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Development of a membrane-controlled transdermal therapeutic system containing isosorbide dinitrate

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Abstract

The formulation of a transdermal delivery system for isosorbide dinitrate (ISDN) was examined. It was found that the target release rate should be 4.01 mg/h per 20 cm^2 for optimal dosing. In order to reach such this zero order release rate, a membrane permeation controlled transdermal therapeutic system (TTS) formulation was developed, with ethylene vinyl acetate copolymer (EVAC) and polyethylene (PE) membranes as rate controlling membranes; a carbomer gel was used as the drug reservoir. The release of ISDN from this drug delivery device was studied in vitro using FDA recommended method. PIB adhesive on the EVAC or PE membrane caused a decreased flux of ISDN; the release kinetics fitted Higuchi matrix kinetics. TTS with EVAC membrane release ISDN at a rate much lower than the calculated target release rate, but with PE membranes, the release rate was very close to the target. Release rate studies have revealed that, as the VA content in EVAC membrane increased, the flux of ISDN increased. All these results were compared with the commercial product Frandol® Tape S from Japan. It was found that the release rate of Frandol was close to target release rate and fitted matrix kinetics. These results suggested that TTS that contain PE membrane as rate controlling membrane, polyisobutylene (PIB) adhesive and carbomer gel as a reservoir can be applicable as a TTS for ISDN.

Keywords: Isosorbide dinitrate; Transdermal therapeutic systems; Diffusion coefficient; Ethylene vinyl acetate; Polyethylene membrane; Release kinetics

1. Introduction

Isosorbide dinitrate (ISDN) is an organic nitrate vasodilator, widely used for the treatment and prophylaxis of angina. The terminal half life of ISDN after single oral dosage to human subject is between 20 and 70 min (Taylor et al., 1982; Straehl and Galeazzi, 1985). After oral doses, ISDN undergoes extensive first pass elimination and inter and intra subject variability of plasma concentration is observed (Fung, 1985; Taylor et

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al., 1985). Because of first pass elimination, oral bioavailability of ISDN in human subjects has been reported to be as low as 22–29%. Denitration of ISDN by liver produces two metabolites, which are potent vasodilators (Down et al., 1974; Chasseaud et al., 1975). The clinical effect of ISDN relates both to the actions ISDN itself, as well its two active metabolites. The duration of clinical effect of oral ISDN is only 3–4 h, which is not long enough to meet therapeutic needs (Johnson et al., 1981). Because of the short half-life and the short therapeutic effects of this drug, long-term treatment is generally carried out with oral sustained release. Especially, the low oral bioavailability of ISDN and the excess variation of intra and intersubject in oral application have brought the subject of transdermal therapeutic application of ISDN to be fore.

Several transdermal therapeutic systems have been developed to achieve systemic medication (Chien, 1990). This administration provides an effective and advantageous alternative to the oral delivery of therapeutic agents. Because of these advantages, transdermal therapeutic systems (TTS) of scopolamine, nitroglycerine, estradiol, clonidine, nicotine and ISDN are in use today. To provide the plateau level of active molecules in the blood, like IV infusion, the drug molecule must be given at a constant rate. Transdermal therapeutic systems, which have rate controlling membranes, provide this condition for drugs which can easily permeate the skin. There are two types of topical preparations of ISDN on the market. The first are aerosol preparations, which are sprayed on the skin. The other is a TTS preparation, which contains 40 mg of ISDN and is produced only in Japan.

The purpose of this study was to compare the release rates and release profiles of trandermal therapeutic systems; namely, the formulation we developed at our labs and the commercial product in the Japanese market.

2. Materials and methods

2.1. Materials

ISDN (25% lactose triturate) was provided by Fako Pharmaceuticals, Inc., Istanbul Turkey. Ethylene vinyl acetate copolymer (EVAC) membranes, which have different vinyl acetate (VA) contents and a polyethylene (PE) membrane as the backing layer was obtained from the 3M Company. Carbopol 934 was from BF Goodrich. All solvents and reagents used during experiments were analytical grade. Spectroscopic analysis was performed on a Perkin Elmer Spectrophotometer Model 200.

2.2. Methods

2.2.1. The recovery of ISDN as pure crystals

In order to get consistent colorimetric assay results, ISDN was separated from the lactose, with which it was diluted. The ISDN/lactose triturate was first mixed with ether. This mixture was kept in an ultrasonic water bath for 5 min and then filtered. The ether was evaporated under nitrogen. The residue was heated to 40°C and enough ethanol was added to dissolve pure ISDN. The crystals dissolved. Cold water was added in drops to this solution until it lost its clarity. The recrystallization of ISDN was made. This suspension was filtered and the crystals were separated and were dried in a desiccator.

2.2.2. Analysis of ISDN

Concentration of drug in each sample solution was measured by UV spectrophotometry at 550 nm, using the method of Dittgen and Bombor (1989).

2.2.3. Dissolution rate study

This was carried out according to the FDA method (Anon., 1980). Distilled and deaerated water was used as the dissolution medium. An 11-cm diameter circle cut from aluminum window screen (about 18 mesh) was molded to fit a 9-cm diameter watch glass. The ISDN containing patch was placed between the concave side of the watch glass and the screen with the exposed drug side of the patch facing the screen. This assembly was placed at the bottom of a dissolution vessel containing 1000 ml of deaerated water with screen facing upwards. The assembly was leveled, and paddle was lowered to within 2.5 ± 0.5 cm from

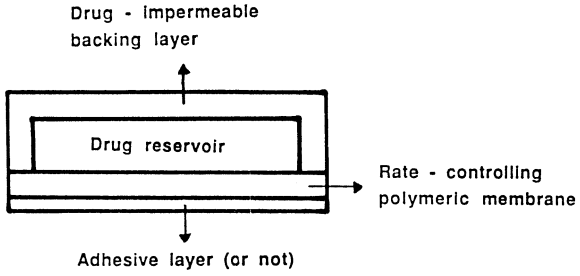

Fig. 1. Schematic illustration of transdermal therapeutic system.

the bottom of the paddle to the top of screen. The paddle speed was 50 rpm. Temperature of dissolution medium was 32 ± 0.5°C. The vessel was covered with a plastic cover to minimize evaporation. 5-ml sample aliquots were collected with filtering at 1 h intervals during 10 h and the withdrawn sample volume was replaced by distilled and deaerated water.

2.2.4. Preparation of drug delivery devices

In order to prepare the target transdermal therapeutic system, 1% Carbopol reservoir gel, PE(3M, MSP 61588) and EVAC membranes (3M, MSP 98744, MSP 98722, MSP 987194) were used for rate control (Fig. 1).

The gel was prepared by the addition of propylene glycol, since ISDN does not dissolve in the water making up this gel. The formulation of this gel is shown in Table 1.

First, 0.15 g of ISDN was added to 7.5 g of propylene glycol. ISDN crystals were solved by shaking. 7.5 g of propylene glycol, including 0.15 g of ISDN was mixed with 0.1 g of carbopol resin and the resultant mixture was neutralized using 5% w/w sodium hydroxide solution,

Table 1
ISDN gel formulation

Formulation	g
Carbopol	0.1
ISDN	0.15
Sodium hydroxide sol. (5% in propylene glycol)	0.169
Propylene glycol q.s.	10

Table 2
Components of TTS including ISDN[a]

Formulation No.[b]	Rate controlling membrane	Adhesive
F18	PE(3M, MSP 61588)	—
F20	PE(3M, MSP 61588)	PIB
F21	EVAC(2% VA content)	—
F22	EVAC(2% VA content)	PIB
F23	EVAC(4.5% VA content)	—
F24	EVAC(4.5% VA content)	PIB
F25	EVAC(19% VA content)	—
F26	EVAC(19% VA content)	PIB

[a] Backing layer is 3M, No 1009 Scotchpak.
[b] Reservoir is 1% Carbopol containing gel.

which was prepared with propylene glycol. 4 g of the ISDN gel was placed on a sheet of backing layer (3M, No 1009 Scotcpak) covering 5×4 cm area. A rate controlling membrane (PE or EVAC membrane) was placed over the gel and the edges of 5×4 cm area was sealed by heat to obtain a leakproof device. On this patch, polyisobutylene (PIB) (5 ml, 10% w/v in petroleum ether) was applied. The release rate studies were carried out immediately. The components of the prepared patches are shown Table 2.

3. Results and discussion

3.1. Sustained release dosage design

The purpose of this design is to provide a constant blood drug level. In order to accomplish this, zero-order release of ISDN from TTS is needed. In this design, an initial priming dose, which provides a prompt therapeutic level, must be administered sublingually and separately. As a starting point, the absorption rate constant (k_a) and elimination rate constant (k_d) of ISDN were calculated using the blood concentrations, which were obtained by a 60 mg ISDN application on skin by an aerosol was used (Wildfeuer et al., 1985). Employing these data and using ESTRIP stripping and LSNLR (Marquardt algorithm) nonlinear regression computer prog-

rams, the pharmacokinetic model of ISDN in the body was represented by one compartment model and the final pharmacokinetic parameters of ISDN were calculated. The target release rate (k_r^0), maintenance dose(D_m), dosing interval (τ) and release duration time (h) were calculated according to Robinson and Eriksen, 1966. The target profile was plotted by these parameters. Then we developed the required formulation, consistent with this release rate and profile.

As a known, the skin is a very important barrier for the percutaneous absorption of molecules. If the absorption rate of a active molecule through the skin is lower than its release rate from TTS, molecules will accumulate in the skin. Therefore, the development of a TTS formulation, which releases the drug molecule at the same rate as absorption was aimed.

During dosage calculation, the release rate (k_r) which is equal to the absorption rate is calculated. This release rate produces the effective blood concentration (C_{max}). Theoretically, TTS formulations, which possess this release rate, will give the C_{max} value. The maintenance dose ensures durability of constant C_{max} value and constant release rates during the release periods (h).

The required theoretical release rate to achieve optimum therapeutic effect was calculated considering the pharmacokinetic parameters. Having determined the consistency of these data with one compartment model, we calculated the percutaneous absorption rate constant, elimination rate constant, C_{max} and t_{max} values. The calculated C_{max} value was used as the sustained plasma concentration. Although the maintenance dose was calculated to be 44.5 mg/20 cm^2, the drug reservoir was loaded with 60 mg/20 cm^2 ISDN in order to have a better thermodynamic activity. The calculated pharmacokinetic parameters and sustained release design values are shown in Table 3.

3.2. Release studies

3.2.1. Release studies with EVAC membranes

Different EVAC membranes are the main components used to control the rate of drug release from many transdermal drug delivery devices. Transport through EVAC membranes occurs via a two step process: partitioning from a reservoir into the EVAC membrane and diffusion through the membrane. Moreover, the release rate studies revealed that, as the vinyl acetate content in copolymer increases, the cumulative drug release increase, i.e. the membrane shows a lower resistance to the penetration of the drug molecules (Kagayama et al., 1984; Morimoto et al., 1988; Peterson et al., 1990).

The release rate data of these transdermal therapeutic systems, in which EVAC membranes were used, have been calculated by a program which evaluated the information in terms of release kinetics (Ağabeyoğlu, 1984). Release kinetics of patches basically obey zero order and $Q \rightarrow t^{\frac{1}{2}}$ kinetics. The kinetic parameters for ISDN from these TTS are summarized in Table 4.

As can been seen in the release profiles (Fig. 2), none of the formulation profiles fit the target profile. When analyzed in terms of release kinetics, it was obvious that these formulations have released ISDN at a much slower rate than target release rate (4.01 mg/h). In such cases most probably, the inefficient release rate will not be able to attain the target 2.66 ng/ml blood concentration.

Through the release rate data and by the use of Eq. (1), the flux (J, mg/cm^2 per h) has been calculated.

$$M_t = PC_s t \quad (1)$$

In this equation, M_t is the drug amount released from unit area (mg/cm^2), P*C$_s$ is flux (J, mg/cm^2 per h), P is permeability of membrane, C_s is the solubility of ISDN in the membrane.

The application of PIB adhesive on the EVAC membrane has caused a decrease of flux. When the flux values versus vinyl acetate content is investigated, a considerable increase in flux values

Table 3
Pharmacokinetic and sustained release dosage design parameters

$k_a = 0.485$ h^{-1}	$t = 4$ h
$k_d = 0.105$ h^{-1}	$h = 11.1$ h
$C_{max} = 2.66$ ng/ml	$k_r^0 = 4.01$ mg/h (for 20 cm^2)
$t_{max} = 4.02$ h	$D_m = 44.5$ mg

Table 4
Kinetic assessment of release data of ISDN from patches

Formulation No.	Release kinetics models			
	Zero order		$Q \rightarrow t^{\frac{1}{2}}$	
	k_r^{0a} (mg/h)	r^{2b}	K^c (mg/h$^{\frac{1}{2}}$)	r^2
F18	5.43	0.999	7.76×10^{-3}	0.975
F20	3.58	0.982	4.46×10^{-3}	0.989
F21	1.61	0.973	8.47×10^{-4}	0.982
F22	1.28	0.973	3.49×10^{-4}	0.979
F23	2.17	0.998	1.54×10^{-3}	0.965
F24	2.02	0.994	9.29×10^{-4}	0.965
F25	3	0.997	5.23×10^{-3}	0.975
F26	2.31	0.979	2.69×10^{-3}	0.917
Frandol® Tape	3.19	0.976	4.40×10^{-3}	0.998

[a] k_r^0 is the zero order release constant.
[b] r^2 is the coefficient of determination.
[c] K is the rate constant obtained from slope of the linear regression of cumulative amount released versus square root of time.

with increase in VA content is seen, despite few data points (Table 5).

3.2.2. Release studies with PE membranes

The polyethylene membrane has microporous characteristics (Anon., 1988). Transport of drug through this membrane occurs by diffusion through liquid-filled pore media. The release profiles and dissolution rate kinetic parameters of the patches, which have been prepared by using

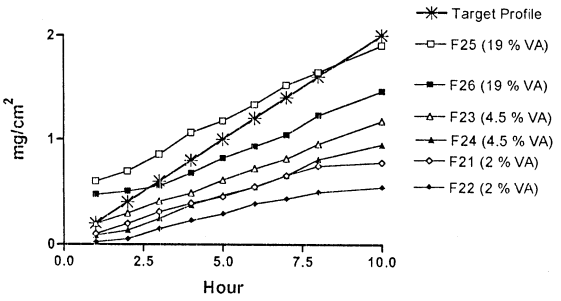

Fig. 2. Release profile from patches with EVAC membranes.

polyethylene membrane, are shown in Fig. 3 and Table 4.

When the adhesive was not used, it is observed that the release fits zero order kinetics. The membranes being microporous, enables the release of ISDN within the reservoir, which has been dissolved in propylene glycol, to be released into the dissolution medium, which penetrates these pores. Therefore this condition directly affects the ISDN release. In this case, ISDN is being released at a rate of 5.43 mg/h. As can be seen in Fig. 3, this release is faster than the target release rate.

On the other hand, PIB adhesive has blocked the pores of polyethylene membrane and therefore this material has partly caused the release to fit Higuchi matrix kinetics. This patch releases ISDN at a rate of 3.58 mg/h, a value to the target release rate. It was concluded that the F20 formulation was the most appropriate formulation for this. As in other patches, which have been prepared with EVAC membranes, the flux of these transdermal

Table 5
Flux from patches through different EVAC and PE membranes

Formulation No.	Membrane	PIB adhesive	Flux[a] (mg/h per cm^2)
F18	PE	−	0.272 ± 0.011
F20	PE	+	0.179 ± 0.019
F21	EVAC (2% VA)	−	0.0805 ± 0.0159
F22	EVAC (2% VA)	+	0.0640 ± 0.0125
F23	EVAC (4.5% VA)	−	0.109 ± 0.015
F24	EVAC (24.5% VA)	+	0.101 ± 0.008
F25	EVAC (19% VA)	−	0.150 ± 0.012
F26	EVAC(19% VA)	+	0.116 ± 0.005

[a] Each value represents the mean $\pm$95 C.I. of three runs.

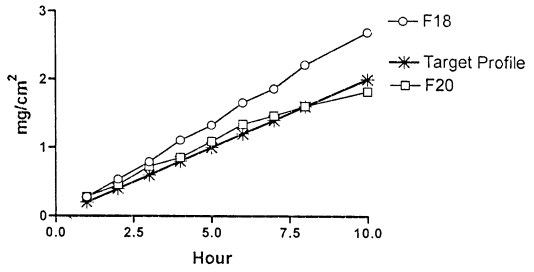

Fig. 3. ISDN release profile from patches with PE membrane.

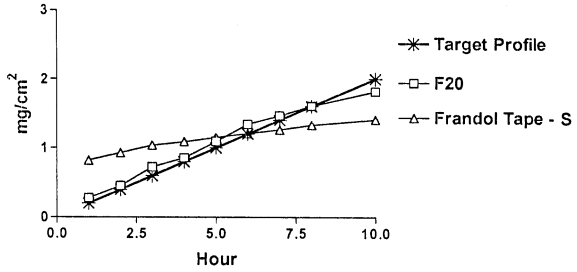

Fig. 4. Release profile of commercial product (Frandol® Tape-S).

therapeutic systems have been calculated (Table 5).

3.2.3. Release studies with commercial product (Frandol® Tape-S)

Besides the formulations prepared in this study, the release of ISDN from commercial TTS was measured; the release profile drawn and its release kinetics observed (Fig. 4, Table 4). The release properties of Frandol was compared and contrasted with F20 formulation. We concluded that, the rapid release rate for the first hour in commercial product was due to the accumulated ISDN on the surface of the adhesive matrix. However, we were not able to find the similar results in the F20 formulation we prepared. This might be due to the reason that, we carried out the release experiments right after the preparation of patches. The release of this commercial product fitted matrix kinetics. ISDN was released at a rate of 3.19 mg/h. This value was close to the target release rate.

It has been reported that, with this commercial product, constant blood concentrations have been obtained for 48 h (Takada et al., 1990). Formulation F20 releases ISDN at a rate very close to both the commercial product's active release rate and the calculated target release rate. We are aware that, in vitro release profiles or rates per se, do not predict the in vivo absorption rate or profile, although similar in vitro release profiles with the commercial product may result in similar blood profiles and clinical efficacy. Some preliminary tests with patients here at Gazi University Hospital seemed to support this. However, it is obvious that extensive in vivo studies must be carried out.

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