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Effect of solvents on rectal absorption rate of paracetamol in man: an in vitro approach

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Summary

In the case of poorly water-soluble drugs the solubility can be improved by the addition of certain solvents, such as propylene glycol, glycofurol or polyethylene glycols, resulting in an increase of the concentration gradient ΔC. However, one has to take into account at the same time a decrease of the polarity of the solvent–water vehicle, resulting in a decrease of the mass transport coefficient K.

The aim of this study was to investigate the influence of these competitive factors on the rectal absorption process in human volunteers, using paracetamol as a poorly soluble model drug. A simple diffusion apparatus was developed in order to measure in vitro diffusion flows of the test drug from various solvent–water mixtures.

We conclude that the product of K and ΔC can be seen as an indication to which extent the actual absorption phase will be influenced. Using an in vitro model as described in this study, a sort of optimum in the concentration of the particular solvent used can be established.

Introduction

Conflicting results have been obtained in attempts to improve the driving force for absorption using certain solvents in the case of rectal dosing with poorly

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dissolving drugs. Rectal absorption of indomethacin, diazepam or metronidazol was remarkably increased whereas no such an effect on rectal absorption was observed using drugs such as diflunisal and paracetamol (De Boer et al., 1982; Moolenaar et al., 1984; Vromans et al., 1984). Thus, more complete dissolution using such promoting agents does not necessarily result in a positive effect on absorption. In this respect Kakemi et al. (1965) could clearly demonstrate in experiments with rats that the absorption rate of several sulfonamides was reduced in the presence of various amounts of solvents such as propylene glycol or polyethylene glycols. This reduction was supposed to be caused by a decrease of liquid–vehicle partition which could be related to the dielectric constants of the bases used. From these studies it appeared that water-soluble vehicles tend to decrease the polarity of the aqueous phase which may result in a decrease of the partitioning into the direction of the lipoidal membrane. Similar conclusions were reported by others (Shangraw and Walking, 1971; Pagay et al., 1974; Stavchansky et al., 1979). They used the test drug, paracetamol, and observed a relationship between the bioavailability and the solubility of the drug in the vehicle, the latter being affected by the dielectric properties of the bases used.

It can be argued therefore that, by adding solvents to an aqueous formulation, one has to consider at least two phenomena at the same time: a decreased partition of the drug under study, a factor that may counteract the positive effect of the increased solubility on the driving force for absorption.

The aim of this study was to investigate the influence of these competitive factors on the absorption process in vivo more quantitatively, using various solvent–water vehicles and paracetamol as poorly soluble model drug. Assuming that partitioning of paracetamol from the solute state is the rate-limiting step in drug absorption, diffusion rates were measured in vitro and compared with the rectal absorption rates of paracetamol in human volunteers.

Experimental

Drugs and solvents

The test drug in this study was paracetamol (Ph.Eur.) which has a poor solubility characteristic (1.0 g in 70 ml water at 20°C). As solvents, propylene glycol, glycofurol (Merck) and polyethylene glycol 200, 600, 1000 and 6000 were used.

Solubility measurements

Saturation concentrations were determined at 37°C. An excess of the test drug was shaked with mixtures of the aqueous solvents (% w/w) during 24 h. After equilibrium the test tubes were centrifugated at 2000 rpm for 10 min. Samples of the supernatant were diluted and analyzed spectrophotometrically. Concentrations were determined from absorbance at 245 nm.

Diffusion measurements

An apparatus as is shown in Fig. 1 was designed to study the rate of diffusion of the test drug from the solvent water mixtures. The model consisted of two aqueous

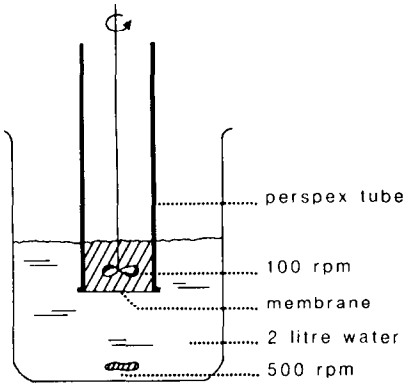

Fig. 1. In vitro apparatus for diffusion measurements.

phases separated by a membrane (Spectrapor, 12-14.000). The upper compartment was filled with solutions of the test drug using various concentrations of the aqueous solvent mixtures. The pH of this compartment was adjusted to 7.0 and its content was stirred by a 3-blade stirrer at a rate of 100 rpm. The lower compartment containing 2000 ml of distilled water (pH = 7.0) which was circulated with a speed of 500 rpm. Diffusion of the drug through the membrane was measured as an increase of concentration in the outside compartment with the aid of a Beckman spectrophotometer model 25. The results are mean values of four runs. The experiments were performed at 37°C.

With respect to the reproducibility and utility of the in vitro model presented, the following points are important: (1) although the solvents used may also diffuse through the membrane, conditions in the inside compartment only changed negligibly within the short time of sampling (up to 60 min); a constant diffusion rate was obtained indicating sink conditions and a constant concentration gradient ΔC; (2) it was experimentally established that during the short time of sampling the induced osmotic water flow from the outside phase to the inside phase did not disturb the diffusion flow; and (3) using methylcellulose as a reference it was observed that the increase of viscosity, as will occur after addition of the solvents used, did not contribute to the decrease in diffusion rate as found with the particular solvents added.

The value K (= mass transport coefficient, see Results and Discussion) of a particular drug dissolved in a solvent–water system can be determined as follows: various concentrations of the model drug are dissolved in the solvent–water compartment of the in vitro apparatus. According to Fick's law it was observed that a plot of the concentrations measured in the outside compartment ($\Delta C'$) against time (ΔT) did produce straight lines, resulting in a slope $\Delta C'/\Delta T$ which is a measure for the mass flow, ϕ (Fig. 2). A plot of the slopes of these lines against the various concentrations ΔC, as depicted in Fig. 2, results in the line $\phi = k \cdot \Delta C$. The slope k of the particular solvent–water–drug system is a measure for the mass transport

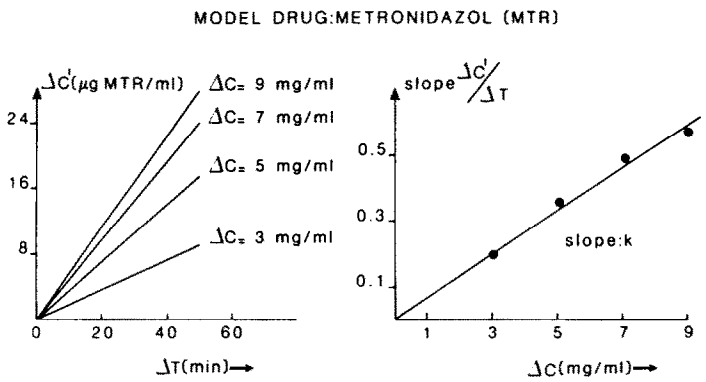

Fig. 2. Determination of the mass transport coefficient K of a drug in a particular solvent–water vehicle.

coefficient; in our study this coefficient is defined as K, where

$$K = \frac{k_{\text{solvent-water}}}{k_{\text{water}}}$$

Human experiments

Rectally administered aqueous solutions of paracetamol were prepared containing 1000 mg of paracetamol dissolved in 10 ml of water together with various concentrations of the solvents under study. The pH was adjusted to 7.0. Six healthy human volunteers, ranging in age from 23 to 35 years and in body weight from 54 to 72 kg, participated in the cross-over pilot studies. No drugs were taken for two weeks prior to or during the study. The experiments were initiated in the morning and the volunteers were asked to remain in a lying position. No discomfort following application of any rectal micro-enema was reported by the volunteers. Blood samples of 10 ml were taken using Venoject tubes (Terumo corporation) containing 15 mg sodium EDTA granules at 0, 15, 30, 60, 90 and 120 min after administration; plasma obtained by centrifugation was immediately frozen until analyzed by means of HPLC analysis (Moolenaar et al., 1979).

Pharmacokinetic analysis and calculations

In a previous study rectal absorption of paracetamol after dosing with aqueous micro-enemas was extensively studied in man (Moolenaar et al., 1979). It was concluded that rectal absorption of paracetamol was rather fast and fairly complete compared with oral dosing. Within 2 h after administration the rectal absorption process was accomplished. Since the aim of the present study was to compare in vitro diffusion flows with rectal absorption rates, the plasma concentration–time profiles were only followed during the first 2 h after rectal administration. c_{max} and t_{max} were used to characterize the rate of the absorption process. As a consequence the present data do not allow conclusions as to the value of the bioavailability. Statistical evaluations were done by Student's *t*-test ($P < 0.05$) for paired data.

Results and Discussion

In a previous study it has been established that the partition coefficients of sulfonamides are reduced with the increase of the concentrations solvent used (PEG 4000) to the water phase (Kakemi et al., 1965). It is important to realize, however, that partition coefficients are only measurements of an equilibrium situation in which there is, in contrast to the actual absorption phase, no net mass transport. In fact, measurement of the diffusion flow from the solvent–water system used might be a better reflection of the driving force for absorption. The diffusion flow can be represented by the simple equation: $\phi = K \cdot \Delta C$, where ϕ is the mass flow, ΔC is the concentration fall (driving force), while K is the mass transport coefficient. K can be considered to be the flow conductivity, a factor which may depend on several parameters: for instance, the viscosity, the diffusion constant and the partition coefficient. Using a fixed driving force, ΔC, mass flow, ϕ, and mass transport coefficient, K, are changed equally. As can be seen from Fig. 3 the K value for paracetamol is remarkably decreased depending on the concentration of the solvent (PEG 6000) used. Moreover, it appears that, for instance, the addition of 10% PEG 6000 has no substantial influence on the solubility characteristics of paracetamol, whereas on the other hand the K value is dramatically reduced.

The foregoing experiments clearly demonstrate that in the case of poorly water-soluble drugs, by adding solvents to an aqueous drug system in attempts to improve the solubility profile of a particular drug, one has to consider at the same time a decreased diffusion flow of the drug under study.

In order to study this phenomenon in vivo, paracetamol was rectally applied to human volunteers, using various solvent–water vehicles.

Paracetamol is a slowly-dissolving drug in water with a saturation concentration of 24 mg/ml at 37°C (Table 1). Therefore it is clear that after rectal dosing with

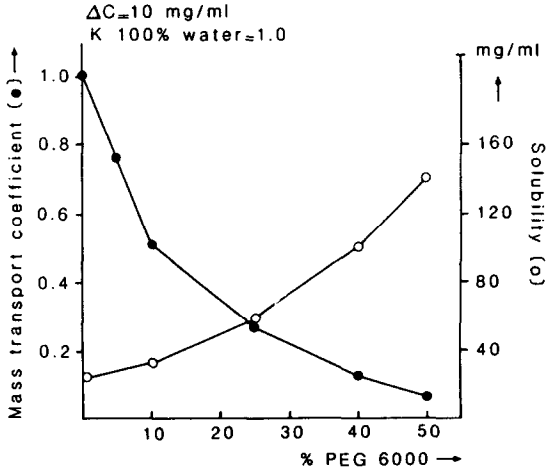

Fig. 3. The influence of the concentration PEG 6000 used on the solubility and the mass transport coefficient K or paracetamol.

TABLE 1

SATURATION CONCENTRATIONS, C_{sat}, DRIVING FORCE, ΔC, MASS TRANSPORT COEFFICIENTS, K, AND DIFFUSION FLOWS, ϕ_{vitro}, OF PARACETAMOL, DISSOLVED IN VARIOUS CONCENTRATIONS SOLVENT–WATER VEHICLES (% w/w) AT 37°C, USING THE IN VITRO DIFFUSION MODEL AS DEPICTED IN FIG. 1

	C_{sat} (mg/ml)	ΔC (mg/ml) *	K **	ϕ_{vitro}
A:				
water	24	24	1.00	24
glycofurol 50%	214	100	0.15	15
propylene glycol 50%	108	100	0.20	20
PEG 600 50%	121	100	0.10	10
B:				
glycofurol 30%	118	100	0.38	38
PEG 200 25%	46	46	0.40	18
PEG 200 50%	114	100	0.16	16

* The maximal driving force, ΔC, is 100 mg/ml; namely, 1000 mg paracetamol added to a 10 ml micro-enema.

** The value K is expressed as $\frac{k_{solvent\text{-}water}}{k_{water}}$.

paracetamol (1000 mg) in pure water (10 ml) the drug will be available as an aqueous suspension enema. Addition of 50% glycofurol, propylene glycol or polyethylene glycol 600 is sufficient to dissolve the drug completely, resulting in the maximal concentration ΔC of 100 mg/ml vehicle. However, ϕ_{vitro} values (Table 1A) may indicate that an increase of the driving force for absorption is not likely to

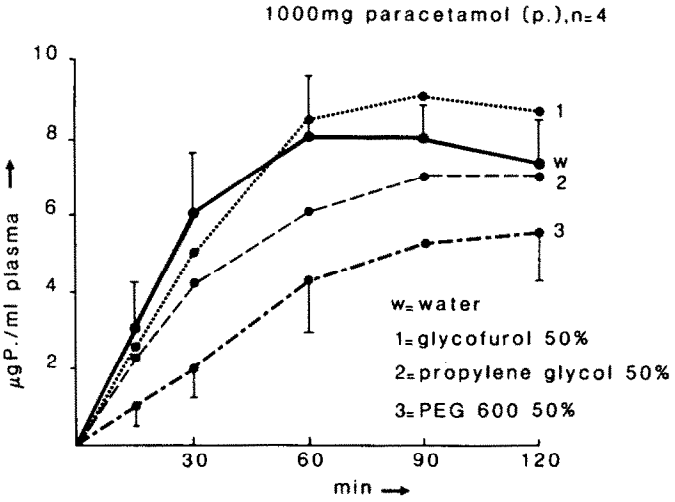

Fig. 4. Plasma absorption profiles of paracetamol after rectal dosing with 1000 mg paracetamol, suspended or dissolved in 10 ml micro-enemas, containing various solvents, to human volunteers.

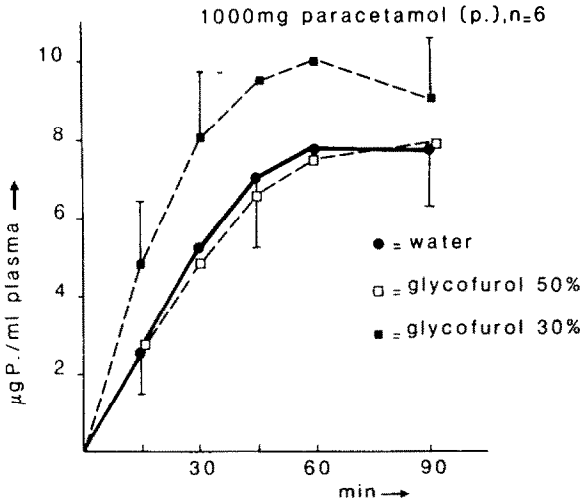

Fig. 5. Plasma absorption profiles of paracetamol after rectal dosing with 1000 mg paracetamol, suspended or dissolved in 10 ml micro-enemas, containing pure water, 30% glycofurol and 50% glycofurol, to human volunteers.

occur if paracetamol is rectally applied in solvent systems as used in Table 1A: although the C_{sat} increases remarkably, the K values change dramatically at the same time, resulting in a complete leveling effect on the ϕ_{vitro} values. From Fig. 4 it appears that indeed there is no improvement of the absorption rate. On the contrary, there is rather a tendency of a decrease in C_{max} and an increase of t_{max}, being significant in the case of PEG 600 ($P < 0.05$).

From Table 1A it can also be learned that especially in the case of glycofurol more solvent has been added than is strictly necessary to solute the total amount of paracetamol used (1000 mg). Table 1B indicates that better results may be expected with a lower concentration of glycofurol: 30% resulted in a saturation concentration just high enough to dissolve all the drug used, whereas the decrease of the K value was less dramatic, as compared with the 50% solvent–water system. The absorption profile depicted in Fig. 5 indeed indicates that in the case of the 30% glycofurol micro-enema the absorption rate of paracetamol is substantially increased compared with the 50% solution: significantly higher plasma levels during the first 60 min after dosing were produced ($P < 0.05$).

Another point of interest is the fact that in the case of PEG 200 the diffusion flow of paracetamol is unfavourably influenced, independent of the concentration solvent used (Table 1B). Support for this finding can be found in the results from the rectal experiments performed with 1000 mg paracetamol in 10 ml of both concentrations PEG 200 (Fig. 6). Significantly lower plasma levels of paracetamol were produced during the first 60 min ($P < 0.05$). Interestingly, there seems to be no concentration of PEG 200 which may give rise to a faster absorption rate than the pure aqueous suspension of paracetamol. In other words, if at any concentration of a particular solvent used, the effect on the driving force ΔC is totally nullified by the decrease of

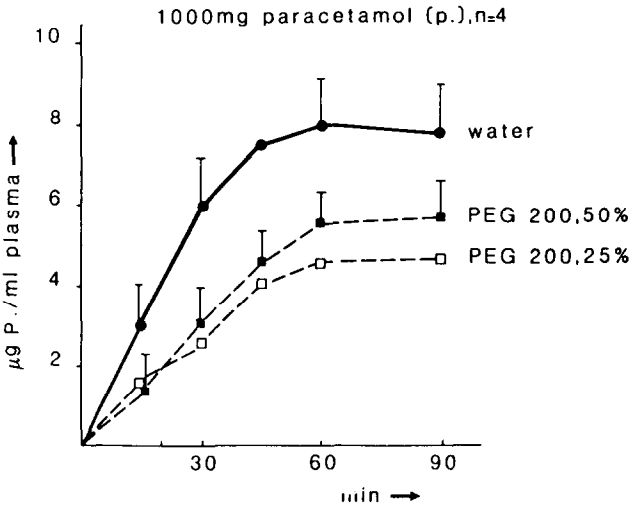

Fig. 6. Plasma absorption profiles of paracetamol after rectal dosing with 1000 mg paracetamol, suspended or dissolved in 10 ml micro-enemas, containing pure water, 25% PEG 200 and 50% PEG 200, to human volunteers.

the mass transport coefficient K, the addition of such a solvent is not rational at all.

It is important to note that besides an influence on the solubility and the polarity, it might be quite well possible that the solvents used may cause additional effects, such as changes in viscosity, osmotic pressure (= tissue hydration) or blood flow, which may result in an influence on the actual absorption process. In addition, Chadwick et al. (1977) reported a progressive increase in intestinal permeability for polyethylene glycols with decreasing molecular weight (range 200–600) in the colon. It is likely therefore that the low molecular weight solvents such as glycofurol, propylene glycol and polyethylene glycol 200 may be absorbed to a certain extent, thereby changing the composition of the vehicle administered during the absorption process. However, in this study these potential influences on the absorption process are left out of consideration and consequently the product of K and ΔC can only be seen as a rough indication to which extent the actual absorption phase will be influenced.

In conclusion, the question as to whether the rate of rectal absorption of a slightly soluble drug may be improved by the addition of certain solvents is closely related to the amount of decrease of the mass transport coefficient, that will occur simultaneously. Using an in vitro model as described in this study, a sort of optimum in the concentration of the particular solvent can be established.

In a previous study we concluded that hepatic first-pass metabolism of paracetamol was strongly dependent upon the rate of uptake of paracetamol from the rectum (Moolenaar et al., 1979). Therefore it is not to be excluded that the addition of solvents may also have a pronounced influence on the rectal bioavailability of paracetamol.

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