug release was determined according to USP XXIII paddle method in distilled water at 50 rpm.

Verapamil HCl (VPH) supraventriküler taşiaritmilerin kontrolünde ve klasik veya çeşitli anjina pektorisin tedavisinde genellikle günde 3 defa 40-120 mg peroral olarak kullanılır. Piyasada tabletleri, uzun etkili tabletleri ve i.v. preparatları mevcuttur. Çalışmanın amacı, ilacın kötü olan akış özelliklerini düzeltmek ve uzatılmış etkili lipofilik matriks tipi tabletlerini hazırlamaktır. Lipofilik matriks ajanı olarak Precirol ATO 5 (gliserol palmitostearat) kullanılmıştır. Tablet formülasyonlarına kaydırıcı olarak Compritol 888 ATO ve dolgu maddesi olarak da laktoz seçilmiş ve hazırlanan formülasyonların akış özellikleri incelenmiştir. Tabletlerdeki VPH'nin miktar tayini için spektrofotometrik metod uygulanmış ve absorbanslar 278 nm'de ölçülmüştür. Precirol ATO 5'in ilacın salımına etkisi, USP XXIII palet yöntemine göre distile su içinde 50 devir/dk'da saptanmıştır.

Keywords: *Verapamil HCl; Sustained release tablets, Lipophilic matrix; Precirol ATO 5*

Anahtar Kelimeler: *Verapamil HCl; Sürekli etkili tablet; Lipophilic matrix; Precirol ATO 5*

Introduction

Matrix systems in which drugs are homogeneously incorporated into inert matrix materials, have been frequently utilized to achieve sustained drug release from a dosage form. Although many types of matrix forms including granules, tablets and microspheres have been extensively studied over a long

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period of time, tablet formulation may be the most suitable form for large-scale production at pharmaceutical industries because of comperative ease in controlling the drug release rate and high reproducibility (1). Sustained release matrix tablets of verapamil HCl (VPH) have previously been prepared using sodium alginate, hydroxypropyl cellulose and ethyl cellulose (2-5). Glycerol palmitostearate (Precirol ATO 5) was used as the lubricant (0.5-5%) in peoral solid dosage forms and as a lipophilic matrix agent (10-50%) for sustained release tablets and capsules (6-8). Glycerol behenate (Compritol 888 ATO) was employed as a lubricant and binding agent (1-3%) and as sustaining material for tablets at concentrations above 10% (9,10).

In this study, the lipophilic matrix tablets of VPH were formulated using Precirol ATO 5, Compritol 888 ATO and lactose. The influence of Precirol ATO 5 on the flow properties (repose angle, flow time, bulk volume, tapped volume and density, apparent density) and release from the dosage form of VPH were investigated. High performance liquid chromatographic, gas chromatographic and fluorometric determinations of VPH have been reported (11-13). In this study the assay of the drug was carried on by a spectrophotometric method.

Materials and Methods

The materials employed were: Verapamil HCl (Orion Corporation, Fermion, Finland), Précirol ATO 5 and Compritol 888 ATO (Gattefossé S.A., France), lactose (D.M.V., International Farma, Holland).

Preparation of lipophilic matrix and tablets of VPH: The contents of the formulations are given in table 1. For lipophilic matrix preparation, fusion technique with subsequent granulation was used (14). Precirol ATO 5 was melted at 70 ± 0.5°C and homogenized with VPH. After cooling at room temperature, the mixture was sieved through ASTM sieve (0.710 mm) and then Compritol 888 ATO and lactose were added. The mixture was blended in a glass jar for 10 min. Powder mixture without Precirol ATO 5 was formed with VPH, Compritol 888 ATO and lactose for comparison. Flow properties of each formulation were investigated. Repose angle, flow time, bulk volume, tapped volume, tapped density and apparent density of the formulations were determined (15,17). The results obtained are shown in table 2. Then the tablets of 325 mg weight were compressed by a single punch tablet machine (Korsch-Berlin) using a flat, nonbeveled punch (10 mm diameter). Tablet hardness was kept constant within the range of 7.0-8.0 kp by a 6D-Schleuniger hardness tester.

Table 1. Tablet formulations containing Verapamil HCl.

Formulation	Verapamil HCl (mg)	PrecirolATO 5 (mg)	Compritol 888 ATO (mg)	Lactose (mg)
F1	240	-	18	67
F2	240	36	18	31
F3	240	42	18	25
F4	240	48	18	19
F5	240	54	18	13
F6	240	60	18	7

Table 2. Physical properties of the formulations.

Formulation	Repose angle (α^{θ})[a]	Flow time (sec/g)[b]	Bulk volume (ml)[c]	Tapped volume (ml)	Apparent density (g/ml)	Tapped density (g/ml)[d]
F1	41°,28 ± 0.49	14.4± 0.82	31.33±1.15	19.83±0.58	0.319±0.012	0.504±0.015
F2	32°,64 ± 0.46	9.64± 0.16	25.66±0.58	17.17±0.29	0.390±0.009	0.582±0.010
F3	31, 08 ± 0.64	8.34± 0.24	25.33±0.29	18.05±0.50	0.395±0.005	0.556±0.015
F4	28°,55 ± 0.92	7.98± 0.18	25.50±1.32	18.17±0.29	0.392±0.020	0.550±0.009
F5	27°,91 ± 0.42	4.54± 0.20	24.33±0.58	18.17±0.29	0.411±0.010	0.550±0.009
F6	22°,50 ± 0.99	3.86± 0.14	24.33±0.29	18.33±0.29	0.411±0.005	0.545±0.009

Results were expressed as the mean ± SD of experiments. (a) 5 g sample was used. (b) Flow was attained after vibration. (c) 10 sample was used. (d) For tapped density, 10 g sample was used and consolidation property was determined after 1250 times tapping.

Physical properties of the tablets: Weight uniformity and friability (Roche Friability Tester) were determined for each formulation and the results are shown the in table 3.

Table 3. Physical properties of the prepared Verapamil HCl tablets.

Formulation	Weight (mg)	Friablity (%)
F1	320.85 ± 8.99	6.15
F2	322.73 ± 8.59	1.09
F3	323.68 ± 10.22	1.94
F4	321.79 ± 7.76	1.18
F5	329.07 ± 8.53	0.80
F6	329.50 ± 9.62	0.60

Assay of verapamil HCl: Accurately weighed 10 mg of VPH was dissolved in 10 ml distilled water. Absorbance of this solution was measured spectrophotometrically (Shimadzu UV- 1601) at 278 nm. The standard curve of VPH was plotted at 2.5-30 μgml^{-1} concentrations. The equation calculated from the standard curve was as follows:

$$y = 0.011x + 0.002 \qquad (r^2 : 0.999)$$

[x: concentration (μgml^{-1}) y: absorbance, r^2: coefficient of determination]

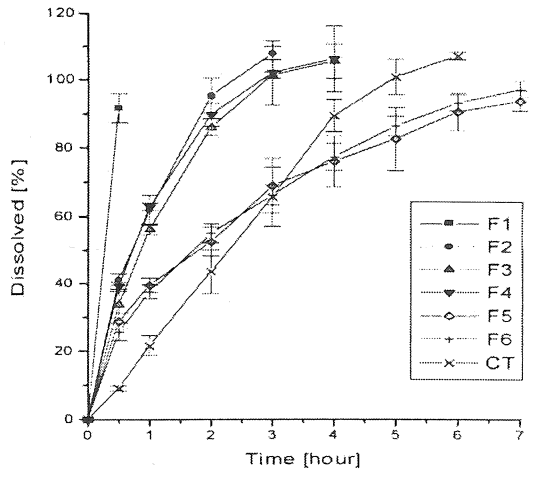
Assay of verapamil HCl in the lipophilic matrix tablets: Ten tablets were powdered, blended thoroughly and 325 mg from this mixture was accurately weighed and suspended in 20 ml distilled water and sonicated in an ultrasonic bath for 5 min. The volume of the suspension was adjusted to 100 ml with distilled water and filtered through Minisart NML (0.2 μm). 1 ml of this filtrate was made up to 100 ml with distilled water. 3 ml of this solution was diluted to 10 ml with distilled water and the absorbance was determined at 278 nm. This procedure was repeated 5 times for each formulation.

Dissolution Studies: USP/NF paddle dissolution method was used with a paddle rotational speed held at 50 rpm and 800 ml of distilled water at 37±0.5°C as the medium. 1 ml of the dissolution medium was pipetted at scheduled intervals and diluted to 10 ml with distilled water and then VPH was determined spectrophotometrically at 278 nm. Six experiments were done for each formulation. Dissolution profiles of VPH matrix tablets were shown in the figure. The release rates of VPH from the matrix tablets were evaluated kinetically (Table 4). In addition, dissolution tests were applied to the commercial VPH sustained release tablets (CT) and the results were compared.

Table 4. Kinetic parameters for in vitro release of Verapamil HCl.

Formulation	Zero order		First order		Higuchi Model	
	k_0	r^2	k_1	r^2	k	r^2
F2	26.878	0.950	0.375	0.900	67.205	0.985
F3	20.360	0.900	0.305	0.821	57.342	0.963
F4	18.616	0.883	0.262	0.808	52.652	0.976
F5	9.936	0.951	0.169	0.874	34.523	0.993
F6	10.868	0.955	0.187	0.861	37.746	0.996
CT	18.709	0.972	0.412	0.838	60.197	0.990

(k_0, k_1, k: release rate constant and k_0: $mg.h^{-1}$, k_1: h^{-1}, k: $mg.cm^{-2}.h^{-0.5}$)
(CT: Commercial tablet)



CT: Commercial tablet

Fig. *In vitro* release of verapamil HCl in the tablets

Results and Discussion

High repose angle and flow time of the powder form without Precirol ATO 5 (F1) were reduced by adding different concentrations of Precirol ATO 5. These results indicated that increasing amounts of the lipophilic matrix agent improved the poor flow property of VPH. But according to required repose angle value, Formulations F4, F5 and F6 were found to be more suitable than the others (Table 2). It was found that all prepared tablets satisfied the USP requirements for weight variation tolerance (18). On the other hand, the friability results were suitable according to the European Pharmacopoeia requirements for only F5 and F6 (19). Dissolution studies of lipophilic matrix tablets containing Precirol ATO 5 (F2-F6) and of the VPH tablets without Precirol ATO 5 (F1) showed that the drug was released completely within 30 min from F1, but the release was prolonged to 3 or 4 hours at formulations F2, F3 and F4. In the case of CT, maximum discharge was realized within 6 hours. For formulations F5 and F6 approximately 95% of VPH was released within 7 hours. These results indicated that formulations F5 and F6, were superior to CT. Table 4 shows the kinetic data of VPH released from lipophilic matrix tablets. It was found that the Higuchi kinetic was the best model to describe the release

kinetics from formulations F2- F6 and CT.

In conclusion, the poor flow property of VPH was improved and prolonged release of the drug was obtained by using Precirol ATO 5 as a lipophilic matrix agent. As a result, among the prepared formulations, F5 and F6 were more suitable than the other formulations in respect of the results mentioned above. According to the Student's *t*- test, there was no significant difference ($p>0.05$) between F5 and F6 with respect to the physical parameters and drug release from the formulations. Thus, it can be stated that formulation F5 is favourable for sustained release tablets of VPH.

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