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EVALUATION OF THE USEFULNESS OF CLOUD POINT ELEVATION TO PREDICT TRANSDERMAL DELIVERY ENHANCERS

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ABSTRACT

The use of cloud point temperature elevation to predict transdermal delivery enhancers was evaluated by conducting cloud point experiments on penetration enhancers of known ability. The ability of a compound to elevate the cloud point temperature could not be related to penetration enhancement neither in ranking nor magnitude. After comparison of the molecular interactions that cause cloud point elevation and transdermal delivery enhancement, no correlation between these two mechanisms could be established.

INTRODUCTION

The successful manufacturing and marketing of transdermal drug delivery systems has caused increased research concerned with finding compounds that enhance the rate that a drug penetrates intact skin. [1,2] Early work on penetration enhancers such as dimethyl sulfoxide [3,4] demonstrated the necessity of an enhancer to be non-irritating to the skin and preferably to be effective at relatively low concentrations. In vitro studies using either cadaver or animal skin are usually required to establish the ability of a material to enhance percutaneous penetration. The development of an alternative method for rapidly screening single compounds or complete formulations for their enhancing abilities would dramatically reduce the time required to optimize a topical drug delivery formulation.

In a recent European Patent Application [5], a cloud point elevation method was described for screening nonelectrolytes as transdermal activity enhancers. In this application, an activity enhancer was considered any compound whose presence improved delivery of an amphiphillic drug (log octanol/water partition coefficient between 0.5 and 3.5) to the skin by effectively increasing the partition of the drug into the skin. In their studies, the inventors observed that the compounds that functioned as activity enhancers were all capable of substantially increasing the cloud point temperature of a nonionic surfactant. The

criteria for a non-electrolyte to be considered an activity enhancer was that at a concentration of 5% by weight it could increase the cloud point temperature of a 0.025 M aqueous solution of polyoxyethylene (8) nonylphenyl ether by at least 10°C. In the patent application, the inventors did not speculate how a non-electrolyte's ability to elevate the cloud point temperature related to increasing partitioning of a drug into the skin.

To evaluate the usefulness of this method for screening either single component penetration enhancers or formulations containing penetration enhancers, requires an understanding of the mechanisms involved in both cloud point elevation and penetration through the stratum corneum. Comparison of a polyoxyethylene alcohol nonionic surfactant system to polyoxyethylene (8) nonylphenyl ether was completed to determine if the ranking of enhancing ability is specific to a surfactant or general for nonionic surfactant systems. Finally, the ability of relating the magnitude of cloud point elevation to the magnitude of enhanced transdermal drug delivery was evaluated. From these studies, a critical evaluation of this enhancer screening method could be completed.

PROCEDURES

Cloud points were determined using an apparatus as shown in Figure 1. Multiple determinations for each of the mixtures showed the cloud points to be reproducible within $\pm$ 0.5°C. Tergitol

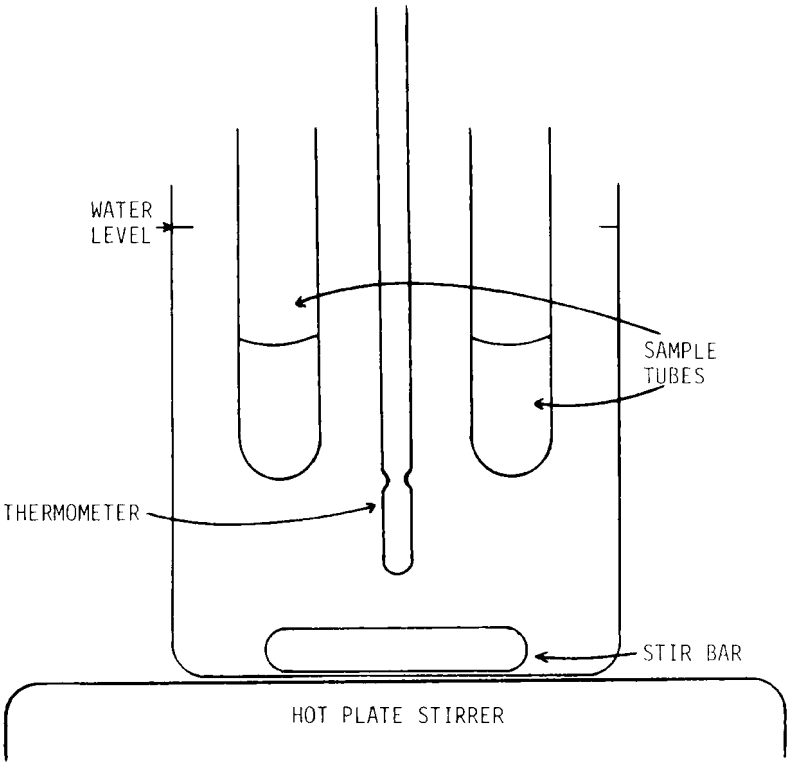

Figure 1. Schematic of Cloud Point Temperature Appartus.

15-S-7 was obtained from Union Carbide, and Igepal CO-610 (polyoxyethylene (8) nonylphenyl ether) was obtained from GAF Corporation. The alcohols were highest quality available from J.T. Baker Chemical. Acetone, tetrahydrofuran, 1,4 dioxane, and cyclohexane were chromatography grade solvents from American Burdick and Jackson Company. Azone was technical grade, while the diols and other nonelectrolytes were highest quality available from Aldrich Chemical.

TABLE I

The Nonionic Surfactant Systems With Cloud Point Temperatures For Added Non-electrolytes

Non-electrolyte Added (5% w/w)	Cloud Point of Igepal CO-610 (1.0% aqueous solution)	Cloud Point of Tergitol 15-S-7 (1.0% aqueous solution)
None (Control)	24.5	38.0
1-butanol	38.8	26.0
1-hexanol	5.0	5.0
1-octanol	5.0	5.0
1-decanol	5.0	5.0
Propylene Glycol	28.0	42.5
1,3 Propanediol	28.4	41.2
1,4 butanediol	32.3	44.3
1,5 Pentanediol	42.0	49.0
1,2,6 Trihydroxyhexane	30.3	42.4
1,7 Heptanediol	57.5	56.0
Azone	5.0	5.0
Oleyl Alcohol	5.0	5.0
Ethyl Caprate	5.0	5.0
Dibutyl Phathalate	5.0	5.0
Triethanolamine	25.8	39.5
Tetrahydrofuran	33.5	44.0
Acetone	34.4	44.5

RESULTS

The effect of a 5% nonelectrolyte solution on the cloud point temperature of a 1% Tergitol 15-S-7 and 1% Igepal CO-610 aqueous solutions is given in Table I. The effect of a given non-electrolyte is significantly different for the different nonionic surfactants. Not only is the magnitude of the effect different,

TABLE II

Cloud Point Temperatures for Nonionic Surfactant Systems With Added Non-electrolyte Mixtures

Non-electrolyte Added (5% of Mixture w/w)	Cloud Point of Igepal CO-610 (1.0% aqueous solution)	Cloud Point of Tergitol 15-S-7 (1.0% aqueous solution)
None (Control)	24.5	38.0
Butanol/Propylene Glycol (Mole Ratio 0.25)	27.8	42.4
Hexanol/Propylene Glycol (Mole Ratio 0.25)	5.0	7.0
Octanol/Propylene Glycol (Mole Ratio 0.25)	5.0	5.0
Decanol/Propylene Glycol (Mole Ratio 0.25)	5.0	5.0

but, also the ranking. The most dramatic example being 1-butanol which elevates the Igepal CO-610 cloud point 14.3°C but decreases the Tergitol 15-S-7 cloud point 12.0°C.

Table II gives cloud point data for a series of binary enhancing systems that were investigated by Cooper [6] using in vitro transdermal delivery methods. For this series the delivery of salicylic acid (log P = 2.24) had the penetration ranking decanol-propylene glycol (greatest), hexanol-propylene glycol, octanol-propylene glycol, butanol-propylene glycol, propylene glycol (least). This ranking is opposite of the cloud point elevating ability of the enhancer systems.

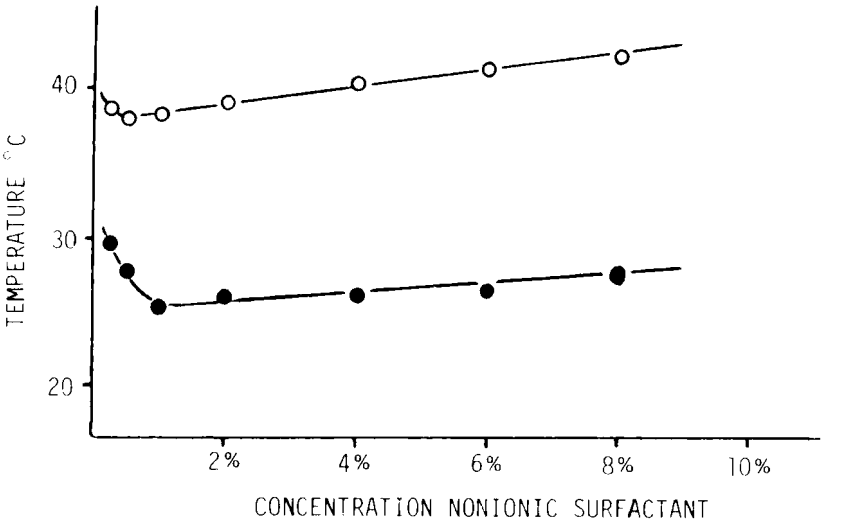

Figure 2. Cloud Temperature Diagrams for the Commercial Nonionic Surfactant Systems Tergitol 15-S-7 (○), and Igepal CO-610 (●).

The effect on the cloud point of varying the surfactant concentration is shown in Figure 2. It is seen that Tergitol 15-S-7 and Igepal CO-610 behave similarily to purer nonionic systems [7].

DISCUSSION

The cloud point phenomenon of a polyoxyethylene type nonionic surfactant can be attributed to the effect increasing temperature has on hydration of the nonionic headgroup. The water hydrogen bonded to the ether oxygens apparently decreases as temperature increases. Since this hydration of the ether oxygens is the primary interaction keeping the nonionic surfactant in solution, the micellar weight of the polyoxyethylene-type non-

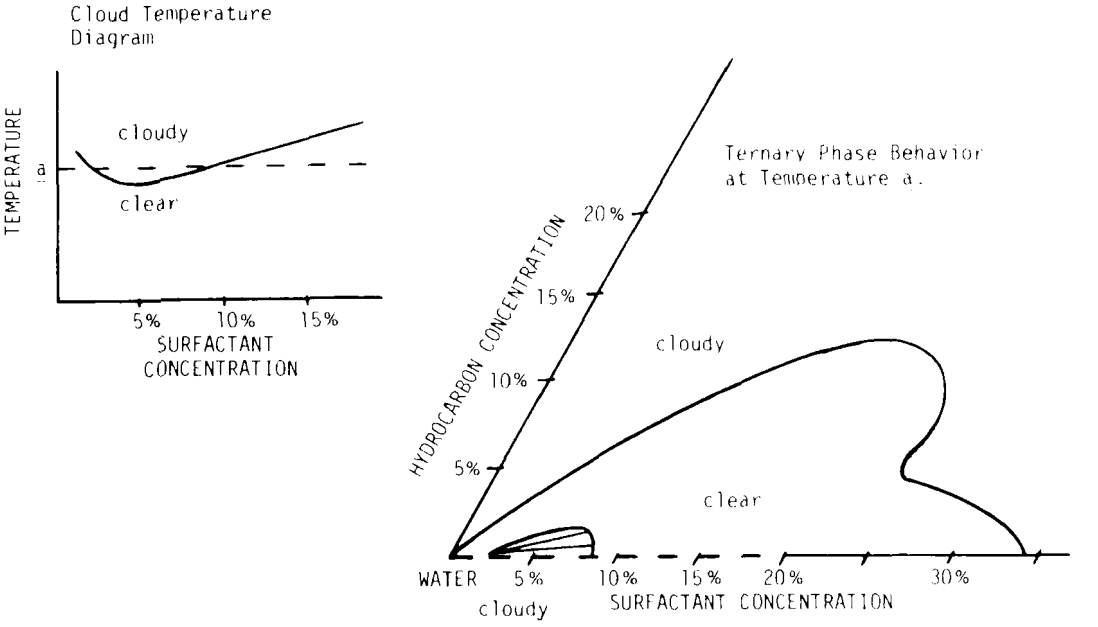

Figure 3. Relationship Between a Cloud Temperature Diagram for a Nonionic Surfactant System, and the Corresponding Idealized Ternary Phase Behavior when a Hydrocarbon Nonelectrolyte is added.

ionic surfactant solutions increases with increasing temperature i.e., decreasing hydration. This increase in size ultimately causes the solution to become turbid (cloud point temperature) followed by separation into two phases.

Figure 2 shows that the cloud point behavior of these commercial surfactants is very similar to the behavior of purer surfactants studied in the literature [7]. Such plots give considerable insight into the association properties of these nonionic systems. For an idealized system, cloud point temperature plotted against surfactant concentration (Figure 3), the corresponding water/hydrocarbon/nonionic surfactant ternary phase

behavior can be estimated. As seen, the minimum in the cloud point temperature versus surfactant concentration curve corresponds to a two phase region within the normal micelle area on the diagram. As temperature is increased, the ternary phase behavior will change as outlined by Friberg [8]. For added non-electrolytes that are structurally similar to hydrocarbons, the cloud point temperature elevating or depressing capabilities of the added non-electrolyte can be understood by examining these ternary diagrams. Cloudiness results when the addition of 5% non-electrolyte causes the final composition to fall outside the micellar single phase region. If the added non-electrolyte is more soluble in the micellar region, or if it alters the phase behavior by changing the phase transition temperatures of the surfactant, then the final composition will be a clear solution. Similar arguments hold for when the alcohol and diol activity enhancers are the added non-electrolyte.

Transdermal penetration enhancers are substances that either reversibly or irreversibly alter the barrier function (the stratum corneum) of the skin in such a way that drugs or other topically applied substances can more readily pass into the viable epidermis. Molecularly, the enhancer is probably either disrupting the protein structures of the keratin squames of the stratum corneum, or disrupting the hydrated bilayer structured lipids of the stratum corneum intercellular regions. Alteration of the bilayer structured lipids is a likely explanation of how

propylene glycol-alcohol binary enhancer systems function. The propylene glycol molecule can disrupt the interfacial interactions that are required for maintaining a bilayer structure. Once the bilayer is disarranged, the alcohol can readily align within the bilayer, causing it to remain more fluid even after the propylene glycol is removed systemically or by evaporation. Considering this, the effect of an enhancer on a model epidermal lipid [9] might be a more accurate in vitro predictive test.

With this understanding of the mechanisms involved in both cloud point elevation and penetration through the stratum corneum, it is not apparent how cloud point elevation could indicate which non-electrolyte will best disrupt the structures of the stratum corneum.

Comparisons of a polyoxyethylene alcohol nonionic surfactant to a polyoxyethylene alkylphenol nonionic surfactant showed that neither the ranking nor the magnitude of cloud point temperature change was the same for these two types of nonionic surfactants. Therefore, any conclusions based upon results for a particular surfactant type appear to be specific for that surfactant and cannot be compared with results for other surfactant systems.

Finally, the ability of cloud point elevation to rank the degree that a mixture can enhance penetration of a drug was not confirmed by in vitro transdermal studies. In fact, for the system examined here, cloud point elevation predicted a ranking virtually opposite that found from in vitro experiments.

In conclusion, for the systems studied here, cloud point elevation does not reflect a non-electrolyte mixture's ability to enhance transdermal delivery. Neither an experimental nor theoretical link between the two phenomena is apparent. Further, any correlation between cloud point elevation and transdermal activity enhancing for a non-electrolyte should be considered specific for a single nonionic surfactant, namely polyoxyethylene (3) nonylphenyl ether.

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