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CHARACTERIZATION OF THE ENHANCING EFFECT OF A VEHICLE IN A TRANSDERMAL SYSTEM

F.RIEG-FALSON, L.HUERTAS, P.BLOUQUIN, G.CONRATH, G.COUARRAZE*

Laboratoire de Pharmacie Galénique et Biopharmacie,UA CNRS 1218,
Laboratoire de Biophysique*
UNIVERSITE DE PARIS SUD,92296 CHATENAY-MALABRY Cedex,FRANCE

ABSTRACT : The percutaneous absorption of Morphine and Morphine hydrochloride is optimized using binary solvent systems as vehicle of the drugs. Release kinectics through hairless mouse skin are performed in vitro : variations of the flux, of the lagtime and of the cumulative released quantities as a function of the vehicle composition point out a synergistic effect of the two solvents (Labrafac hydrophile and Transcutol). Independant determinations of the skin/vehicle partition coefficient, of the solubility and of the diffusion coefficient are realized; the results allow us to explain the different enhancing effects of each solvent: the first one has an enhancing effect on the drug concentration in the skin, and the second one modifies the mobility of the drug in the skin.

The rate of the drug release is usually optimized increasing the drug activity in the donor in relation with the solubility variation. With transdermal system (matrix, film) a more accurate approach is to increase the skin permeation of the drug (1) (2). This effect is commonly attempted with enhancers contained in the system, but a particular vehicle can act as an

enhancer and as a solvent (3 - 7). In this case,we optimize the permeation coefficient, P = (K D / e), where K is the skin/vehicle partition coefficient, D is the diffusion coefficient and e is the skin thickness. The partition coefficient allows variation of the drug concentration in the skin, while the diffusion coefficient represents the mobility of the drug in the skin.

The aim of this presentation is to analyze , on experimental data, the variation of the permeation to identifie ,to localize, and to explain the role of a such vehicle. We studied the morphine permeation through hairless mouse skin with a binary solvents system. The solvents used are a diethylene glycol monoether (T) and a glycolysed ethoxylated glyceride (L). We propose to analyze the influence of the mixture composition on the partition and diffusion coefficient of morphine. We used an hydrophilic specie, morphine hydrochloride (MHCl) , and a lipophilic specie, basic morphine (M), assuming that their routes of penetration are different: etheir hydrophilic inter or intra cellular route, or lipidic intercellular route. We suppose that each solvent can modifie the physical or chemical structure of these routes and consequently, the permeation of one particular specie of morphine.

MATERIALS AND METHODS

MATERIALS

The drugs used are Morphine and Morphine hydrochloride (FRANCOPIA) and the corresponding radio isotopes: (1-3H)-Morphine (AMERSHAM) with a specific activity of 3.48 GBq/mg (94 mCi/mg) , and (17 Me-14C)-Morphine HCl (AMERSHAM) with a specific activity of 1.85TBq/g (50 mCi/mg).

The solvents used are a diethylene glycol mono ether (T) (TRANSCUTOL from GATTEFOSSE S.A) and a glycolysed ethoxylated glyceride (L) (LABRAFAC HYDROPHILE from GATTEFOSSE S.A). Their dielectric constants are respectively 14 and 4 . Composition of the binary systems varies from pure Transcutol (T100-L0) to pure Labrafac hydrophile (T0-L100).

Gels of these solvents are prepared with 10% of Ethocel 20 Premium (LAMBERT & RIVIERE). The gels loaded with radiolabelled morphine have a specific activity of 74 KBq/g (2 mCi/mg) and the morphine concentration is 40 mg/g. The gels loaded with morphine hydrochloride have a specific activity of 22,2 KBq/g (0.6 mCi/mg) and the concentration of MHCl is 30 mg/g.

Picofluor, Instagel, Soluene, Hionic fluor (all from PACKARD) are used for the assay of the drugs by liquid scintillation.

SOLUBILITY STUDIES

The solubilities of M and MHCl in the solvent systems were determined at 37°C by successive additions of small quantities of solute until saturation was obtained.

SKIN/VEHICLE PARTITION COEFFICIENT DETERMINATION

Abdominal skin of hairless mouse (IFFA CREDO) was equilibrated with the solvent previously saturated with the radiolabelled drug for 48 hours at 37°C. Thus, the skin was isolated and dried; the solute concentration in the skin and in the solvent were determined by liquid scintillation. Five experiments are conducted for each solvents system.
The partition coefficient K is the ratio of the skin concentration to the vehicle concentration.

PERMEATION STUDIES

The release kinetics are performed at 37°C in a diffusion cell consisting of a donor compartment containing 1g of sursaturated gel, and a receptor compartment with 80 ml of an aqueous solution maintained in sink conditions (the aqueous solution contains 0.9% of Na Cl for the MHCl permeation; a 40% bovin Albumin is added for the M experiments). The two

compartments are separated by a hairless mouse skin of 2.54 cm^2 area previously equilibrated with the receptor solution for 12 hours. The loaded drug gel contains radiolabelled drug so the radioactivity is evaluated in the receptor compartment at different times ranging from 0 to 96 hours. Each samples of the receptor (2ml) is replaced with fresch solution. Six experiments are conducted for each solvents system.

RESULTS AND DISCUSSION

1. SOLUBILITIES AND SKIN/VEHICLE PARTITION COEFFICIENTS

Values of solubility S varie with the composition of the vehicle (Table 1). The M solubilities are hundred times higher than those of MHCl in all the solvent systems. However, the evolution in the mixtures is similar for both: the highest solubility is achieved with the pure T.

As expected, values of K varie also with the composition of the mixture (Table 1): one can observe the increase of the drug affinity to the skin, high value of K, with the increase of the L ratio in the system. We note that a similar variation of K with the composition of the system is exhibited wherever the basic or salt mophine is used.

2. MORPHINE PERMEATION

Figure 1 represents the variation of the released cumulative quantity after 72 hours (Q/A, mg/cm^2), the flux (J, $mg.cm^{-2}.h^{-1}$) through the skin, and the lag time (t_L , h) as a function of the vehicle composition.

We can notice that: (i) with the pure solvent, Q/A and J are lower than with the solvent mixtures,

(ii) Q/A decreases as the percentage of T increases.

TABLE 1

Solubility (S, mg/ml) and skin/vehicle partition coefficient (K) of M and MHCL in the binary solvent systems (T-L) and the normalized functions (K%), (1/S)%.

Vehicle	T0 L100	T20 L80	T30 L70	T40 L60	T50 L50	T60 L40	T70 L30	T80 L20	T100 L0
Morphine									
S	3	3.5	9	8	9	9	14	15	39
K	9.6	2.2	1.5	1.6	1.3	1.2	1.4	1	3.54
(1/S)%	100	85.9	33.3	37.5	33.3	33.3	21.3	19.8	7.8
K%	100	22.5	15.3	16.3	13	11.8	14.3	10.2	36.8
Morphine Hydrochloride									
S x 100	3	6	7	12	14	15	20	25	52
K	9.7	4.2	3.0	2.7	2.3	2.4	2.0	2.0	1.8
(1/S)%	100	49.8	42.9	25	21.4	18.6	15	12	5.7
K%	100	43	31.1	28.2	24.1	24.6	20.5	20.2	18.8

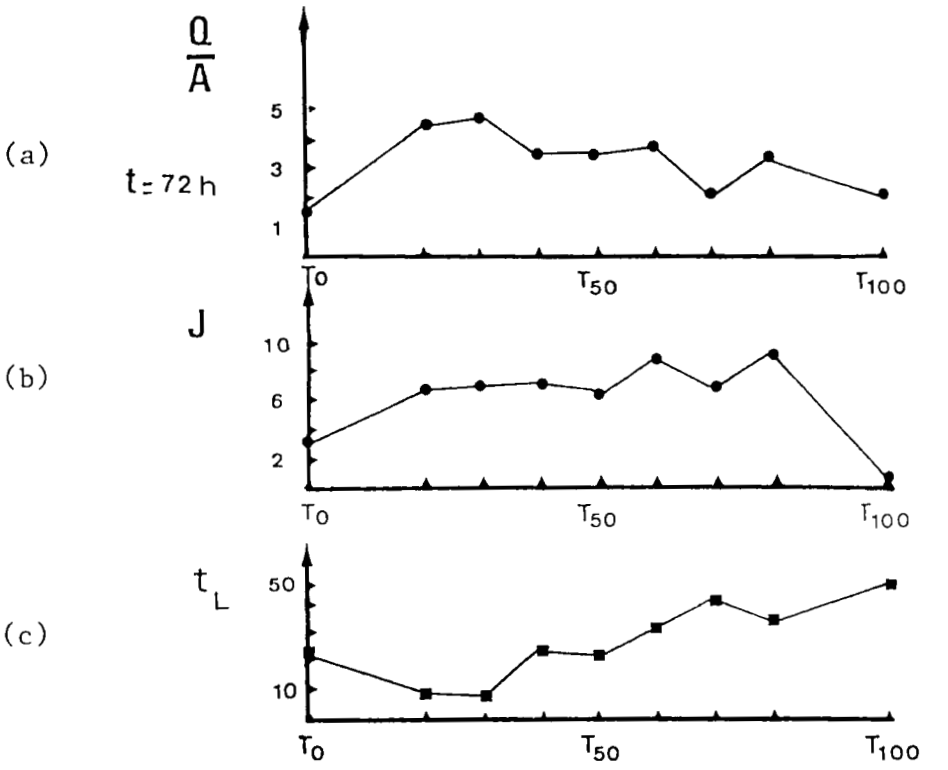

FIGURE 1

Basic morphine release kinetics through hairless mouse skin. Variations of :
a- the cumulative released quantity Q/A ($mg.cm^{-2}$) after 72 hours
b- the flux J ($mg.cm^{-2}.h^{-1}$)
c- the lagtime t_L , h
as functions of the vehicle composition:
T_0 : vehicle with 100% Labrafac hydrophile, 0% Transcutol
T_{100} : vehicle with 0% Labrafac hydrophile, 100% Transcutol.

However, Q/A depends on J and t_L and on their combined effect:

(i) J increases with the percentage of T and the largest values are obtained for 50% and 80% of T mixtures.

(ii) t_L also increases in the same way and explains the lower value of Q/A obtained at 72 hours.

This synergistic effect of the two solvents on the flux is similar to this reported by other authors with different multicomponent systems (1)(9 - 12).

3. MORPHINE HYDROCHLORIDE PERMEATION

The variations of the parameters Q/A, J and t_L obtained for the MHCl are represented in Figure 2.
They are similar to those of the basic morphine; they increase with the percentage of T, but they decrease over 50% of T as the lag time value becomes very high.
It is remarquable that the flux obtained with the hydrophilic specie is not very low compared to the basic morphine. This indicates that there is no dissociation of the ionic specie in the vehicles used and in the skin because of their low dielectric constant value (less than 30)(8).

4. EVALUATION OF THE PERMEATION COEFFICIENTS

The permeation coefficients, P, are calculated from the relationship P = J/S, where S is the solubility of the drug in the vehicle (Table 2). Large variations are observed with the composition of the vehicle ant P is higher for MHCl than for M because of the difference in solubility of the two species

5. DISCUSSION ABOUT THE ENHANCING EFFECT ON THE DRUG CONCENTRATION IN THE SKIN

The enhancing effect of the vehicle on the drug concentration in the skin is evaluated by comparison of the normalized functions K% and (1/S)% versus the vehicle composition (Figures 3 & 4).

The normalized value is the percentage relative to the highest value of the corresponding parameter taken as 100%. Here, the reference is the system containing 100% of Labrafac hydrophile (T0-L100) exhibiting the highest values of K and 1/S. In the opposite, the reference for S% is the system with pure Transcutol (T100-L0).

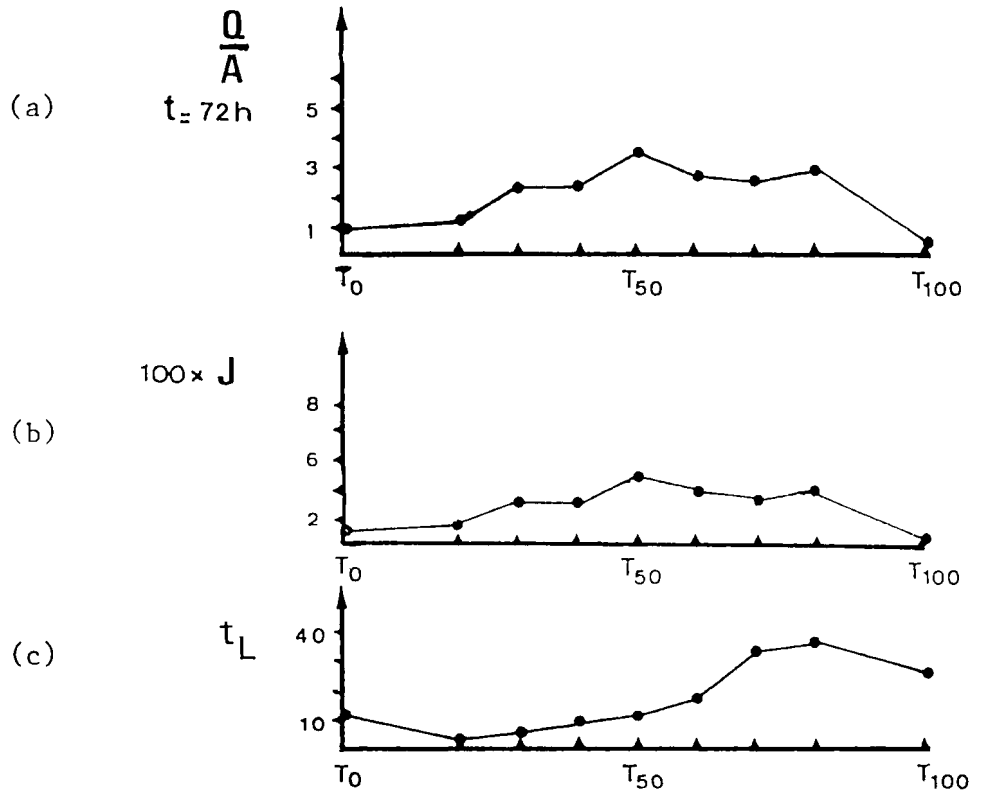

FIGURE 2

Morphine hydrochloride release kinetics through hairless mouse skin. Variations of :

a- the cumulative released quantity Q/A ($mg.cm^{-2}$) after 72 hours

b- the flux J ($mg.cm^{-2}.h^{-1}$)

c- the lagtime t_L , h

as functions of the vehicle composition:

T_0 : vehicle with 100% Labrafac hydrophile, 0% Transcutol

T_{100} : vehicle with 0% Labrafac hydrophile, 100% Transcutol.

For any vehicle, x, containing a drug, the skin/vehicle partition coefficient K_X of this drug is defined with the relation:

$$K_X = C'_X / C_X = S'_X / S_X \qquad \text{(equation 1)}$$

where C'_X is the drug concentration in the skin equilibrated with the unsaturated vehicle of drug concentration C_X,

TABLE 2.

Flux (J, $mg.cm^{-2}.h^{-1}$), Permeation coefficient (P, cm/h), Diffusion coefficient (D, cm2/h) of M and MHCl through hairless mouse skin with the binary solvent systems (T-L).

Vehicle	T0 L100	T20 L80	T30 L70	T40 L60	T50 L50	T60 L40	T70 L30	T80 L20	T100 L0
Morphine									
$J \times 10^2$	3.6	7	6.9	7.4	6.6	9.3	7.3	9.2	0.84
$P \times 10^2$	1.3	2.	0.8	0.9	0.7	1	0.5	0.6	0.2
$D \times 10^4$	0.74	5.5	3.1	3.6	3.6	5.4	2.3	3.8	0.03
Morphine Hydrochloride									
$J \times 10^2$	1.3	1.7	3.1	3.2	4.9	3.8	3.4	3.9	0.6
$P \times 10^2$	43	28	44	27	35	25	17	15	1
$D \times 10^4$	8.8	13	29	20	30	21	17	15	1

S'X is the drug solubility in the skin equilibrated with the saturated vehicle of solubility SX.

The normalized KX% reported to the skin/Labrafac hydrophile partition coefficient K_L is :

$$K_X\% = K_X / K_L \qquad \text{(equation 2)}$$

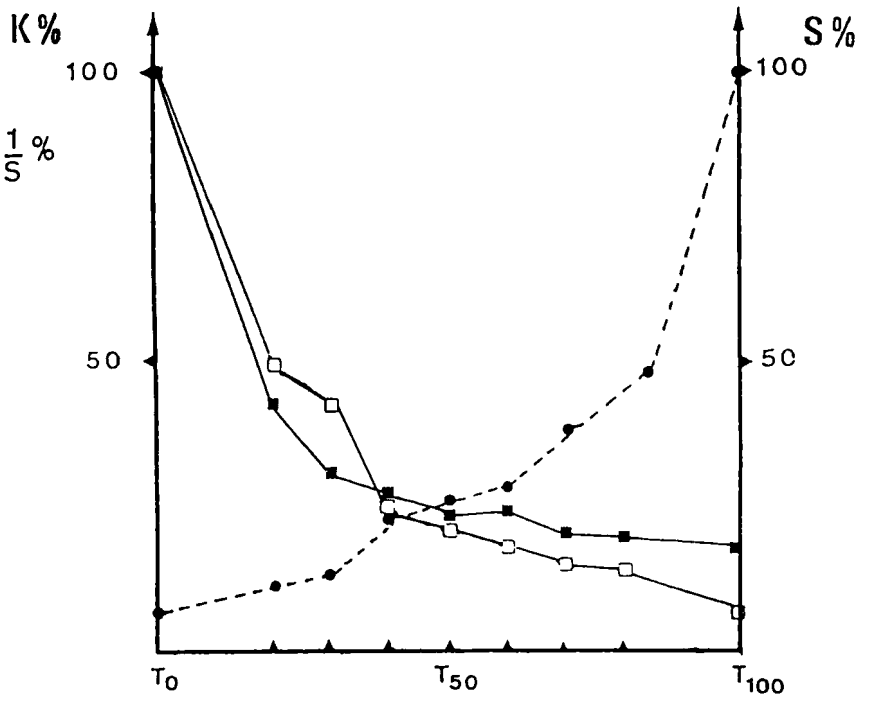

FIGURE 3
Normalized functions K% (■) S% (●) (1/S)% (□) of morphine hydrochloride vs the composition of the vehicle (T-L)
from T_0: 100% Labrafac hydrophile, 0% Transcutol
to T_{100}: 0% Labrafac hydrophile, 100% Transcutol

Combining eq.1 and eq.2, we obtain:

$$K_X\% = (S'_X / S_X)(S_L / S'_L) \qquad \text{(equation3)}$$

where S'_L and S_L are the solubilities of the drug respectively in the skin equilibrated with L and in the Labrafac hydrophile.

By definition, the normalized $(1/S_X)\%$ is :

$$(1/S_X)\% = (1/S_X) / (1/S_L) = S_L / S_X \qquad \text{(equation 4)}$$

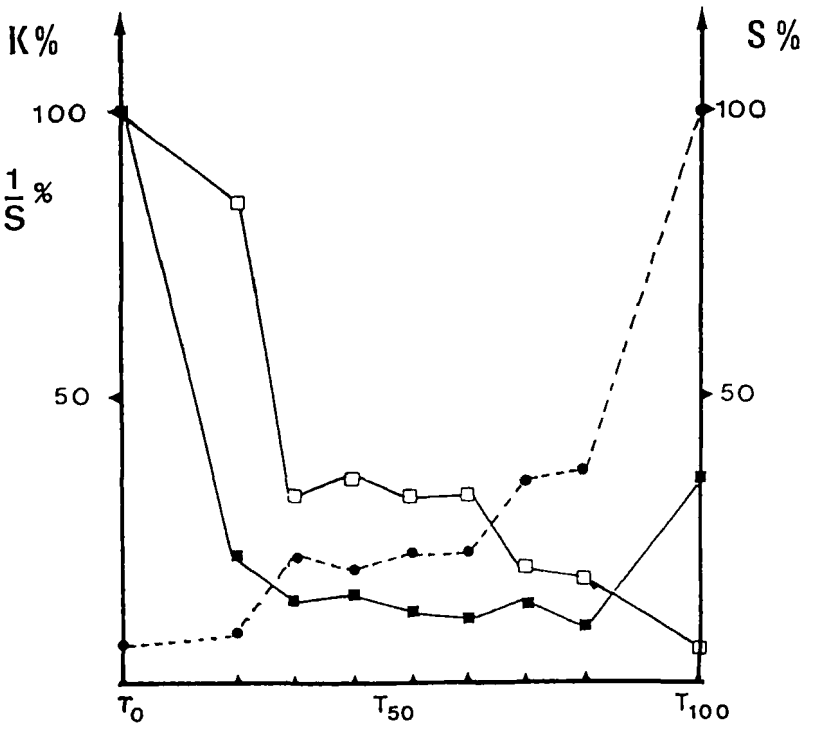

FIGURE 4
Normalized functions K% (■) S% (●) (1/S)% (□) of basic morphine vs the composition of the vehicle (T-L)
from T_0: 100% Labrafac hydrophile, 0% Transcutol
to T_{100}: 0% Labrafac hydrophile, 100% Transcutol

Combining eq. 3 and eq.4, we obtain :

$$[(1/S_X)\%]\,(1/K_X\%) = S'_L / S'_X \qquad \text{(equation 5)}$$

If there is no effect of the vehicle on the drug concentration in the skin, the ratio $S'_L/S'_X = 1$ and the normalized functions $K_X\%$ and $(1/S_X)\%$ are similar. Any variations of the concentration in the skin, due to an enhancing effect of the vehicle, is exhibited by a ratio

$$S'_L/S'_X \neq 1 \qquad \text{and} \qquad K_X\% \neq (1/S_X)\%$$

With morphine hydrochloride (Figure 3),K% and (1/S)% are similar in all the vehicles used. In this case, the solvents don't act on the MHCl concentration in the skin.

In the other hand, with the basic morphine, we can observe significant difference between K% and (1/S)% (Figure 4). The (1/S)% values are higher than the K% values, indicating that $S'_L > S'_X$ .The solubility of M in the skin is higher with the pure Labrafac hydrophile than with any other system used here.

Those results prove that L can modifie the skin properties acting on the permeation of the basic morphine. For this reason, we assume that L modifies the lipidic regions of the stratum corneum, representing the preferential route of the lipophilic drug.

6. DISCUSSION ABOUT THE ENHANCING EFFECT ON THE MOBILITY OF THE DRUG IN THE SKIN

The second enhancing effect is the possibility for a vehicle to modifie the mobility of the drug in the skin. We analyzed the diffusion coefficient D to exhibit this effect.

Assuming that the solvent L is the only one to enhance the mobility of morphine (similarly to the concentration effect) , D should not varie for MHCl and should have the highest value for M in the L solvent. Regarding the large variations of D (table 2) for the both species of morphine, we can assume that the second solvent, T, interacts with L to modifie the skin structures. The mechanism of acting is probably an insertion of the Transcutol into the lipidic bilayers of the intercellular regions of the stratum corneum.

Consequently, (i) new hydrophilic pathways appear, enhancing the MHCl penetration,

(ii) a desorganization of the lipidic chains allows a good mobility of the basic morphine.

CONCLUSIONS

Basic morphine and morphine hydrochloride can penetrate the skin and the rate of permeation can be optimized with an appropriate vehicle. The binary solvents system used here is a good enhancer of these drugs; each solvent ,Transcutol and Labrafac hydrophile has a specific action in the enhancement of the permeation and they have a synergistic action on the flux of the percutaneaous absorption of morphine. Comparison of the parameters K%,(1/S)% and J , obtained from independant mesurements, is a good approach to evaluate and explain the mechanism of enhancement of such vehicle.

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