J. Pharm. Pharmacol. 1991, 43: 198–200
Communicated May 28, 1990

COMMUNICATIONS

Thixotropic phenomenon in flocculated aqueous dispersions of acrylate methacrylate copolymers

R. S. OKOR, *Department of Pharmaceutics, University of Benin, Benin City, Nigeria*

Abstract—Aqueous gels of two analogous, water-insoluble copolymers A and B have been formed by addition of excess water to concentrated ethanol solutions of the polymers. A and B differed only in their content of cationic groups in a ratio 2:1 (A:B). The gels were converted permanently to fluids (i.e. gel-sol transformation) at high shear rates. Stability of the resulting polymer dispersions depended on the presence and mutual repulsion of the polymer cations. Polymer B dispersions were less stable to the flocculating effect of an electrolyte (sodium chloride). At certain critical concentrations, 0·2 M NaCl (for polymer A), or 0·1 M NaCl (for polymer B) the electrolyte flocculated the otherwise stable dispersions to a gel structure. The electrolyte-flocculated gels were readily redispersed to fluids by shaking but reverted to gels on standing (thixotropic). In contrast the original coacervated gels (without electrolyte) could not be redispersed easily with manual shaking. Lower polymer-polymer interaction in the thixotropic system relates possibly to increases in particle size and irregularity of particle shape during flocculation.

The acrylate-methacrylates are water-insoluble copolymers. Their aqueous dispersions can be formed by direct but prolonged mixing in hot water (Lehmann 1989), or more readily by a coacervation technique (Okor 1990). In the latter procedure excess water (non-solvent for the polymer) is added to an ethanol solution of the polymer. The resulting aqueous dispersions have film coating applications (Okor 1990). High polymer concentrations (e.g. 10% w/v) form gels during coacervation. In this report evidence is presented that these gels can be transformed permanently to fluid aqueous dispersions (i.e. gel-sol transformation), and that addition of an electrolyte imparts a thixotropic property to the systems.

Materials and methods

Two analogous copolymers designated A and B (Eudragit RL 100 and RS 100 Rhom Pharma, Darmstadt) differing only in their content of quaternary ammonium (cation) groups in a ratio 2:1 (A:B) were used. Ethanol (95% alcohol BP) was used as solvent for the polymers in the coacervation procedure.

Coacervation technique. The polymer (1–10 g) was dissolved in ethanol (15 mL). Water (85 mL) was added with vigorous shaking. The coacervated systems were fluids up to a polymer concentration of 6·5%; beyond this point they formed gels. The gels were converted to fluids by stirring (1500 rev min^{-1}) for 15 min with a Silverson mixer (model V 5104) fitted with a dispersator head.

Stability to electrolyte. Sodium chloride solutions in water of various molar concentrations were prepared by serial dilution. A sample of the electrolyte solution (1 mL) was added to the polymer dispersion (9 mL). After standing for 1 h, the samples were centrifuged for 5 min with the speed setting at No. 3 using the Gallenkamp Junior centrifuge. The minimum concentration of the electrolyte which produced an observable precipitate was taken as the index of stability of the polymer dispersion to the electrolyte.

Test for change from sol to gel consistency. The change in the consistency of the polymer dispersions on standing from a fluid to a gel was determined by a penetrometer. In the test a plunger was allowed to drop freely through a guide from a standard height, 4 cm above a sample of the polymer dispersion (90 mL) contained in a 100 mL measuring cylinder. After penetration, the height of the exposed portion of the plunger was measured and the depth of penetration calculated by difference from the total height of the plunger. To prepare samples for the test the electrolyte solution (5 mL) was added to the polymer dispersion (100 mL) and stirred with a glass rod for 1 min. The electrolyte-flocculated dispersion (90 mL) was immediately transferred to the 100 mL glass measuring cylinder. Depth of penetration was measured immediately (time 0) and at 5 min intervals for 1 h. The extent of penetration decreased with time indicating a change from a fluid to a gel consistency. At the consistency corresponding to a depth of penetration of 4 cm the dispersion could not be poured readily from the container; this consistency was taken as the gel point and the time taken to attain it was taken as the time-lag for gel reformation. In the design of the apparatus, a slightly tapered stick (length 37 cm, mean thickness $1·3 \pm 0·2$ mm) served as the plunger and was selected because of its light weight, 0·62 g. Crude as the design seems, results of 3 replicates were reproducible to $\pm 7·5\%$ of the mean.

Results and discussion

Dispersions of polymer A were generally more stable to the electrolyte compared with B (Fig. 1); this observation is associated with the higher cation content of A. The cations produced mutual repulsion of the polymer particles (Okor 1982) and stabilized the dispersions by this mechanism. Stability of the dispersions was strongly dependent on polymer concentration. An initial increase attributable to an increase in particle-surface charges was followed by a decrease attributable to increased particle-particle interactions at high polymer concentrations.

High shearing forces broke down the cohesive forces in the coacervated gels containing the polymer, 10% w/v, and thus converted the systems permanently to fluids. No changes in fluid consistency were noted when the samples were observed for 2 weeks. Polymer B however, produced a redispersible compact precipitate. Irreversibility of the dispersion from a fluid to a gel structure when the shear stress was withdrawn is attributable to the mutual repulsion and hence, the deflocculating effect of the polymer cations.

Addition of an electrolyte (sodium chloride) flocculated the dispersions by neutralizing the surface cationic charges and caused the fluid systems to revert to a gel consistency on standing

Table 1. Time-lag for the conversion of polymer dispersions from a fluid to a gel consistency.

Electrolyte concn (M)	Time-lag (min)	
	Polymer A	Polymer B
0	—	—
0·05	—	—
0·1	—	25
0·2	15	15
0·3	10	10

—no reversion to a gel consistency.

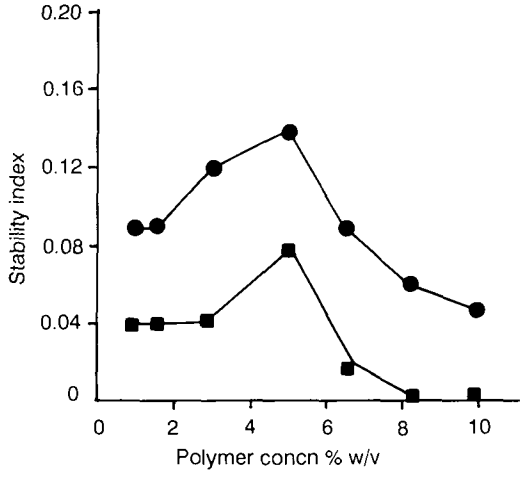

FIG. 1. Effect of polymer concentration on the stability of dispersions of polymers A (●) and B (■), to electrolyte (sodium chloride).

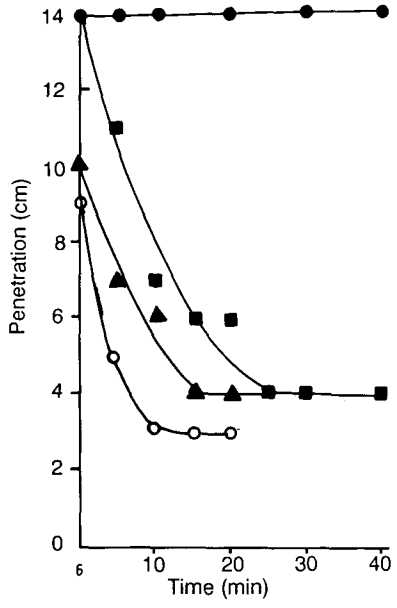

FIG. 3. Changes in the sol to gel consistency of 10% w/v dispersion of polymer B on standing after addition of sodium chloride to concentrations 0·05 M (●), 0·1 M (■), 0·2 M (▲), and 0·3 M (○).

(Figs 2, 3). The effective gelling concentrations of the electrolyte depended on the polymer cation. Polymer B which has the lower cation content was more readily gelled by low concentrations of the electrolyte. Also the time-lags for the sol to gel transformation was determined by the electrolyte concentration (Table 1), decreasing with increase in electrolyte concentration.

Resulting electrolyte-flocculated gels were readily converted to a fluid consistency by shaking manually for 1 min. In contrast the original coacervated gels required high speed (1500 rev

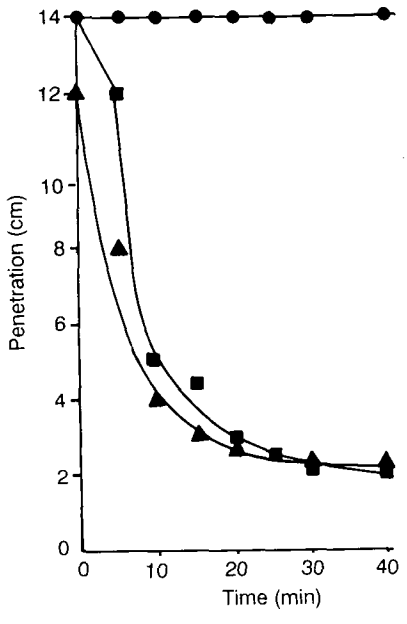

FIG. 2. Changes in the sol to gel consistency of 10% w/v dispersions of polymer A on standing after addition of sodium chloride to concentrations 0·1 M (●), 0·2 M (■) and 0·3 M (▲).

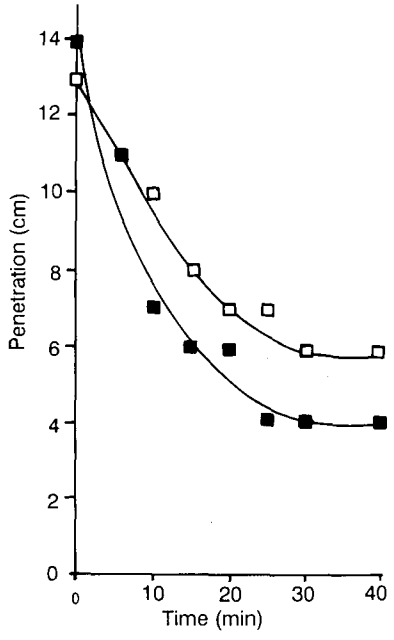

FIG. 4. Differences in the rate of sol to gel transformation in the flocculated dispersion of 10% polymer B (■) and in the gel of the same system redispersed to a fluid by shaking (□).

min^{-1}) shearing with the Silverson mixer before a similar change could be effected. This difference suggests a weaker degree of polymer-polymer interaction in the electrolyte-flocculated gels. Perhaps the increase in particle size and the irregularity of particle shape in the flocculated systems led to the weaker cohesion. A redispersion of the electrolyte-flocculated gel (produced by shaking) tended to retain fluidity longer than the original dispersion challenged by the electrolyte (Fig. 4), but the difference was not significant.

The conclusion is that aqueous coacervated gels of the polymers studied have inherent strong interactions that can only be broken down at high shear rates to produce liquid dispersions. Their stability depended on the presence of polymer cations. Addition of an electrolyte imparted a thixotropic property to the polymer dispersions. This flow property may be exploited in the formulation of muco-adhesive gels which are pourable upon shaking but revert to a gel consistency after administration.

References

Lehmann, K. (1989) Aqueous polymeric coatings for pharmaceutical dosage forms. Drugs Pharm. Sciences 36: 1–95

Okor, R. S. (1982) Effect of polymer cation content on certain film properties. J. Pharm. Pharmacol. 34: 83–86

Okor, R. S. (1990) Drug release through aqueous-based film coatings of an acrylate-methacrylate, a water-insoluble copolymer. Int. J. Pharmaceutics 58: 89–91

J. Pharm. Pharmacol. 1991, 43: 200–203
Communicated September 15, 1990

Effect of chronic administration of nicotine or cocaine on steroidogenesis in rat adrenocortical cells

RICK J. KRUEGER, CHAOMEI LIN, YIU K. FUNG*, *Department of Biochemistry and School of Biological Sciences, University of Nebraska-Lincoln, Lincoln, NE 68583-0718 and * Department of Oral Biology, College of Dentistry, University of Nebraska Medical Center, Lincoln, NE 68583-0740, USA*

Abstract—Rats were implanted subcutaneously with osmotic minipumps containing either 0·9% NaCl, nicotine (1·5 or 4·5 mg kg^{-1} day^{-1}), or cocaine (30 mg kg^{-1} day^{-1}), for 14 days. Neither nicotine nor cocaine treatment significantly altered the maximal rate of steroidogenesis in adrenocortical cell preparations from the animals. However, pretreatment with cocaine increased the sensitivity of the preparation to stimulation by ACTH, the ED50 was 5 pM compared with 10 pM from control animals. Addition of nicotine or cocaine at concentrations up to 100 μM to adrenal cell suspensions from naive rats did not stimulate steroidogenesis or increase the sensitivity of cells to ACTH stimulation. These results suggest that the primary chronic effect of nicotine on steroidogenesis is exerted at the level of the hypothalamus and/or pituitary and not directly on adrenocortical cells. On the contrary, pretreatment with cocaine causes persistent changes in adrenocortical cells.

Nicotine has been shown to produce marked neuroendocrine changes in laboratory animals and man (Andersson et al 1982, 1988; Cam & Bassett 1983; Fuxe et al 1989). Its acute administration increases the plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone (Conte-Devolx et al 1981; Cam & Bassett 1983). Fuxe et al (1989) suggested that some endocrine related health problems result from nicotine derived from cigarette smoke. This effect may involve central nicotinic cholinergic receptors at the hypothalamic cholinergic neurons (Hillhouse et al 1975; Weidenfeld et al 1983). This is supported by the observation that nicotine stimulates the secretion of ACTH in a dose-dependent manner when applied directly to the hypothalamus, but not to the pituitary of an isolated perfused mouse-brain preparation (Marts et al 1985). Although most of the studies have been directed primarily towards examining the effects of nicotine on the hypothalamic-pituitary portion of the glucocorticoid regulatory system, nicotine may exert an acute direct effect at the level of the adrenocortical cells (Rubin & Warner 1975).

Correspondence to: R. J. Krueger, 314 BcH, Department of Biochemistry, University of Nebraska-Lincoln, Lincoln, NE 68583-0718, USA.

Similarly to nicotine, cocaine is a central nervous system stimulant which interacts with several central monoaminergic neurons to exert its psychotropic effects (Gregler & Marks 1986; Hanson et al 1987; Ritz et al 1987). Acute intravenous administration of cocaine to rats has been shown to stimulate the release of ACTH, which can be abolished by the administration of corticotropin releasing factor (CRF) antiserum (Rivier & Vale 1987). This suggests that cocaine acts within the brain to release endogenous CRF. Direct stimulation of ACTH release by cocaine under conditions where CRF release was inhibited has also been reported (Moldow & Fischman 1987).

In light of the close interaction between the central nervous system and the endocrine system, stimulants such as nicotine and cocaine may have profound effects on the neuroendocrine system. Most studies that have examined their effects on the secretion of ACTH and corticosterone have involved systemic administration of drug. Little information is available about the direct effects of their continuous administration on the secretion of hormones at the level of the adrenocortical cell. We have examined the effects in the rat of continuous administration of nicotine or cocaine via subcutaneous implantation of an osmotic mini-pump containing the drug.

Materials and methods

Materials. Corticosterone, collagenase, DNase I, N^6, 2′-*O*-dibutyryl cAMP (bt_2cAMP), porcine ACTH, nicotine tartrate and cocaine hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO). ACTH was purified by ion-exchange (Yamashiro et al 1984) and reversed phase chromatography. Ham's F-12 medium was obtained from Gibco (Grand Island, NY). 20(*R*),22(*R*)-dihydroxycholesterol was a generous gift of Dr Nanette Orme-Johnson, Tufts University School of Medicine (Boston, MA). Alzet osmotic mini-pumps model 2002 were obtained from Alza Corp (Palo Alto, CA).

Animals. Male Sprague-Dawley rats (Sasco, Inc., Omaha, NE),