DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(11), 1905-1909 (1994)

COMMUNICATIONS

ADHESIVE MATRIX TYPE TRANSDERMAL DRUG DELIVERY SYSTEM FOR NITROGLYCERIN

Rajesh M. Pai, Meenal S. Desai, Ashish D. Babtiwale and R. Shrivastava*.

The Bombay College of Pharmacy, Kalina, Santacruz (E), Bombay - 400 098.

ABSTRACT

The kinetics of release of nitroglycerin from adhesive matrix type patches was studied. At a high drug to adhesive ratio the patch consisted of nitroglycerin in part dispersed as droplets in the adhesive and in part dissolved in the adhesive. This patch showed instant release of a major fraction of nitroglycerin in the patch and thereafter release kinetics similar to that which may be expected for a solution system. The rate of skin permeation of nitroglycerin was influenced by the drug to adhesive ratio; first increasing with increase in drug to adhesive ratio and then showing no significant change at a high drug to adhesive ratio at which the system was apparently an emulsion of nitroglycerin in the adhesive.

INTRODUCTION

Rezakovic (1) on the basis of a review of 94 publications on 124 clinical trials on 42, 152 patients concluded that transdermal delivery of nitroglycerin appears to be beneficial in angina pectoris and in congestive heart failure in the greatest part of the patient population. This paper presents some of the work done on adhesive matrix type patches of nitroglycerin.

EXPERIMENTAL

Materials

The components of the transdermal patch were obtained from 3M Medica, GmbH, Health Care Department, Germany. Nitroglycerin sample was supplied as a 10.39% w/w lactose triturate by Burroughs Wellcome (India) Ltd. Ethyl acetate A.R. grade (S.D.Fine Chemicals) was used as a solvent.

* To whom correspondence should be addressed

Method of Preparation

A stock solution containing nitroglycerin and pressure sensitive adhesive in ethyl acetate was delivered onto a cavity on the backing membrane and allowed to dry in air under ambient conditions of humidity. The patches coded as NA48,NA44,NA42 and NA41 contained 4 mg of nitroglycerin each and 8,4,2 and 1 mg pressure sensitive adhesive,respectively in 1 sq.cm. area.

In-vitro Release

Keshary-Chien diffusion cells were used to evaluate the in-vitro release of nitroglycerin from the transdermal systems. A freshly prepared aqueous solution of 20% w/w PEG 400 in the receptor compartment was stirred by means of magnetic stirrer and maintained at a constant temperature of 37 ± 1°C, with the help of a constant temperature circulating water bath (Siskin-Julabo V). Samples were analyzed by the colorimetric method of Bell et al (2).

Skin Permeation Studies

A piece of full thickness abdominal skin freshly excised from female guinea pigs (Hindustan Lever Research Division, Bombay) was used for the study of skin permeation using Keshary-Chien diffusion cells. The study was carried out in two sets. Each set consisted of studies on skin obtained from three guinea pigs; with the skin permeation profile of each system in the set tested on each of the three guinea pigs. In set I systems NA48,NA44 and NA42 were evaluated and in set II the study was performed on systems NA42,NA41 and Transderm-Nitro®. Conditions maintained were identical to those in in-vitro release studies.

RESULTS AND DISCUSSION

Release Kinetics

The release profiles of the adhesive matrix systems NA44,NA42 and NA41 are given in Figure 1. Microscopic observation revealed that the matrix systems NA44 and NA42 were translucent gels, the latter showing a granular matrix during the initial phase of the two hour drying period and thereafter it also appeared to be a translucent gel. At least microscopy did not reveal the presence of a dispersed phase in the adhesive matrix of systems NA44 and NA42. The matrix system, NA41, was an emulsion with the droplets of nitroglycerin distributed throughout a translucent gel matrix.

Takeru Higuchi(3,4) and William Higuchi(5) showed that for a system consisting of an active agent dissolved in the matrix release occurs in two kinetic phases and in the initial phase, a linear Q vs $t^{1/2}$ relationship is followed. However, in our study such two phases of release did not become apparent on a Q versus $t^{1/2}$ plot because initial 50% of release occurred so rapidly that sufficient data was not available during this initial phase.

Kubota et al(6) proposed an in-vitro evaluation method to distinguish between solution and suspension systems. For a solution system it can be shown that

$$\frac{dQ}{dt} = 2C_0 D_v/h \sum_{m=0}^{\infty} \exp\left[-D_v(2m+1)^2 \prod^2 t/4h^2\right]$$

where, m is an integer. The equation shows that the release rate declines in a multi-exponential manner. A dQ/dt versus t curve on a semilogarithmic scale may be

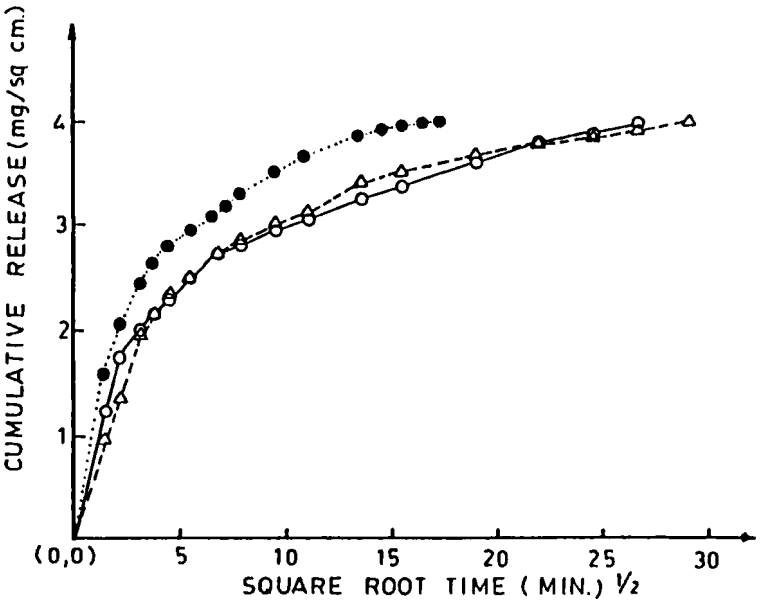

FIGURE 1

Cumulative amount released versus square root time plot for release of nitroglycerin from adhesive matrix systems into 20% w/w PEG 400 at 37 ± 1°C.
(Key: -- ● --, NA41; —O—, NA42; and —Δ—, NA44.)

expected to show a terminal linear segment where the decline in release rate is monoexponential. Figure 2 shows that the systems NA44 and NA42 showed a terminal linear segment where the decline in release rate was monoexponential. However release from the system NA41 which was apparently an emulsion of nitroglycerin in the adhesive also conformed to that which is theoretically expected for a solution system. This was because for the NA41 system, the transition from suspension state to solution state occurred in the first two minutes and it was not possible to obtain sufficient points before the transition occurred. Kubota et al further showed that after the suspended phase is depleted at time 'to' release conforms to the equations -

$$\frac{dQ}{dt} = \frac{C_s D_v}{h} \sum_{m=0}^{\infty} \frac{4(-1)^m}{(2m+1)\prod} \exp \frac{-D_v (2m+1)^2 \prod^2 (t - t_0)}{4h^2}$$

for the case where release occurs by diffusion through the matrix ,and by

$$\frac{dQ}{dt} = \frac{\in C_s D_f}{\tau h} \sum_{m=0}^{\infty} \frac{4(-1)^m}{(2m+1)\prod} \exp \frac{-D_f (2m+1)^2 \prod^2 (t - t_0)}{4 \tau h^2}$$

for the case where release occurs by dissolution in and diffusion through dissolution medium filled channels. Thus dQ/dt versus 't' curves on semilog scale would show initial multiexponential decline followed by a terminal linear segment.

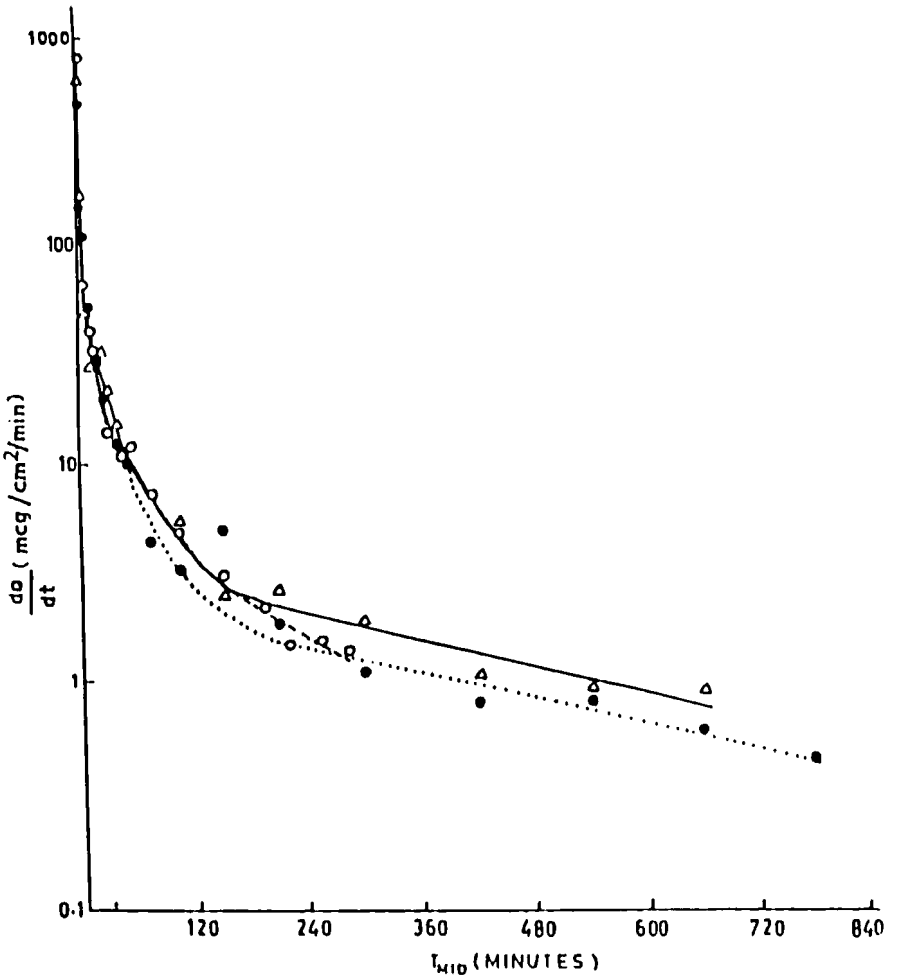

FIGURE 2

Semilogarithmic plot of mean release rate versus time for adhesive matrix systems. (Key : —O—, NA41; —Δ—, NA42; and -- ● --, NA44.)

Skin Permeation Studies

Table 1 gives the skin permeation rates for system NA48,NA44,NA42,NA41 and Transderm-Nitro®. The F-test for parallelism(7) to determine the equality of slopes was employed to investigate whether there was a significant difference in skin permeation rates amongst the systems of a particular set at the 1% level of significance. The skin permeation of nitroglycerin from Transderm-Nitro® and NA48 was significantly slower than from systems NA44,NA42 and NA41. The skin permeation rate from system NA42 was significantly faster than from system NA44. This occurs inspite of the identical loading

TABLE 1

Skin Permeation Rates of Nitroglycerin from Transdermal Systems

System	Skin permeation rates(mg/sq.cm./hr.) (mean ± s.d.)	
	SET I	SET II
NA48	0.0250 ± 0.0100	–
NA44	0.0443 ± 0.0015	–
NA42	0.0493 ± 0.0006	0.0483 ± 0.0060
NA41	–	0.0460 ± 0.0010
Transderm-Nitro®	–	0.0300 ± 0.0025

doses in NA48,NA44 and NA42 because a decrease in adhesive amount to 2.0 mg/sq.cm. in NA42 as compared to 8.0 mg/sq.cm.in NA48 results in higher concentration of dissolved nitroglycerin in NA42 as compared to that in NA48. However, there was no significant difference in skin permeation rate between adhesive matrix systems NA41 and NA42. This could be because saturation may have been achieved on decreasing the adhesive amount from 2.0 mg/sq.cm. in NA42 to 1.0 mg/sq.cm. in NA41.

ACKNOWLEDGEMENTS

The authors wish to acknowledge with thanks, the financial support by Cipla Ltd. The gift samples provided by 3M Medica, Germany and Burroughs Wellcome (India) Ltd. are gratefully acknowledged. The authors thank Dr. Y. K. Hamied and Mr. Ram Gulwadi of Cipla Ltd.for their useful suggestions.

REFERENCES

1. Rezakovic, D.E.,"Transdermal Delivery of Nitroglycerin- II",in Transdermal Controlled Systemic Medications, Chien, Y.W., Ed., Marcell Dekker, Inc., New York and Basel, 1987,pp 245.
2. Bell, F.K., J. Pharm. Sci., 53, pp 752, 1964.
3. Higuchi, T., J. Pharm. Sci, 50, pp 874,1961.
4. Higuchi, T., J. Pharm. Sci, 52, pp 1145, 1963.
5. Higuchi, W. I., J. Pharm. Sci, 51, pp 802, 1962.
6. Kubota, K., Yamada, T., Ogura, A. and Ishizaki, T., J. Pharm. Sci., 79(2), pp 179, 1990.
7. Bolton, S., "Comparison of Two Dose-Response Lines: Determination of Relative Potency", in Pharmaceutical Statistics-Practical and Clinical Application. Vol.25, S. Bolton, Ed, Marcel Dekker, Inc., New York and Basel,1984,pp 457-463.