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THE DETERMINATION OF THE ENTRAPMENT EFFICIENCY FOR A MOLECULAR DISPERSION SYSTEM

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ABSTRACT

The entrapment of d-propoxyphene in ethylcellulose pseudolatex systems was studied. Heat of fusion measurements were used to determine the extent of molecular scale entrapment. When $\Delta H_f = 0$, the drug was assumed to be entrapped on a molecular level while ΔH_f values greater than zero indicated the presence of crystal structure. Zeta potential measurements were also used to indicate the point of maximum entrapment efficiency. A good correlation was obtained between zeta potential and heat of fusion measurements.

INTRODUCTION

Molecular dispersions of a variety of types, have increasingly been employed for entrapment of drugs. In some instances, the goal of molecular dispersion is the enhancement of the drug's bioavailability. For example, a solid solution of griseofulvin in a high molecular weight polyethylene glycol has recently been marketed with enhanced bioavailability. Other molecular dispersions are designed to produce prolonged drug release effects. Regardless of the form of the molecular dispersion, or its pharmaceutical purpose, the performance of the product may be expected to be related to the completeness of the dispersion, i.e., the presence or amount of crystalline drug and its ratio to moleculary dispersed drug. Improved physical-analytical methods are needed to characterize the entrapment ratios (molecularly dispersed to crystalline drug) for quality control purposes. Additionally, such methods are needed for research and development purposes to study new molecular dispersion systems utilizing new drugs in established systems; to develop new or improved systems (utilizing FDA approved polymers for example), or to evaluate the best processing methods for the maximum molecular dispersion.

METHODS

Latex Preparation - Ethylcellulose, premium grade, (10 cps) was prepared as a pseudolatex as previously described (8). A model drug, propoxyphene (Eli Lilly Co.) was entrapped from an organic solvent by the molecular entrapment procedure reported previously (1-7).

Determination of Zeta potential - One-half gram of each pseudolatex was diluted in 50 ml of distilled water and the zeta potential was determined using a Zeta-Meter at 50 V at $22^{o}C \pm 0.5$. The counting scale used was 8X and the total magnification was 120X. For all samples the specific conductance was under 20 μmhos/cm. The zeta potentials were calculated from the electrophoretic mobilities using the Helmholtz-Smuluchoski equation[9]. In all cases the particle analyzed was negatively charged. At least three replicates were made for each pseudolatex.

Measurement of the transition energy, ΔH_f, of the d-propoxyphene in the dried latex - Pseudolaticies containing various amounts of d-propoxyphene were evaporated to dryness in a rotary evaporator at 45^{o}. The water remaining was less than 1% as determined by a moisture balance. The temperature of transition[10] was determined with a differential scanning calorimeter calibrated with Indium. The measurement of the area under the curve provided the direct base for the calculation of the energy needed for the transition, ΔH_f. The determination of the area was done by measuring the weight of the endothermic peaks of the latex and subsequent comparison with the standard Indium peak. The heat of transition was calculated by the following general equation[11]:

$$\Delta H_{f\ sa} = \frac{\Delta H_{f\ st} \cdot W_{st} \cdot A_{sa}}{W_{sa} \cdot A_{st}}$$

where

$\Delta H_{f\ sa}$ = Transition energy of sample

$\Delta H_{f\ st}$ = Transition energy of standard

W_{st} = Weight of standard

W_{sa} = Weight of sample

A_{st} = Area of peak of standard

A_{sa} = Area of peak of sample

At least six replicates were made for each d-propoxyphene/ethylcellulose pseudolatex.

X-Ray Diffraction Study of Polymer Containing Drug - X-ray diffraction patterns were obtained with copper K-2 radiation generated at 40000 V using a General Electric XRD-5 source and the General Electric powder diffraction camera, 143.2 mm diameter. Half millimeter glass capillary tubes were used to rotate the sample in the beam over a 24 hour period.

pH Measurement - All pH determinations were made on a pH meter (Sargent-Welch model NX) equipped with a glass electrode (Sargent-Welch type 5 - 300F2 - 15) at 22°C.

RESULTS AND DISCUSSION

Molecular scale entrapment implies that the crystal structure of the drug has been eliminated during the entrapment process. It is obvious that loss of crystal structure will always occur when a drug is subdivided to a molecular level. The heat of fusion, then, should change from a finite value for the normal crystalline solid (or for that matter an amorphous solid), to zero when the solid is dispersed on a molecular level. In the latter case there is no bond energy to be overcome as this was accomplished during the entrapment process, usually by solution of the drug. Therefore, the magnitude of ΔH_f for entrapped drug should permit a determination of the extent of molecular scale drug entrapment, i.e., if $\Delta H_f=0$, the drug is molecularly entrapped while a ΔH_f 0 indicates crystal structure remains. Figure 1 shows the relationship between ΔH_f for d-propoxyphene in ethylcellulose and its concentration in ethylcellulose. It can be seen that ΔH_f approaches zero when the concentration of d-propoxyphene is approximately 21%. This would indicate that at concentrations up to 21%, the d-propoxyphene is entrapped on a molecular level. Beyond this level the polymer, ethylcellulose, and/or the process is no longer capable of efficiently entrapping the d-propoxyphene on a molecular scale. The excess d-propoxyphene remains as a crystalline solid which is evidenced by a $\Delta H_f>0$ for values greater than 21%.

An interesting method for corroborating the above analysis is the measurement of the zeta potential of laticies containing various concentrations of d-propoxyphene. d-Propoxyphene is a weak base with a pK_a of 9.25. At pH's below the pk_a it will then be positively charged and neutral at pH's above the pK_a. For the following discussion it is important to remember from the Experimental section that each of the laticies contains sodium lauryl sulfate. The final sodium lauryl sulfate concentration after solvent evaporation was 1%.

Consider the particles in a pH 8.7 environment depicted in Figure 2. As the concentration of positively charged d-propoxyphene increases, the concentration of lauryl sulfate counter ions at the surface of the latex particle will increase. The surface

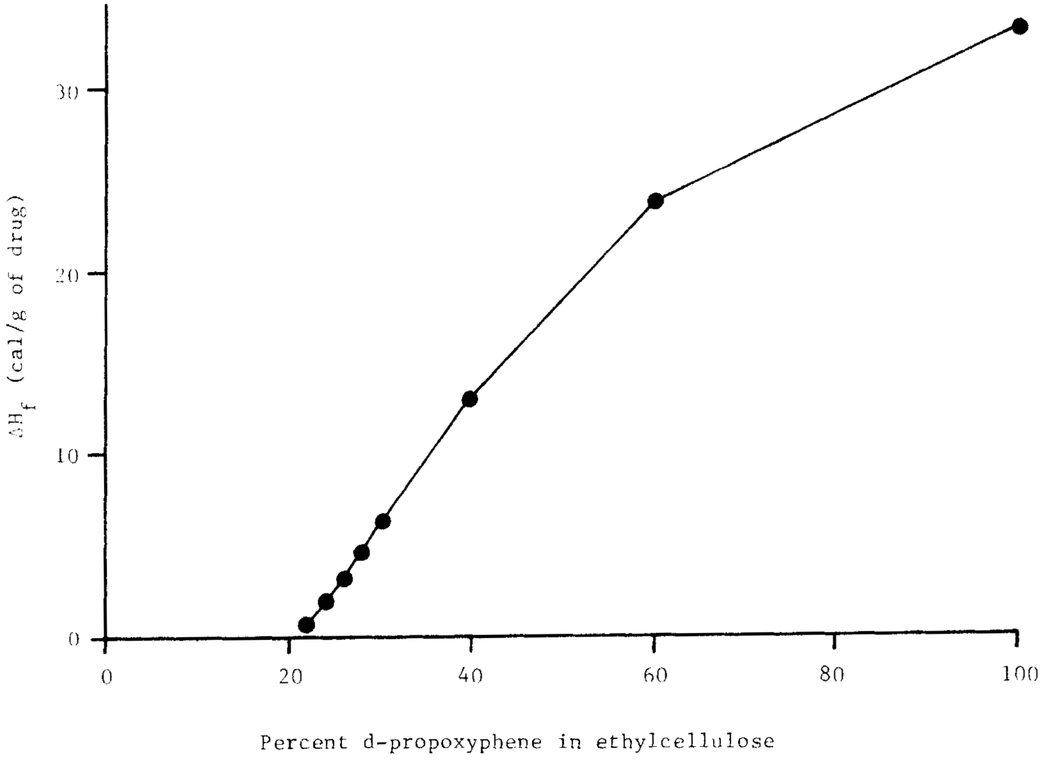

FIGURE 1

Heat of fusion, ΔH_f, of d-propoxyphene in ethylcellulose as influenced by the Drug/Polymer ratio.

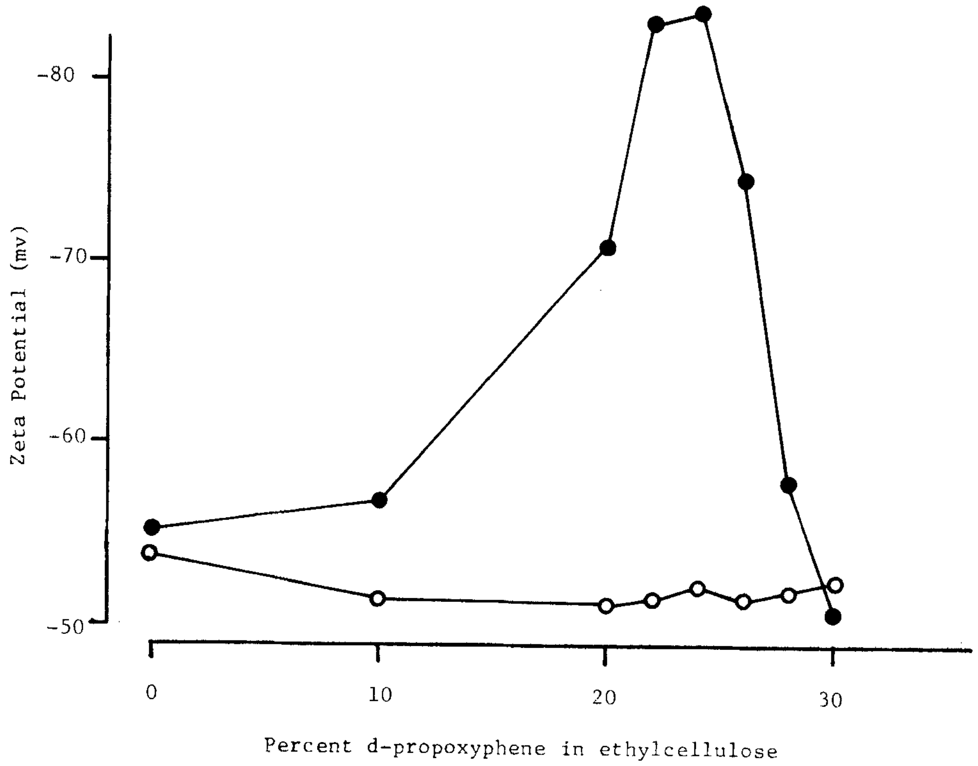

FIGURE 2

Zeta potential of d-propoxyphene-ethycellulose pseudlaticies as influenced by the drug/polymer ratio. Key: -●-, pH 8.7; -o-, pH 10.

concentration of the lauryl sulfate ions will reach a maximum when the entrapped d-propoxyphene reaches a maximum, i.e. 21%. As the concentration of d-propoxyphene is increased further the excess concentration above 21% goes into the bulk solution and begins to draw lauryl sulfate ions away from the polymer surface.

If Figure 2 is representative of the entrapment of d-propoxyphene, the zeta potential of the latex should become more negative up to the point of maximum entrapment, and then decrease with further increases in the d-propoxyphene concentration. This phenomena is shown in Figure 2 with the line for pH 8.7 showing the behavior described above. The point of maximum zeta potential, corresponding to maximum molecular scale entrapment, lies between 22% and 24%. This corresponds very well with the 21% obtained from ΔH_f data.

At pH's above the pK_a, the d-propoxyphene molecules are neutral and the zeta potential of the latex should be independent of the d-propoxyphene concentration. This is confirmed by zeta potentials determined at pH 10 as shown in Figure 2.

X-ray studies also confirm the above data. At 20% d-propoxyphene added, the powder diffraction study showed no evidence of crystallinity; however, crystallinity is present at the 40% level.

CONCLUSION

The determination of ΔH_f is an excellent method for determining the maximum entrapment efficiency for d-propoxyphene. The ΔH_f values remain zero as long as the polymer is able to entrap the added drug; once the polymers maximum capacity has been reach-ed, however, non-zero values of ΔH_f are obtained. This type of analysis is most likely applicable to other drugs as well.

For a charged drug, zeta potential measurement also indicates the point of maximum entrapment efficiency. It should be noted that an added benefit accrues from the entrapment of positively charged d-propoxyphene as the point of maximum entrapment at the molecular level also produces maximum suspension stability. Additional studies involving other drugs are presently in progress.

REFERENCES

1. G. S. Banker and H. Goodman, U.S. pat., 3.629.392 (December 21, 1971)
2. G. S. Banker, U.S. pat., 3.608.063 (September 21, 1971)
3. H. Goodman and G. S. Banker, J. Pharm. Sci., 59, 1131 (1970)
4. C. T. Rhodes, K. Wai, and G. S. Banker, J. Pharm. Sci., 59, 1578 (1970)
5. Ibid., 59, 1581 (1970)
6. J. C. Boylan and G. S. Banker, J. Pharm. Sci., 62, 1177 (1973)
7. J. B. Larson and G. S. Banker, J. Pharm. Sci., 65, 838 (1976)
8. Advances in Emulsion Polymerisation and Latex Technology, 6th annual short course, Lehigh University, PA (1975)
9. Zeta - Meter Manual, 2nd edition (1968)
10. H. H. Willard, L. L. Merritt Jr., and J. A. Dean, Instrumental Methods of Analysis, 5th ed., D. Van Nostrand Co., New York, p. 469 (1974)
11. Instructions DSC, 990 - 9556, Perkin - Elmer (1970)