International Journal of Pharmaceutics, 58 (1990) 73–77
Elsevier

IJP 01967

Application of intrinsic viscosity and interaction constant as a formulation tool for film coating II. Studies on different grades of ethyl cellulose in organic solvent systems

Hans Arwidsson [1] and Martin Nicklasson [2,*]

[1] *Astra Läkemedel AB, S-151 85 Södertälje (Sweden) and* [2] *Astra Research Centre AB, Södertälje (Sweden)*

(Received 26 June 1989)
(Accepted 26 July 1989)

Key words: Controlled release; Dilute solution properties; Ethyl cellulose; Interaction constant; Intrinsic viscosity; Organic solvent system

Summary

Intrinsic viscosity, [η], and interaction constant, k', have been determined for ethyl cellulose 7, 22, and 50 cps in 5 different organic solvent systems in order to select suitable systems for a coating process applicable for a wide range of ethyl cellulose grades of different molecular weight. The results indicate that methylene chloride/ethanol (60:40, % w/w) is an advantageous solvent system for each of the polymer grades studied. The interaction constant shows corresponding values for the different ethyl cellulose grades in each solvent system studied, apparently independent of molecular weight. Thus, k' was found to be more generally applicable than [η] when searching for a solvent system with high-solvent power for ethyl cellulose since [η] is a function of the molecular weight

Introduction

Ethyl cellulose is widely applied in order to control the release of drugs from pharmaceutical formulations, e.g. as a film-former or as a matrix forming agent. It has long been known that the properties of polymers are influenced by the solvent used at the preparation of e.g. a film (Haas et al., 1952; Boberski, 1975; Eskilsson et al., 1976; Azoury et al., 1988). Hence, the solvent system used at the production of a film-coated controlled release formulation has to be carefully selected.

Intrinsic viscosity, [η], per se has been suggested as a tool for selecting suitable solvents for ethyl cellulose (Kent and Rowe, 1978) as well as in combination with an interaction constant, k' (Alfrey, 1947; Arwidsson and Nicklasson, 1989). The interaction constant, k', which is derived from the same set of experimental viscosity data as [η], seems to be a more sensitive parameter for sterically rigid polymers such as cellulose ethers (Alfrey, 1947; Arwidsson and Nicklasson, 1989). Furthermore, the interaction constant reflects the interaction between the polymer molecules in solution independently of the molecular weight (Huggins, 1942; Alfrey, 1947). Thus, a more general

Correspondence: H. Arwidsson, Astra Läkemedel AB, S-151 85 Södertälje, Sweden.
* Present address: Kabi Pharma, P.O. Box 1828, S-171 26 Solna, Sweden.

selection of a suitable solvent system for a polymer may be obtained by using the interaction constant, k'.

A combination of a poor hydrogen bonding solvent and a strong hydrogen bonding solvent, e.g. methylene chloride/ethanol (60:40, % w/w), has been suggested as a good solvent system for ethyl cellulose 10 cps (Arwidsson and Nicklasson, 1989). The aim of this study has been to investigate the generality of the conclusions found for ethyl cellulose 10 cps with respect to different molecular weights of the polymer. Five of the solvent systems studied (Arwidsson and Nicklasson, 1989) were chosen for detailed studies in this paper. Intrinsic viscosity, $[\eta]$, and interaction constant, k', have been determined for three different grades of ethyl cellulose in the solvent systems. The applicability of the two parameters on ethyl cellulose of different grades will be discussed.

Materials and Methods

Intrinsic viscosity, $[\eta]$, and interaction constant, k', were determined for ethyl cellulose 7, 22, and 50 cps (Hercules Inc., U.S.A.) in ethanol, methylene chloride, toluene, methylene chloride/ethanol (60:40, % w/w), and toluene/ethanol (80:20, % w/w). The experimental procedures have been described elsewhere (Arwidsson and Nicklasson, 1989). Each polymer grade was characterized by gel permeation chromatography (GPC), ethoxyl content analysis and by determination of the dynamic viscosity in toluene/ethanol (80:20, % w/w) as described earlier (Arwidsson and Nicklasson, 1989).

Statistical calculations

A two-way analysis of variance was performed on the intrinsic viscosity as well as the interaction constant data obtained ($n = 20$ for each analysis). Ethyl cellulose grade and solvent system were the two variables for categorizing the data. The probabilities (P values) that the responses $[\eta]$ and k' might be unaffected by the variables were calculated.

Results and Discussion

The dynamic viscosities, the molecular weights, and the ethoxyl contents found for the ethyl cellulose grades are presented in Table 1. The corresponding values for an ethyl cellulose 10 cps lot earlier reported (Arwidsson and Nicklasson, 1989) are also included.

The linear regression lines for the three ethyl cellulose grades in ethanol according to Eqn 1,

$$\eta_{sp}/c = [\eta] + k'[\eta]^2 c \qquad (1)$$

are presented in Fig. 1, as well as the results from ethyl cellulose 10 cps published earlier (Arwidsson and Nicklasson, 1989). η_{sp} = specific viscosity at the concentration c, $[\eta]$ = intrinsic viscosity, and k' = interaction constant. The slopes, representing the total interaction between the polymer molecules in solution (Alfrey, 1947), increase with increasing viscosity grade of ethyl cellulose as can be expected from the intrinsic viscosity factor, $[\eta]^2$, in the interaction term. The interaction constant, k', which is compensated for this component is thus not dependent on the molecular weight (Alfrey, 1947; Huggins, 1942). The k' values for the different ethyl cellulose grades in ethanol were found to be between 0.50 and 0.63.

The correlation coefficients, r, were found to be ≥ 0.99 for each of the polymer grades in each of the solvent systems studied when applying the same relationship as described in Fig. 1. In meth-

TABLE 1

Properties of the studied ethyl cellulose grades

Property	Ethyl cellulose grade			
	7 cps	10 cps [a]	22 cps	50 cps
Dynamic viscosity, η (mPa) [b]	7.3	9.7	20.3	48.0
Average molecular weight, by weight, M_w (g/mol)	31200	38300	45600	57400
Ethoxyl content (% w/w)	47.0	48.3	49.0	49.6

[a] Data taken from Arwidsson and Nicklasson, 1989.
[b] A 5% w/w solution in toluene/ethanol (80:20, % w/w) at 25 °C.

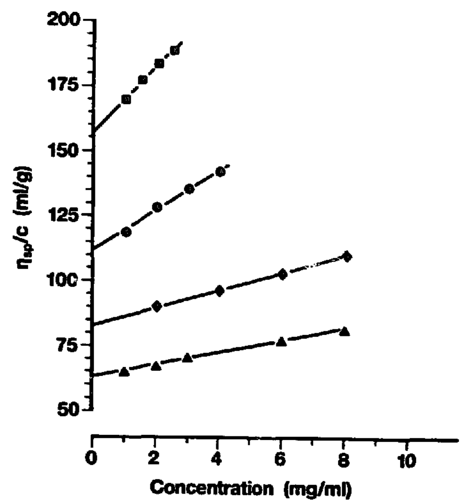

Fig. 1. Specific viscosity/concentration, η_{sp}/c, vs. concentration, for different grades of ethyl cellulose in ethanol. The straight lines were obtained by linear regression according to Equation (1). (▲) 7 cps. (◆) 10 cps, data taken from Arwidsson and Nicklasson, 1989. (●) 22 cps, (■) 50 cps.

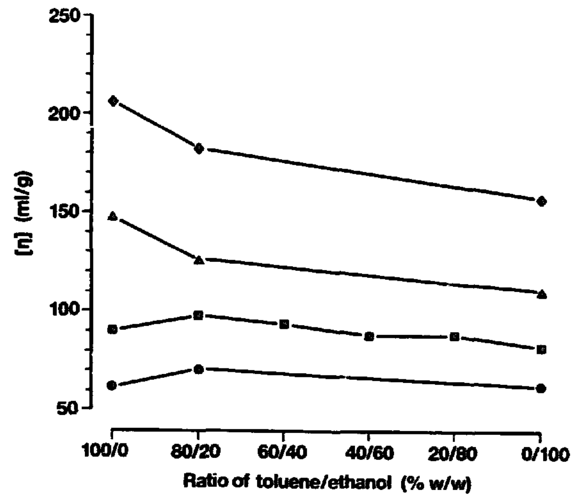

Fig. 3. Intrinsic viscosity, [η], for different grades of ethyl cellulose as a function of the toluene/ethanol ratio. (●) 7 cps. (■) 10 cps, data taken from Arwidsson and Nicklasson, 1989. (▲) 22 cps, (◆) 50 cps.

ylene chloride, 95% confidence intervals were calculated for k' and [η] to 0.59 ± 0.021 and 93 ml/g $\pm$ 1.6 ml/g, respectively, based on 5 separate series of ethyl cellulose 10 cps solutions (Arwidsson and Nicklasson, 1989).

Fig. 2 shows k' as a function of the ratio of toluene/ethanol in single or binary solvent systems. The minimum k' value found at a solvent ratio of 80:20 (% w/w) for ethyl cellulose 10 cps (Arwidsson and Nicklasson, 1989) was found for ethyl cellulose 7, 22, and 50 cps grades as well, indicating that this solvent system shows a high solvent power for ethyl cellulose. The maximum values for [η] which are found for ethyl cellulose 7 cps and 10 cps, as can be seen in Fig. 3, support

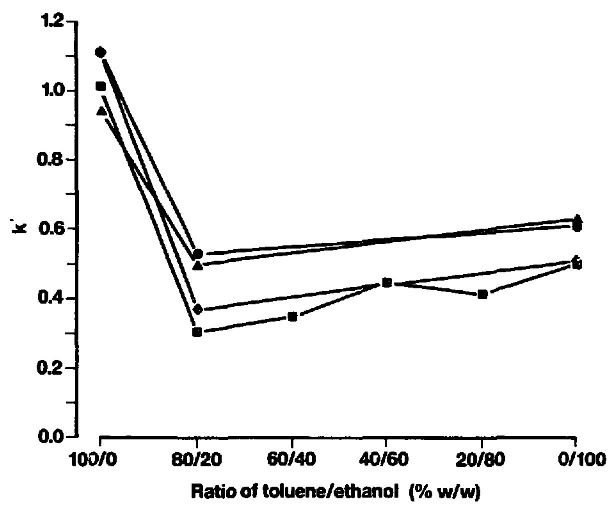

Fig. 2. Interaction constant, k', for different grades of ethyl cellulose as a function of the toluene/ethanol ratio. (●) 7 cps. (■) 10 cps, data taken from Arwidsson and Nicklasson, 1989. (▲) 22 cps, (◆) 50 cps.

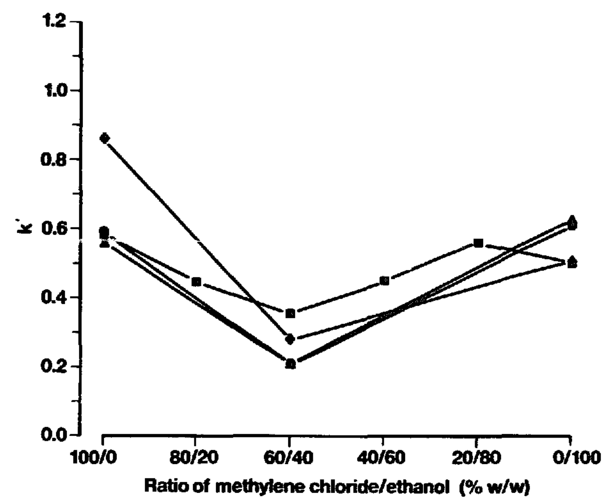

Fig. 4. Interaction constant, k', for different grades of ethyl cellulose as a function of the methylene chloride/ethanol ratio. (●) 7 cps. (■) 10 cps, data taken from Arwidsson and Nicklasson, 1989. (▲) 22 cps, (◆) 50 cps.

this theory. However, the higher viscosity grades of ethyl cellulose, i.e. 22 and 50 cps, show higher [η] values for toluene than for toluene/ethanol (80:20, % w/w). This cannot be explained based on the currently available data.

The binary mixtures of methylene chloride and ethanol generated the k' values shown in Fig. 4. At the ratio of 60:40 (% v/w), a minimum is obtained for k' indicating that this solvent system solves each of the polymer grades studied more effectively than methylene chloride or ethanol per se. In Fig. 5, [η] values are shown for the same series of solvent mixtures. As can be seen, the relationships between the solvent systems studied are the same for each of the ethyl cellulose grades.

The results from the two-way analyses of variance shown in Table 2 reveal that the intrinsic viscosity as well as the interaction constant for ethyl cellulose significantly depend on the solvent system applied ($P \leq 0.01$). The ethyl cellulose grade has a significant impact on the intrinsic viscosity values ($P < 0.01$) as can be expected from the relationship described by Eqn 2,

$$[\eta] = KM_w^a \quad (2)$$

where M_w is the molecular weight and K and a are constants (Braudrup, 1975). The straight lines

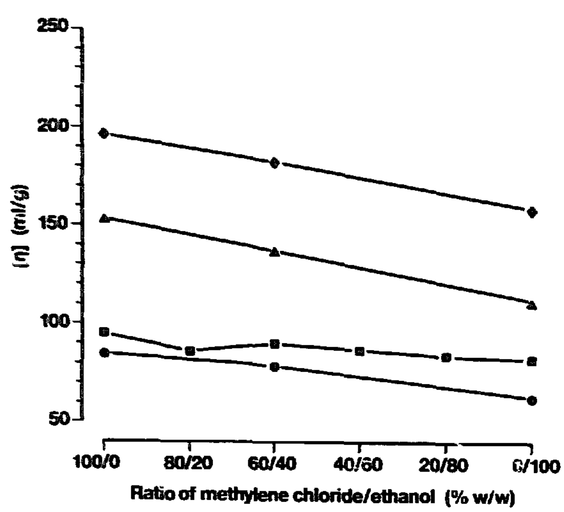

Fig. 5. Intrinsic viscosity, [η], for different grades of ethyl cellulose as a function of the methylene chloride/ethanol ratio. (●) 7 cps, (■) 10 cps, data taken from Arwidsson and Nicklasson, 1989. (▲) 22 cps, (◆) 50 cps.

TABLE 2

An overall statistical analysis (two-way analysis of variance, n = 20) on the dependency of solvent system and ethyl cellulose grade on interaction constant and intrinsic viscosity response, respectively (the P values are given in the Table; a low P value indicates that the response obtained is dependent on the variable studied)

Response	Variable	
	Solvent system	Ethyl cellulose grade
Intrinsic viscosity, [η]	0.01	< 0.01
Interaction constant, k'	< 0.01	0.64

obtained by linear regression analysis on a plot of log[η] vs log M_w show correlation coefficients which are ≥ 0.97 for each solvent system applied. However, unlike the intrinsic viscosity, the interaction constant is independent of the ethyl cellulose grade within the range studied ($P = 0.64$). These results indicate that k' may be used as a more powerful criterion compared to [η] for evaluating the solvent power of different solvent systems for ethyl cellulose even if the values are obtained from different molecular weights of the polymer. This possibility is of considerable importance since the molecular weight is a useful formulation variable in film coating. The tensile strength of a film has been found to increase with increasing molecular weight and the incidence of e.g. edge splitting is thus reduced (Rowe, 1980, 1982). In order to avoid mechanical damage of the film and thus dose-dumping from a film-coated extended release formulation, the tensile strength of the film has to be sufficiently high. Hence, the molecular weight of the coating polymer may be one of the most critical variables when formulating an extended release system in which a high internal pressure is built up during the release process. In such a formulation program, k' may serve as a convenient tool for selecting the solvent system for ethyl cellulose.

Conclusions

The interaction constants, k', obtained for 4 different grades of ethyl cellulose show the lowest values for mixtures of methylene choride/ethanol (60:40, % w/w) and for toluene/ethanol (80:20, % w/w), respectively, compared to the single solvents per se, indicating that the two binary solvent mixtures show a relatively strong solvent power for ethyl cellulose. Thus, a mixture of a poorly hydrogen bonding solvent and an alcohol, e.g. methylene chloride/ethanol (60:40, % w/w), may be an advantageous solvent system for a spray coating process of a controlled release formulation. The concept of the interaction constant can be used within the range of ethyl cellulose grades studied independent of molecular weight in order to select the most suitable solvent system. Intrinsic viscosity, $[\eta]$, which is molecular weight-dependent, is not as generally applicable as k'. However, it may be advantageous to use the two parameters in combination when studying a single polymer grade. The application of dilute solution viscosity data in order to select optimum solvent systems for a coating process is a powerful tool at an early stage of a formulation program for a film-coated controlled release system.

Acknowledgements

Thank are due to Dr. Anders Garå, Astra Pain Control and Dr. Göran Östling, Astra Pharmaceutical Production AB for skillful accomplishment of the GPC and ethoxyl analyses. The authors also want to thank Ms. Birgitta Klingberg for valuable assistance with the experiments.

References

Alfrey, T., The influence of solvent composition on the specific viscosities of polymer sol ıtions. *J. Coll. Sci.*, 2 (1947) 99–114.

Arwidsson, H. and Nicklasson, M., Application of intrinsic viscosity and interaction constant as a formulation tool for film coating. I. Studies on ethyl cellulose 10 cps in organic solvents. *Int. J. Pharm.*, 56 (1989) 187–193.

Azoury, R., Elkayam, R. and Friedman, M., Nuclear magnetic resonance study of an ethyl cellulose sustained-release delivery system. 1. Effect of casting solvent on hydration properties. *J. Pharm. Sci.*, 77 (1988) 425–427.

Boberski, W.G., Amorphous polymers-potentials for ordered domains in property regulation of polymer coatings. *Ind. Eng. Chem. Prod. Res. Dev.*, 14 (1975) 139–140.

Braudrup, J. and Immergut, E.H., Viscosity-molecular weight relationships and unperturbed dimensions of linear chain molecules. In Braudrup, J. and Immergut, E.H. (Eds.) *Polymer Handbook, 2nd edn.*, Wiley, New York, 1975, pp. IV1–IV60.

Eskilsson, C., Appelgren, C. and Bogentoft, C., A note on the properties of ethyl cellulose-propylene glycol membranes. *Acta Pharm. Suecica*, 13 (1976) 285–288.

Haas, H.C., Farney, L. and Valle, Jr., C., Some properties of ethyl cellulose films. *J. Colloid Sci.*, 1 (1952) 584–599.

Huggins, M.L., The viscosity of dilute solutions of long-chain molecules. IV. Dependence of concentration. *J. Am. Chem. Soc.*, 64 (1942) 2716–2718.

Kent, D.J. and Rowe, R.C., Solubility studies on ethyl cellulose used in film coating. *J. Pharm. Pharmacol.*, 30 (1978) 808–810.

Rowe, R.C., The molecular weight and molecular weight distribution of hydroxypropyl methylcellulose used in film coating of tablets. *J. Pharm. Pharmacol.*, 32 (1980) 116–119.

Rowe, R.C., Some fundamental properties of polymeric materials and their application in film coating formulations – A review. *Int. J. Pharm. Technol. Product Manuf.*, 3 (1982) 3–8.