

of Compounds Ia–Id were prepared by bubbling methyl bromide through a solution of the appropriate 5-phenylnicotinamide in ethyl acetate for 3–6 hr. The quaternary salts were not recrystallized prior to use. The methobromides separated very cleanly and in high yields from the reaction medium (Table I). They were filtered, washed thoroughly with cold ethyl acetate, air dried, and converted directly to the corresponding 1-methyl-5-phenylnipecotamide by the general procedure described here.

A solution of 1.5 g. of the methobromide in 75 ml. of ethanol containing 75 mg. of platinum oxide was hydrogenated at room temperature for 3–6 hr. at an initial pressure of 0.7 kg./cm.². The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in methylene chloride, washed with 2 N NaOH and water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was crystallized from the appropriate solvent or dissolved in ether, treated with anhydrous hydrogen chloride to yield the corresponding hydrochloride, and then recrystallized. The recrystallization solvents, melting points, and yields are listed in Table II, and elemental analysis data are given in Table IV.

REFERENCES

- (1) E. Campaigne and D. R. Knapp, *J. Pharm. Sci.*, **60**, 809 (1971).
- (2) S. Kang and J. P. Green, *Proc. Nat. Acad. Sci. USA*, **67**, 62(1970).

- (3) F. N. Johnson, I. E. Ary, D. G. Teiger, and R. J. Kassel, *J. Med. Chem.*, **16**, 532(1973).
- (4) M. Julia, H. Pinhas, and J. Igolen, *Bull. Soc. Chim. Fr.*, **7**, 2387(1966).
- (5) S. Irwin, *Psychopharmacologia*, **13**, 222(1968).
- (6) W. J. Lennox, U. S. Clearinghouse Fed. Sci. Tech. Inform., AD 1969, No. 852897; through *Chem. Abstr.*, **75**, 33401(1971).
- (7) W. R. Thompson, *Bacteriol. Rev.*, **11**, 115(1947).
- (8) C. S. Weil, *Biometrics*, **8**, 249(1952).
- (9) A. Stoll, T. Petrzilka, J. Rutschmann, A. Hoffman, and H. H. Gunthard, *Helv. Chim. Acta*, **37**, 2039(1954).
- (10) C. P. Farley and E. Eliel, *J. Amer. Chem. Soc.*, **78**, 3477 (1956).

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Phase Separation of Cellulose Derivatives: Effects of Polymer Viscosity and Dielectric Constant of Nonsolvent

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Abstract □ In systems containing either cellulose acetate butyrate or ethylcellulose, the intrinsic viscosity of the polymer in the appropriate solvent had no effect on the phase type separated. The latter was dependent on the dielectric constant of the nonsolvent added. Nonsolvents possessing relatively high dielectric constants produced a flocculate phase, while either a coacervate or gel was formed after the addition of nonsolvents of lower dielectric constant.

Keyphrases □ Cellulose derivatives (cellulose acetate butyrate and ethylcellulose)—effects of polymer viscosity and dielectric constant of nonsolvent on phase separation □ Phase separation, cellulose derivatives—effects of polymer viscosity and dielectric constant of nonsolvent □ Nonsolvents—effect on phase separation of cellulose acetate butyrate and ethylcellulose

Starting from a polymer solution in a suitable solvent, the addition of an appropriate concentration of a nonsolvent may produce phase separation. The type of phase separating may be a flocculate, gel, or coacervate (liquid–liquid phase separation). While factors such as pH and electrolytes were reported to govern the phase type in polyelectrolyte systems (1, 2), no studies have been made on nonelectrolytic polymers. Phase separation of cellulose derivatives is of special interest in pharmacy because of its application to microencapsulation of pharmaceuticals (3, 4). The present article re-

ports the effect of various solvent–nonsolvent systems on the type of phase separating in two polymers: ethylcellulose and cellulose acetate butyrate. An attempt was made to study the effect of solvent–nonsolvent systems on the phase type as determined by the viscosity of the polymer (in the appropriate solvent) and the dielectric constant of the nonsolvent added.

EXPERIMENTAL

Materials—The ethylcellulose¹ used had a 48% ethoxyl content. Cellulose acetate butyrate², 171-2 grade, had a 17% butyryl content. All solvents and nonsolvents were analytical reagent grade or pure reagents.

Methods—*Determination of Phase Type*—To a solution of the polymer in the appropriate solvent, placed in glass-stoppered centrifuge tubes, the nonsolvent was gradually added until a visual phase change was noted. The stoppered tubes were equilibrated at 25 ± 0.1° for completion of phase separation (4–6 hr.). The separated phase was examined and classified as a flocculate, gel, or coacervate. The latter was found microscopically to exhibit coacervate droplets (10–25 μ in diameter) which rapidly coalesced to a clear oily layer upon standing. The gel phase showed no coacervate droplets and was highly viscous, frequently adhering to the walls of the container.

¹ British Drug Houses Ltd., Poole, England.

² Eastman Kodak.

Table I—Effect of Solvent–Nonsolvent Systems on the Phase Type Separated in 5% (w/v) Cellulose Acetate Butyrate^a

Nonsolvent	Solvent ^c			
	Dielectric ^b Constant (at 20°)	Acetone (0.37)	Cyclo- hexanone (0.55)	Methy- lene Chlo- ride (0.49)
Water	80.4	F	—	—
Methanol	33.7	F	F	F
Ethanol	25.7	F	F	F
<i>n</i> -Butanol	17.8	F	F	F
Hexane	1.9	C	C	C
Petroleum ether (b.p. 40–60°)	1.9	G	G	G

^a Phase types are: F = flocculate, C = coacervate, and G = gel.
^b Values obtained from "Handbook of Chemistry and Physics," 50th ed., R. C. Weast, Ed., Chemical Rubber Co., Cleveland, Ohio, 1969, pp. E61–E63. ^c The figures in parentheses are the determined intrinsic viscosities of the polymer solution in the appropriate solvent. Values were determined at 25 ± 0.1°.

Determination of Intrinsic Viscosity—The intrinsic viscosity of the polymer in the appropriate solvent was determined at 25 ± 0.1° using a viscometer³. The polymer concentration range was 0.1–0.6 g./100 ml.

RESULTS AND DISCUSSION

Tables I and II show the various phases that separated upon the addition of several nonsolvents to 5% w/v solutions of the polymer in different solvents. The phase types produced were independent of the initial polymer concentration in the range used (1–5% w/v). The slight difference observed in the intrinsic viscosities of the polymers (and possibly a change in the molecular configuration) had no effect on the phase type separated. Of the six nonsolvents tested, only two showed a different effect on phase type while four produced the same phase (flocculate). Thus, it was not the nonsolvent *per se* that produced the effect but some other inherent property. It is suggested that the dielectric constant of the nonsolvent has a decisive role in determining the phase type. Nonsolvents possessing relatively high dielectric constants (the first four nonsolvents in Table I) yielded the same phase (flocculate). However, hexane and petroleum ether produced either a coacervate or gel phase, since these nonsolvents have a much lower dielectric constant (about 1.9). These observations were the same in both polymer systems.

In general, the reported results suggest that care should be taken in selecting the nonsolvent during microencapsulation of drugs by phase separation of polymeric nonelectrolytes. A previous report (5) showed that the *in vitro* release of ferrous sulfate from cellulose-

³ Ostwald type.

Table II—Effect of Solvent–Nonsolvent System on the Phase Type Separated in 5% (w/v) Ethylcellulose^a

Nonsolvent	Dielectric ^b Constant (at 20°)	Solvent ^c		
		Acetone (0.41)	Ethanol (0.53)	Toluene (0.62)
Water	80.4	F	F	—
Hexane	1.9	C	C	C
Petroleum ether (b.p. 40–60°)	1.9	G	G	G

^a Phase types are: F = flocculate, C = coacervate, and G = gel.
^b Values obtained from "Handbook of Chemistry and Physics," 50th ed., R. C. Weast, Ed., Chemical Rubber Co., Cleveland, Ohio, 1969, pp. E61–E63. ^c The figures in parentheses are the determined intrinsic viscosities of the polymer solution in the appropriate solvent. Values were determined at 25 ± 0.1°.

coated formulations, prepared by phase separation, was dependent on the phase type separated.

SUMMARY

1. Three phase types are produced in the phase separation of systems containing either cellulose acetate butyrate or ethylcellulose. These phase types are flocculate, gel, and coacervate.
2. The intrinsic viscosity of the polymer, in the appropriate solvent, had no effect on the phase type separated.
3. The dielectric constant of the nonsolvent added appears to control the phase type. A flocculate phase was formed upon the addition of nonsolvents possessing relatively high dielectric constants. Either a coacervate or gel phase was produced with nonsolvents having a much lower dielectric constant.

REFERENCES

- (1) S. A. H. Khalil, J. R. Nixon, and J. E. Carless, *J. Pharm. Pharmacol.*, **20**, 215(1968).
- (2) J. R. Nixon, S. A. H. Khalil, and J. E. Carless, *ibid.*, **20**, 348(1968).
- (3) L. A. Luzzi, *J. Pharm. Sci.*, **59**, 1367(1970).
- (4) The Upjohn Co., British pat. 931,150 (1963).
- (5) S. A. H. Khalil and S. S. ElGamal, *Pharmazie*, **28**, 405 (1973).

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