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Letter to the Editor

Classification of percutaneous penetration enhancers: a conceptional diagram

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The stratum corneum has long been considered a major barrier to penetration of topically applied chemicals (Marzulli 1962; Vinson et al 1965). Many compounds have low permeabilities through skin. Consequently, some transdermal drug delivery systems have utilized enhancers to accelerate drug permeability (Barry 1983). Percutaneous delivery enhancers may offer a means of increasing drug permeation; at present, a cohesive theoretical basis for choosing and formulating such agents is incomplete.

If quantitative structure activity relationships could be developed for percutaneous enhancers, it would facilitate selection of chemicals to be screened as putative enhancers. We propose a classification of chemicals using a conceptional diagram to estimate their potential as enhancers. This diagram was originally developed to predict the properties of organic compounds (Fujita 1954) and has been applied in diverse research (Kouda 1984); e.g. the level of bioaccumulation of organic compounds in fish can be predicted (Matsuo 1979, 1980a, b, 1981).

Fujita (1954) determined an organic and inorganic value for each compound of interest depending on its structural components. These values are based on boiling point. He assumed the organic properties depend on carbon atoms and inorganic character depends on substituted groups. An organic value is derived by summing up the number of the carbon atoms, one carbon atom having a value of 20. Other organic and inorganic values were calculated using Fujita's table (Fujita 1954; Kouda 1984). We calculated the organic and inorganic values for chemicals reported to enhance percutaneous penetration (Table 1). Fig. 1 depicts the location of these cutaneous enhancers, when the organic value is plotted against the inorganic value.

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The enhancers are located in two different areas on the diagram. Area I includes ethanol, propylene glycol, *N*-methyl pyrrolidone, and dimethyl sulfoxide and area II includes 1-dodecylazacycloheptan-2-one (Table 1, no. 14), oleic acid, and lauryl alcohol. The different locations suggest that the chemicals in the two groups may have different physicochemical properties.

Table 1. Organic and inorganic values of percutaneous penetration enhancers.

Enhancer	Organic	Inorganic
1. Water	0	100
2. Ethanol (a)	40	100
3. Propylene glycol (a)	60	200
4. *N,N*-Dimethyl acetamide (a)	80	200
5. *N,N*-Dimethyl foramide (a)	60	200
6. 2-pyrrolidone (a)	80	145
7. *N*-Methyl pyrrolidone (a)	100	145
8. 5-Methyl-2-pyrrolidone (a)	100	145
9. 1,5-Dimethyl-2-pyrrolidone (a)	120	145
10. 1-ethyl-2-pyrrolidone (a)	120	145
11. 2-Pyrrolidone-5-carboxylic acid (a)	100	295
12. Dimethyl sulfoxide (b)	80	140
13. Oleic acid (c)	360	152
14. 1-Dodecylazacycloheptan-2-one (d)	360	145
15. *N,N*-Dimethyl-m-toluamide (e)	240	215
16. n-Decyl methyl sulfoxide (f)	260	140
17. Lauryl alcohol (g)	240	100
18. Lauric acid (g)	240	150
19. Isopropyl myristate	330	60

Organic and inorganic values of enhancers were calculated from Fujita's table (Fujita 1954; Kouda 1984). Enhancers are from: a (Barry 1983), b (Chandrasekaran et al 1977), c (Cooper 1984), d (Stoughton 1982), e (Windheuser et al 1982), f (Cooper 1982), g (Aungst et al 1986).

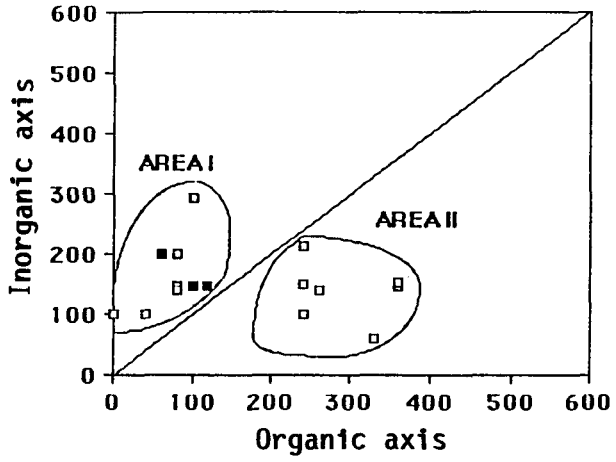

FIG. 1. Location of percutaneous penetration enhancers on an organic diagram. Closed squares indicate two enhancers. Enhancers are shown in Table 1.

Cooper (1984) showed that the combination of propylene glycol and oleic acid increased the penetration of salicylic acid compared with each vehicle alone. Wotton et al (1985) showed that the choice of vehicle is an important factor, e.g. propylene glycol promoted the effect of 1-dodecylazacycloheptan-2-one on the cutaneous permeation of metronidazole. These data show that the combination of vehicles is more effective than vehicle alone, and in the diagram, the individual enhancers are located in two distinct areas. The combination of vehicles from these different areas apparently promote absorption better than one vehicle alone. In general, chemicals found in area I are efficient solvents. We tentatively classify 2-pyrrolidone, dimethyl sulfoxide, or propylene glycol as solvents (Area I) rather than enhancers and this combination of vehicles (solvent and enhancer) a binary system.

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