Viscometric Study of Polyacrylic Acid Systems as Mucoadhesive Sustained-Release Gels

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This report describes a novel nonaqueous polymeric formulation that exhibits low-viscosity fluid behavior for ease of spraying with conventional nebulizer, which when sprayed into the nasal cavity, transforms to a high-viscosity gel for efficient retention and drug absorption. The transformation occurs because of the rheological changes induced by a change in the solvent composition of the polymeric formulation in the moist nasal cavity. Such a rheological change would then facilitate enhanced residence time of the drug at the site of administration in order to avoid drainage losses. This study reports the results of the effects of a variety of factors such as solvent composition and polymer concentration on the rheological properties of a polyacrylic acid polymer. An attempt to correlate viscosity enhancement effects with enhanced and sustained-release behavior of propranolol, a drug that undergoes extensive first-pass effects, from such formulations via nasal administration in beagle dogs is also described.

KEY WORDS: pharmaceutical gel formulation; Carbopol gel; viscosity; propranolol; solvent effects on polymer gel rheology.

INTRODUCTION

Polymers have been widely used in the pharmaceutical field as enteric coatings and for drug encapsulation in various dosage forms, in order to control the intensity and duration of drug action (1,2). The use of polymers as viscosity enhancers for a variety of administration modes is also well known. For nasal formulations, viscosity enhancers may be necessary in order to prevent drainage of the formulation. However, a simple boost in viscosity of the nasal formulation is disadvantageous due to the inconvenience associated with delivering high-viscosity gels with ease and consistency. Ideally, the polymer used in the formulation should be such that it undergoes marked rheological changes *after* it is administered to the site. This would then provide (a) ease of delivery using conventional metered-dose dispensers and (b) enhanced drug residence time and bioavailability due to the enhanced viscosity *at the site of administration.*

For most polymers, the rheological behavior is critically dependent on the interaction of the polymeric chains with the solvent (3). In the case of water–soluble polymers that are covalently cross-linked, a change from a nonaqueous environment to one that is aqueous may produce dramatic changes in polymer conformation and rheology. This dramatic transformation could be gainfully exploited to formulate a low viscosity, sprayable nonaqueous polymeric system containing a desired drug that would, upon contact with moisture in a body cavity, transform to a high-viscosity gel in the body cavity. This enhancement in viscosity upon inclusion of water would then provide suitable adhesion and residence time characteristics in the cavity. The increased residence time would allow enhanced absorption of the drug. This polymeric vehicle may especially be useful for delivery of drugs to a local site or when absorption of the drug when administered orally is poor because of degradation of the drug in the gastrointestinal tract or when the drug cannot be administered parenterally. The formulation may also be used wherever the route of administration involves moist body cavities. Thus the formulation might be appropriate for drug delivery in ophthalmic, rectal, vaginal, otic, and buccal applications.

This paper investigates the effect of solvents on the rheological properties of a water-soluble acrylic acid polymer, Carbopol 934P. Carbopol 934P is a synthetic high molecular weight polymer (4) and exhibits marked rheological consistency and suspending properties at low concentrations (5,6). It is also compatible with several nonaqueous solvents and has been widely used in the preparation of gels and ointments for topical use in the pharmaceutical and cosmetic fields. The paper also describes the optimization of the nonaqueous formulation based on the optimization of rheology behavior in the presence of water. Propranolol formulations in such nonaqueous polymeric systems were prepared and tested for bioavailability and sustained drug action after nasal administration in male beagle dogs. The *in vivo* experiments were carried out in order to establish simple correlations between rheological behavior and efficacy of the polymeric formulations.

MATERIALS AND METHODS

Materials

Carbopol 934P (B. F. Goodrich Chemical Co., Cleveland, OH), with an average molecular weight of approximately 3,000,000, was used as received. Polymer equivalent weight as determined by potentiometric titration was 76.32 ± 0.80, in agreement with the manufacturer's reported value. Monoethanolamine (MEA), diisopropanolamine (DIPA), and triethanolamine (TEA), used as neutralizing agents, were obtained from Sigma Chemical Co. (St. Louis, MO). Propylene glycol (PG) and glycerol formal (GF) were obtained from Fisher Chemical Company. Distilled water (W) filtered using a Milli-Q system was used.

Preparation of Polymer Gels or Dispersions

Accurately weighed amounts of Carbopol 934P were added slowly into the vortex of pure solvents or solvent

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mixtures and stirred using a Teflon-covered magnetic stir at 500 rpm, in tightly capped bottles, overnight, to obtain homogeneous dispersions. If partially wetted polymer lumps remained, the system was not studied. The concentrations of stock dispersions prepared were 1.5% by weight. Lower concentrations of polymer dispersions were prepared by dilution of the stock solutions with appropriate amounts of pure solvents or solvent mixtures. Neutralized polymer dispersions were obtained by adding the neutralizing agent at various desired equivalent ratios and mixing the systems thoroughly. All systems were stored overnight and centrifuged for 15 min at 3,000 rpm to remove any entrapped air in the gel. The final pH of each polymer gel or dispersion was determined using a pH meter (Model 61, Beckman Co., Irvine, CA) at 25°C. The final pH of the neutralized gels was in the range of 7.9–8.3.

Continuous Shear Measurements

The apparent viscosity of unneutralized and neutralized Carbopol 934P dispersions or gels in various solvent mixtures was measured using a Rheomat 135S (Contraves Co., Cincinnati, OH) viscometer at 30°C. Appropriate concentric cylinder measuring attachments were employed. The shear rates were changed continuously from 10 to 500 sec^{-1} over a period of 10 min and cyclic measurements were carried out to ascertain hysteresis effects.

In Vivo Bioavailability Studies

Four healthy 4- to 5-year-old male beagle dogs were used in the evaluation of several intranasal propranolol formulations. Each formulation was tested in all four dogs. Dogs were restrained in a dog sling (Alice King Chatman Medical Arts, Los Angeles, CA) and fasted overnight before the experiment. Food and water were withheld until the end of the experiment. Blood samples (1 ml) were withdrawn at predetermined time periods from a catheter (Angiocath, 18-G, 2 in.; Desert Medical Inc., Sandy, UT), placed in the front forearm vein. A washout period of longer than 1 week was used throughout the study.

Preparation of Propranolol Solution for Intravenous Administration. A known amount of propranolol hydrochloride powder (Sigma Chemical Cc., St. Louis, MO) was dissolved in normal saline to give a final propranolol solution concentration of approximately 5 mg/ml.

Intravenous Administration. A butterfly infusion set (INT NO. 4721, 21 × ¾- to 3½-in. tubing) was placed into the vein of the other front leg of the dog as the injection site for the propranolol solution. The solution was sterilized by passing it through an on-line Millipore syringe filter (Millex-GV, 0.22 mm; Millipore Corp., Bedford, MA) to catch any contaminants in the drug solution. The dose given was approximately 10 mg in a total volume of 2 ml. The propranolol solution was injected into the vein over a span of 30 sec, then flushed with two 3-ml syringes with normal saline (total 6 ml). Blood samples were taken at 30, 15, and 0 min before injection and at 3, 6, 9, 15, 30, 60, 90, 120, 150, 180, 240, 300, and 360 min after injection.

Preparation of Carbopol 934P-Propranolol Intranasal Formulations. A 1.5 wt% neutralized Carbopol 934P dispersion in a solvent composition of 60.0 wt% propylene glycol (PG) and 40.0 wt% glycerol formal (GF) was selected based on an independent study of optimal experimental design employing response surface methodology (7) and prepared as follows. An appropriate amount of propranolol powder was added to a 1.5 wt% unneutralized Carbopol 934P solution in pure GF. A 1.5 wt% Carbopol 934P gel in PG neutralized using a 1:1 equivalent ratio of Carbopol 934P:TEA was then prepared. Two parts of Carbopol gel in PG were then mixed with one part of the Carbopol–propranolol dispersion in GF. The final mixture, containing above 20 mg/ml of propranolol was quite fluid with an apparent viscosity of around 60 centipoises. A saline solution containing 20 mg/ml of propranolol was also prepared for use in the for nasal experiments.

Nasal Administration. Propranolol dispersions were administered, using a 10-ml metered-dose inhaler (Boehringer Ingelheim Ltd., Ridgefield, CT), twice into each nostril of the dogs. The dose administered was determined by weighing the spray bottle before and after spraying. The total dose given was approximately 10 mg. One-milliliter blood samples were withdrawn at the same intervals as in the iv study.

Sample Handling. Blood samples were immediately put into 3-ml Lavender vacutainer tubes and centrifuged for 5 min. After centrifugation, plasma was separated and stored frozen until assayed.

Assay of Propranolol. Plasma propranolol was determined by an HPLC method developed by Nation *et al.* (8). The mobile phase was prepared by mixing 27 parts of acetonitrile with 73 parts of 0.06% phosphoric acid solution. The fluorescence detector (Model FS 970, Schoeffel Co., Westwood, NJ) was operated at an excitation wavelength of 205 nm and an emission wavelength of 340 nm was used with an aid of an emission filter (KV340).

RESULTS AND DISCUSSION

In most organic solvents, the unneutralized polyacrylic acid polymer is in its coiled and contracted configuration. Neutralization, by the addition of a base such as NaOH or

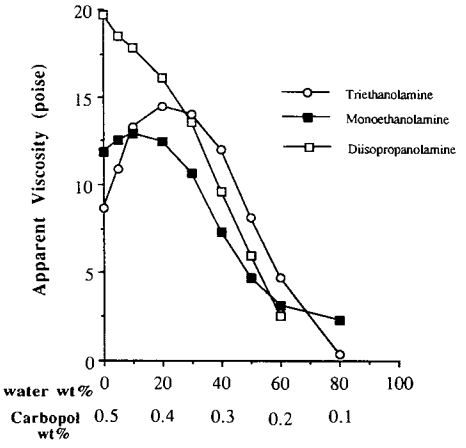

Fig. 1. A comparative study on the changes in viscosity behavior of nonaqueous Carbopol 934P dispersions neutralized using different neutralizing agents upon water inclusion at a shear rate of 100 sec^{-1}.

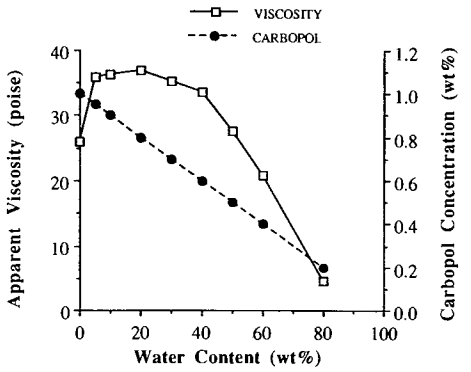

Fig. 2. The addition of water to a nonaqueous Carbopol Dispersion at a shear rate of 100 sec^{-1}.

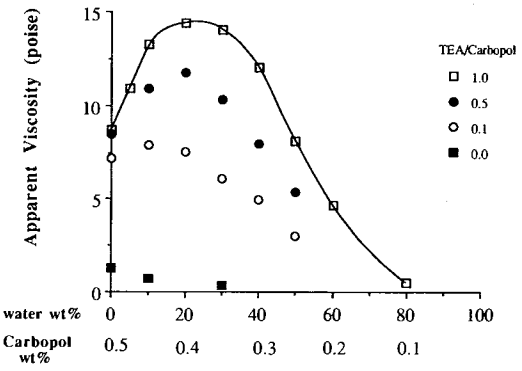

Fig. 4. Effect of water addition on the viscosity of 1.0 wt% Carbopol dispersions in PG neutralized using TEA equivalents less than 1:1.

low molecular weight organic amines, ionizes the polymeric resins and generates significant alterations of the rheological properties (3,4). The extent of the resultant rheological changes in the polymer network is determined by the complex interactions among the neutralizing agents, the solvent systems, and the polymer segments. A comparative study on the changes in the viscosity behavior of nonaqueous Carbopol 934P dispersions neutralized using different neutralizing agents upon water inclusion was examined and is shown in Fig. 1.

The results in Fig. 1 indicate that Carbopol 934P neutralized with tertiary (TEA) and secondary (DIPA) amines exhibit increases in viscosity when the solvent composition is altered by inclusion of water. Carbopol dispersions neutralized with DIPA exhibit a higher viscous behavior in pure PG solvent followed by a decrease in viscosity that appears to be linear with increasing water content. For Carbopol dispersions neutralized with TEA, despite its lowest-viscosity behavior in pure PG solvent, significant enhancement in viscosity occurs when the solvent composition contains 20–30 wt% water.

The addition of water to a nonaqueous Carbopol dispersion not only alters the solvent composition but also results in a concomitant dilution of the polymer concentration. It is important to note that despite the decrease in polymer concentration obtained, the viscosity of the Carbopol dispersion increases dramatically in the initial stages of water addition (Fig. 2). The general pattern in viscosity change during the initial stages of water addition was also observed for various other concentrations of Carbopol dispersions in PG neutralized with TEA.

A brief mechanistic explanation for the viscosity behavior of Carbopol dispersions in PG neutralized with different amines is as follows. Upon neutralization with an organic amine or base in the presence of a hydrophilic solvent, the neutralized polymer uncoils (i.e., is solvated), resulting in an increase in viscosity or formation of gel. It is necessary that the polymer–amine salt be soluble in the solvent system. In the case of Carbopol 934P dispersions in PG neutralized with TEA, MEA, or DIPA, it is reasonable to expect that the solubility of the polymer–amine salt or complex in PG would follow the order of solubility of amines in PG. This order is DIPA > MEA > TEA, because of the higher polar characteristic of TEA compared with MEA and DIPA. Thus the complex with the lowest solubility in PG, Carbopol–TEA, exhibits the lowest viscosity in PG. The order of increasing viscosity for the three systems is TEA > MEA > DIPA, in accordance with the solubility of the salts.

The solvent composition therefore plays a critical role in the viscometrics of the neutralized Carbopol systems. It is apparent that the Carbopol–TEA salt would be more soluble in water than in the less polar PG solvent. The change in solvent composition from pure PG to a PG–water mixture would therefore increase the solubility of Carbopol–TEA salt in the mixture and increase in the entanglement of the polymer chains, resulting in an increase in viscosity when

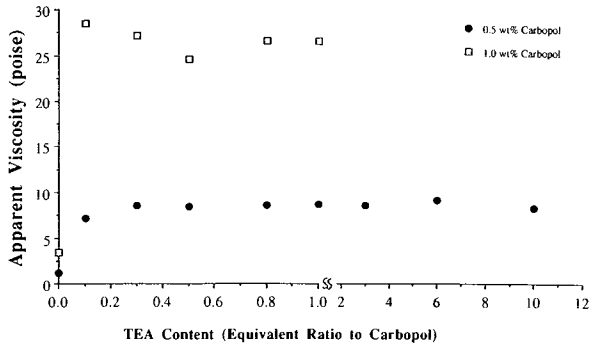

Fig. 3. Changes in viscosity for 0.5–1.0 wt% Carbopol 934P in propylene glycol solvent neutralized with various triethanolamine equivalent ratios at a shear rate of 100 sec^{-1}.

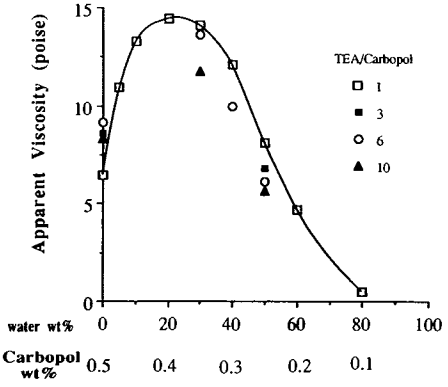

Fig. 5. Effect of water addition on the viscosity of 1.0 wt% Carbopol dispersions in PG neutralized using TEA equivalents larger than 1:1.

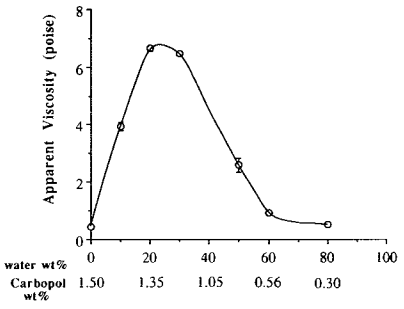

Fig. 6. Viscosity changes upon addition of water to a 1.5 wt% Carbopol formulation with propranolol in a solvent composition of 60 wt% of PG and 40 wt% of GF at a shear rate of 10 sec^{-1}.

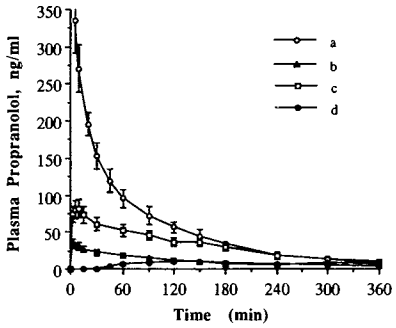

Fig. 7. Plasma propranolol concentration vs time profiles for various routes of administration of 10 mg of propranolol hydrochloride in beagle dogs. Formulations for a–d listed in Table I.

TEA is used as the neutralizing agent. The increase in viscosity is accompanied by a significant decrease in turbidity of the solution and is attributed to the dissolution of any precipitate of polymer segments or polymer–amine salts in PG alone. For less polar amines such as DIPA, the Carbopol–amine salt is expected to be highly soluble in PG, and less so in water. The addition of water to Carbopol dispersion in PG neutralized with DIPA would therefore result in a decrease in viscosity as shown in Fig. 1, due mainly to a dilution of the polymer concentration. The decrease in viscosity appears to be linearly related to the decrease in Carbopol 934P amount.

In addition to the solubility-related swelling phenomenon of Carbopol polymer solutions neutralized with TEA in solvent mixtures, the degree of neutralization upon the viscometric behavior was also examined. Figure 3 shows the minimal changes in viscosity for 0.5–1.0 wt% Carbopol 934P in PG solvent neutralized with various TEA equivalent ratios at a shear rate of 100 sec^{-1}. The viscosity of the unneutralized Carbopol polymeric solution was low. Figures 4 and 5 show the effect of water addition on the viscosity of 1.0 wt% Carbopol dispersions in PG neutralized using various TEA equivalents. In general, the viscosity increases sharply when the mixture contains about 20–30 wt% of water. For systems neutralized with higher TEA equivalents, the viscosity decreases beyond 30 wt% of water. The enhancement in viscosity was the highest for systems neutralized using a 1:1 equivalent ratio of TEA and Carbopol 934P.

An optimal nonaqueous polymer dispersion was obtained from the rheological behavior of systems containing two or more ingredients and response surface methodology (7). The system contained 1.5 wt% polymer dispersion in a solvent composition of PG and GF, with a composition of 60 wt% of PG and 40 wt% of GF, and neutralized using an appropriate equivalent of TEA:Carbopol ratio and propranolol. Figure 6 shows the viscosity changes upon addition of water to the above nonaqueous dispersion. A significant enhancement in apparent viscosity roughly 15-fold was observed. The gels obtained upon inclusion of water were highly viscoelastic in nature.

The nonaqueous polymeric formulation described above was used to formulate propranolol systems. Although well absorbed orally, propranolol exhibits a high first-pass metabolism. *In vivo* nasal studies using propranolol formulations were carried out in beagle dogs in order to evaluate the efficacy of the nonaqueous polymeric systems as compared to an aqueous nonviscous drug solution. The plasma concentration–time profiles and bioavailability results for various routes of administration of 10 mg of propranolol hydrochloride in beagle dogs are shown in Fig. 7 and Table I. The results indicate that the overall bioavailability of propranolol from polymeric formulations administered nasally is significantly higher than that of the drug from a saline solution. The nasal bioavailability was considerably higher than that obtained via oral administration. This suggests that the polymer vehicle facilitates an enhancement in bioavailability of drug by increasing the residence time of the drug in the nasal passage. Indeed, the inverse correlation between clearance rates and viscosities, reported by Pennington *et al.* (9), supports the contention that an enhancement in viscosity would enhance residence time. The known *in vitro* viscosity

Table I. Comparison of iv, Nasal, and Oral Administration of 10 mg of Propranolol Hydrochloride in Beagle Dogs

	Route	Formulation	C_{max} (ng/ml)	T_{max} (min)	AUC/AUC (iv) (0–6 hr)[a]
a	iv	Saline	335	3	100
b	Nasal	Saline	36	3	23.5 ± 5.2
c	Nasal	1.5 wt% Carbopol PG:GF = 40:60 TEA:drug = 2:1	82	9	51.8 ± 7.2
d	Oral	Tablet	10	120	3.6 ± 2.8

[a] Average AUC of four dogs (0–6 hr).

increase of the nonaqueous formulation upon water addition and the increased *in vivo* bioavailability imply that these formulations undergo transformation to a gel in the nasal passage. This would increase the residence time and result in the observed increased bioavailability.

Although a simple correlation between viscosity and residence time or bioavailability is apparent from our results, several other factors may play a role. Further study of the viscoelastic behavior of the present polymeric vehicles indicates that the addition of water to nonaqueous Carbopol 934P polymer systems transforms them from low-viscosity Newtonian solutions to gels with significant elastic behavior involving physical interaction and entanglement of polymer segments with solvents. Therefore, in view of the ciliary motions in the nasal passage, a better understanding of the viscoelastic properties of the polymeric formulations is necessary to correlate rheological properties and clearance rates or drug bioavailabilities.

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REFERENCES

1. R. J. Juliano (ed.). *Drug Delivery Systems,* Oxford, New York, 1980.
2. J. R. Robinson (eds). *Sustained and Controlled Release Drug Delivery Systems,* Marcek Dekker, New York, 1978.
3. P. J. Flory. *Principles of Polymer Chemistry,* Cornell University Press, New York, 1986.
4. B. F. Goodrich Chemical Co. *Carbopol Water-Soluble Resin Service Bulletin* GC-67.
5. B. W. Barry and M. C. Meyer. The rheological properties of Carbopol gels. I. Continuous shear and creep properties of Carbopol gels. *Int. J. Pharm.* **2**:1–25 (1979).
6. B. W. Barry and M. C. Meyer. The rheological properties of Carbopol gels. II. Oscillatory properties of Carbopol gels. *Int. J. Pharm.* **2**:27–40 (1979).
7. J. S. Chu, G. L. Amidon, N. D. Weiner, and A. H. Goldberg. Mixture experimental design in the development of a mucoadhesive gel formulation. *Pharm. Res.* **8**:1401–1407 (1991).
8. R. L. Nation, G. W. Peng, and W. L. Chiou. High-pressure liquid chromatographic method for the simultaneous quantitative analysis of propranolol and 4-hydroxypropranolol in plasma. *J. Chromatogr.* **145**:429–436 (1978).
9. A. K. Pennington, J. H. Ratcliffe, C. G. Wilson, and J. G. Hardy. The influence of solution viscosity on nasal spray deposition and clearance. *Int. J. Pharm.* **43**:221–224 (1988).