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Application of intrinsic viscosity and interaction constant as a formulation tool for film coating.
I. Studies on ethyl cellulose 10 cps in organic solvents

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Summary

The dilute solution properties intrinsic viscosity, $[\eta]$, and interaction constant, k', of ethyl cellulose 10 cps in organic solvent systems have been studied in order to select an appropriate solvent system for a coating process. The results indicate that, when considering a rigid polymer such as ethyl cellulose, both $[\eta]$ and k' have to be taken into consideration when deciding the solvent system of preference since $[\eta]$ or k' alone may show an incomplete picture of the solvent system's ability to solve the polymer. A solvent system consisting of methylene chloride and ethanol in the ratio of 60/40% (w/w) was found to effectively solve the model polymer ethyl cellulose 10 cps. Addition of up to 10% of water, a non-solvent for ethyl cellulose, was found to be advantageous for this solvent system. However, if high water concentrations are present in the film coating system, uncontrolled situations may occur in a coating process during the evaporation of the solvents due to the precipitation of the ethyl cellulose.

Introduction

Polymers are widely used in pharmaceutical formulations, e.g. as binding agents, disintegrants, matrices, and film-forming agents. For polymer films, the demand for optimum performance is especially emphasized since they, in some cases, control the release of the active substance from a formulation. The solvent or solvent mixture used for the preparation of the film can be of great importance for the properties obtained (Azoury et al., 1988; Boberski, 1975; Eskilsson et al., 1976; Haas et al., 1952). An effective method for the selection of a suitable solvent system is, therefore, of importance for the design of many oral controlled-release dosage forms.

The application of intrinsic viscosity, $[\eta]$, and interaction constant, k', has been suggested as a tool for selecting appropriate solvents or solvent mixtures for different polymers (Alfrey, 1947). The $[\eta]$ has been applied as a criterion for selecting a single solvent system for ethyl cellulose used in film coating (Kent and Rowe, 1978). The application of the two parameters in combination in

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order to select a binary solvent system for pharmaceutical purposes has been studied to a very limited extent.

The two parameters [η] and k', are both indirect means of measuring the ability of a solvent system to solve a polymer. [η] is an expression of the hydrodynamic interference between polymer and solvent, thus reflecting the solvent's ability to swell the polymer. Hence, rigid polymer molecules, such as cellulose ethers, can be expected to show relatively small differences in [η] due to solvent changes. k' is regarded as an expression of the interaction between dissolved polymer molecules, compensated for the dependence between [η] and the total interaction (Alfrey, 1947). Thus, k' describes the interaction resulting solely from differences in the chemical structure of the polymer and/or the nature of the solvent system independent of the molecular weight (Alfrey, 1947; Huggins, 1942). A low interaction between the dissolved polymer molecules reflects a high solvent power for the specific polymer. The rigidity of a polymer molecule is not likely to affect the intermolecular interaction described by k', due to the intramolecular nature of the rigidity. Hence, for cellulose ethers, k' may be a better expression of the capability of different solvent systems to solve a polymer than [η].

This paper will describe the application of intrinsic viscosity, [η], and interaction constant, k', in order to evaluate the most suitable organic solvent system for a model polymer (ethyl cellulose 10 cps). The most adequate parameter to be used for screening in a formulation design program will be discussed. Water may be present in low quantities in organic solvents or solvent mixtures, e.g. in alcohols. Hence, the impact on [η] and k' for ethyl cellulose 10 cps in the presence of water in an organic solvent system will also be shown.

Materials and Methods

Chemicals

For the viscosity studies, ethyl cellulose 10 cps (Dow Chemical Company, U.S.A.), 1-butanol, toluene (May & Baker Ltd., U.K.), ethanol 99.5% v/v (AB Svensk Sprit, Sweden), methanol (E. Merck, F.R.G.), methylene chloride (ICI, U.K.), *o*-xylene (Fluka AG, Switzerland) and purified water (USP) were used as obtained. Methylene chloride, 2-propanol (May & Baker Ltd., U.K.) and Standard Calibration Kit Polystyrene S-M-10, M_w 1200–2,950,000, (P.L. Polymer, U.K.) were used for the gel permeation chromatography, GPC. Adipinic acid, ethyl iodide (Fluka AG, Switzerland), hydroiodic acid 57%, toluene and *o*-xylene were used for the ethoxyl content determinations.

Equipment

A Rheomat 135 cup and bob viscometer fitted with measuring system 0/115 (Contraves AG, Switzerland) and Cannon Fenske KPG-viscometers 25, 50, 75, and 100 (Schott-Geräte GmbH, F.R.G.), having internal capillary diameters between 0.30 and 0.63 mm, were used for the viscosity measurements. The GPC studies were performed with μBondagel columns (E-Linear, E500, and E-125), a model 6000 pump (Waters Associates, U.S.A.), a model ERC-7530 refractive index detector (Erma, Japan), and a model SP 4200 integrator with the software GPC + (Spectra-Physics, U.S.A.). A model 5840 A gas chromatograph with a flame ionization detector, FID, equipped with a column of 10% OV-101 on Chromosorb (Hewlett-Packard, U.S.A.) was used for the ethoxyl content determinations.

Dynamic viscosity, η

Ethyl cellulose was dissolved in a mixture of toluene and ethanol in the ratio of 80/20 (% w/w) at a concentration of 5% (w/w). η of the solution was determined at 25.0°C using a Rheomat 135 cup and bob viscometer at 643 rpm, which corresponds to a shear rate of 3000 s^{-1}. The viscosity was found to be approximately constant in the range of 2000–4000 s^{-1}.

Dilute solution properties

Methylene chloride, toluene, *o*-xylene, methanol, ethanol, and 1-butanol were studied as single solvent systems. Methylene chloride or toluene were used in binary solvent mixtures with ethanol in ratios of 80/20, 60/40, 40/60, and 20/80 (% w/w). Tertiary mixtures, consisting of methylene chloride, ethanol, and purified water were used in ratios of 57/38/5, 54/36/10, and 53/35/12 (% w/w/w). The kinematic viscosities, ν, of the solvents or solvent mixtures and in most cases series of 4 polymer solutions of different concentrations in each solvent system were determined at 20.0 °C, using a Cannon Fenske viscometer with suitable capillary diameter. This technique was used in order to obtain a good accuracy at the low concentrations studied, i.e. between 1 and 8 mg/ml. The kinematic viscosities of the solvents and solvent systems, ν_0, were calculated as mean values of two determinations, whereas the kinematic viscosities of the ethyl cellulose solutions, ν_c, were single determinations. For methylene chloride, 5 complete series of ethyl cellulose solutions were studied. Separate mean values of ν_0, each based on duplicate determinations, were used for each series. The differences in density between the solvent systems and the ethyl cellulose solutions in the systems were found to be negligible at the concentrations studied. Thus, the specific viscosities, η_{sp}, were calculated at each concentration using Eqn. 1:

$$\eta_{sp} = \frac{\nu_c - \nu_0}{\nu_0} \tag{1}$$

Intrinsic viscosities, $[\eta]$, and interaction constants, k', were calculated by means of linear regression analysis from a plot of η_{sp}/c versus c according to Eqn. 2 (Alfrey, 1947):

$$\eta_{sp}/c = [\eta] + k'[\eta]^2 c \tag{2}$$

From the slope and the intercept, k' and $[\eta]$ were obtained, respectively. Eqn. 2 is valid at low concentrations only. At higher polymer concentrations, terms considering higher powers of c have to be added to the equation (Huggins, 1942). The concentration ranges studied were all within the linear portion. Mean values and 95% confidence intervals were calculated for $[\eta]$ and k' in methylene chloride, based upon the 5 separate experiments.

Gel permeation chromatography (GPC)

Ethyl cellulose (2% w/v) was dissolved in methylene chloride/2-propanol in the ratio of 72/28 (% v/v). Each polystyrene standard (0.2% w/v) was dissolved in the same eluent. 20 μl of each solution were separately injected into the GPC columns. The weight average molecular weight, M_w, was calculated according to the GPC + program mentioned above.

Analysis of ethoxyl content

The ethoxyl content was determined according to the procedure described in USP XXI for the assay of hydroxypropyl methylcellulose 2906 (USP, 1985) with appropriate modifications. After reaction of about 35 mg ethyl cellulose with hydroiodic acid, the formed ethyl iodide was detected by gas chromatography, using a column of 10% OV-101 on Chromosorb and a FID detector. Standard solutions were prepared from ethyl iodide.

Results and Discussion

Table 1 shows the values found for the studied ethyl cellulose 10 cps lot, regarding viscosity, molecular weight, and ethoxyl content.

Fig. 1 presents the linear regression lines for ethyl cellulose in two of the single solvent systems, i.e. ethanol and toluene. These two systems show different behaviours with respect to interaction and swelling, as can be seen from the slopes and the intercepts. For the single solvents, the binary solvent systems and for methylene chloride, ethanol and water in the ratio of 57/38/5 (% w/w/w) the correlation coefficients, r, were found to be $\geqslant 0.99$ when applying the relationship described in Fig. 1. At a higher percentage of water

TABLE 1

Properties of the studied ethyl cellulose 10 cps lot

Property	Value
Dynamic viscosity, η (mPa) [a]	9.7
Average molecular weight, by weight, M_w (g/mol)	38300
Ethoxyl content (% w/w)	48.3

[a] A 5% (w/w) solution in toluene/ethanol 80/20 (% w/w) at 25 °C.

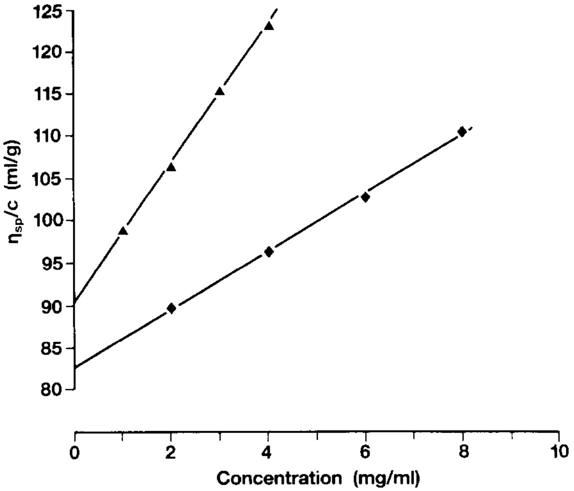

Fig. 1. Specific viscosity/concentration, η_{sp}/c versus concentration, for ethyl cellulose 10 cps in ethanol (◆) and toluene (▲). The straight lines were obtained by linear regression according to Eqn. 2.

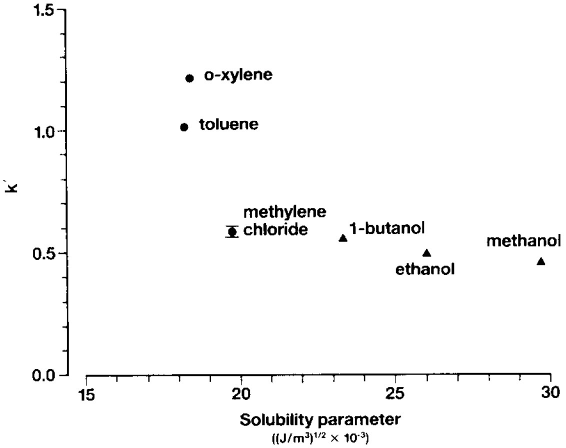

Fig. 2. Interaction constant, k', for ethyl cellulose 10 cps in different solvents as a function of the solubility parameter of the solvents. Solubility parameter data taken from Burrell (1975). (●), Poor hydrogen bonding capacity; (▲), strong hydrogen bonding capacity. Bars denote the 95% confidence interval.

in the methylene chloride/ethanol system, i.e. 10 and 12%, correlation coefficients of 0.95 and 0.96 were found, respectively. The decreasing accuracy in the results at the higher water contents may be explained by the proximity to the precipitation point, which will be discussed below.

In Table 2, the dilute solution properties, k' and $[\eta]$, are shown for ethyl cellulose 10 cps in each of the single organic solvents studied. The range of the $[\eta]$ values is relatively small, i.e. about 3 times the confidence interval for methylene chloride. k', however, shows a comparably higher sensitivity with values ranging from 0.46 to 1.2, i.e. about 18 times the confidence interval for methylene chloride. These findings support the hypothesis that k' may be a more decisive variable for describing solvent power for rigid polymers such as ethyl cellulose than $[\eta]$.

TABLE 2

Intrinsic viscosity, $[\eta]$, and interaction constant, k', for ethyl cellulose 10 cps in different organic solvents, determined from single series of solutions

Solvent	Hydrogen bonding capacity [a]	$[\eta]$ (ml/g)	k'
Methanol	strong	87	0.46
Ethanol	strong	83	0.50
1-Butanol	strong	86	0.56
Methylene chloride	poor	93 ± 1.6 [b]	0.59 ± 0.021 [b]
Toluene	poor	90	1.0
o-Xylene	poor	86	1.2

[a] Taken from Burrell (1975).

[b] Mean value of 5 separate series ± 95% confidence limits.

Fig. 2 shows k' as a function of the solubility parameter for each single solvent. The solubility parameter of ethyl cellulose N grade is 16.6–22.7, and $19.4–29.7 \cdot 10^3\ (J/m^3)^{1/2}$ for poorly and strongly hydrogen-bonding solvents, respectively (Burrell, 1975). Other values reported in the literature are $19.4–19.7 \cdot 10^3\ (J/m^3)^{1/2}$ (Kent and Rowe, 1978) and $16.1–20.6 \cdot 10^3\ (J/m^3)^{1/2}$ (Sakellariou et al., 1986). The poorly hydrogen bonding solvents show high values of k' at low solubility parameter values. Methylene chloride shows a solubility parameter of $19.8 \cdot 10^3\ (J/m^3)^{1/2}$ (Burrell, 1975), which is close to the values reported by Kent and Rowe (1978). Accordingly, the k'-value found for methylene chloride is low compared to the values found for the other poorly hydrogen bonding solvents studied, i.e. toluene and *o*-xylene. For the strongly hydrogen bonding solvents, there are no pronounced differences in k' values.

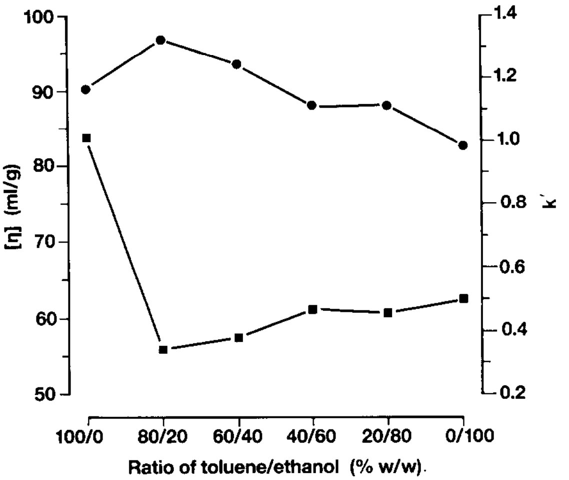

Fig. 3. Intrinsic viscosity, [η], and interaction constant, *k'*, for ethyl cellulose 10 cps as a function of the toluene/ethanol ratio. (●), intrinsic viscosity, [η]; (■), interaction constant, *k'*.

Fig. 3 shows the two parameters, [η] and *k'*, as functions of the ratio of toluene/ethanol in binary solvent systems. In toluene, a pronounced intermolecular interaction was found as shown by a high *k'*-value (1.0). A minimum for *k'* is reached at a 20% (w/w) ethanol content in the solvent mixture followed by a slight increase with increasing ethanol content. [η] shows a maximum at 20% (w/w) ethanol content. Thus, the two parameters show similar pictures regarding polymer–solvent compatibility in the binary solvent mixtures of toluene and ethanol indicating that the ratio of 80% toluene and 20% (w/w) ethanol is the most favourable solvent system for ethyl cellulose. The combination of toluene and ethanol 95% in the ratio of 80/20 (% w/w) is widely used to determine the viscosity of a 5% solution of ethyl cellulose (National Formulary, 1985; Standard, 1983).

Data for the binary mixtures of methylene chloride and ethanol are shown in Fig. 4. At the ratio of 60/40 (% w/w), a minimum is shown for *k'* indicating a low interaction between polymer molecules in solution and, thus, a high power of the solvent system. [η] shows only limited variations between the solvent mixtures studied. Thus, ethanol seems to increase the solvent compatibility with ethyl cellulose when added to toluene or methylene chloride to a level of up to 40% (w/w). When more ethanol is added, a less favourable system is obtained.

Water is well-known as a non-solvent for ethyl cellulose. A solvent system containing water could, therefore, be expected to show a low solvent power for ethyl cellulose compared to the same system without water. A series of solvent mixtures consisting of methylene chloride and ethanol in the ratio of 60/40 (% w/w) with the admixture of different amounts of water was studied and the dilute solution properties obtained are shown in Fig. 5. When quantities of up to 10% (w/w) of water are added to the methylene chloride/ethanol solvent system, somewhat lower *k'*-values are found compared to the original solvent system. The [η] increases somewhat, which is in agreement with the decreasing *k'*-values. This indicates a slightly favourable effect of low water content in this organic solvent mixture when using ethyl cellulose 10 cps as test polymer. At more than 10% addition of water, the interaction between molecules increases rapidly with precipitation at approximately 13% water content. Hence, one has to consider the potential risk of getting too high a concentration of water in the system during evaporation which may be a difficult situation to control in a film-coating process due to the sharp effects shown in Fig. 5. When using hot air to

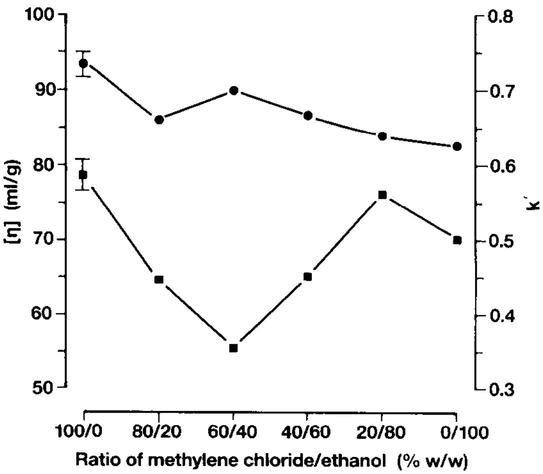

Fig. 4. Intrinsic viscosity, [η], and interaction constant, *k'*, for ethyl cellulose 10 cps as a function of the methylene chloride/ethanol ratio. (●), intrinsic viscosity, [η]; (■), interaction constant, *k'*; bars denote the 95% confidence intervals.

evaporate the solvent, water may be condensed from the air onto the cold evaporating solvent surface, since the evaporating process per se has a cooling effect, giving rise to a further increase of the water content. Thus, a precipitation of the polymer may occur prior to the critical gelation step resulting in radically impaired coating properties.

The two dilute solution parameters studied, $[\eta]$ and k', seem to point in the same direction when considering solvent systems consisting of a single strongly hydrogen bonding solvent or a poorly hydrogen bonding solvent in combination with at least one strongly hydrogen bonding solvent as shown in Fig. 6. As can be seen, a low interaction between molecules in solution (k') is accompanied by a high degree of swelling of the individual molecules ($[\eta]$). This indicates a high ability of the solvent to solve the polymer. A similar relationship is shown in Fig. 6 for single poorly hydrogen bonding solvents. Due to the rigid nature of e.g. ethylcellulose, $[\eta]$ may be a less sensitive expression of the solvent power compared to k', as indicated by the confidence intervals in Fig. 6. Hence, it is recommended to consider the two parameters in combination when deciding the solvent system of preference for cellulose ethers used in a coating process.

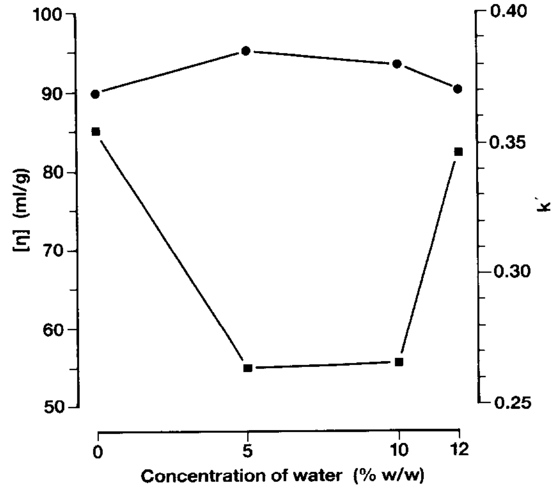

Fig. 5. Intrinsic viscosity, $[\eta]$, and interaction constant, k', for ethyl cellulose 10 cps as a function of the concentration of water added to a mixture of methylene chloride and ethanol in the ratio of 60/40 (% w/w). (●), intrinsic viscosity, $[\eta]$; (■), interaction constant, k'.

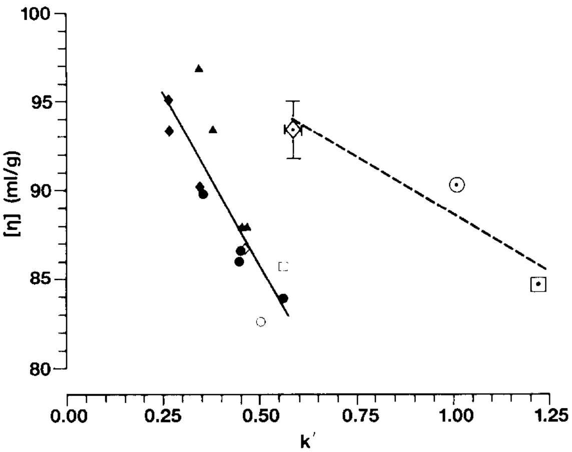

Fig. 6. Intrinsic viscosity, $[\eta]$, as a function of the interaction constant, k', for ethyl cellulose 10 cps in different single, binary or tertiary solvent systems. (●), Methylene chloride/ethanol; (▲), toluene/ethanol; (◆), methylene chloride/ethanol/water; (□), 1-butanol; (○), ethanol; (◇), methanol; (◇), methylene chloride; (⊙), toluene; (⊡), *o*-xylene. The straight lines were obtained by linear regression of the results for solvent systems consisting of at least one strongly hydrogen bonding solvent (———) and for single poorly hydrogen bonding solvent (- - - - -), respectively. Bars denote the 95% confidence intervals.

Conclusions

The dilute solution properties described by k' and $[\eta]$ can be of great theoretical and practical importance when selecting solvent systems for e.g. film coating operations aiming at oral controlled-release dosage forms. The two parameters indirectly reflect the ability of a solvent system to solve a polymer from theoretically different points of view. A combination of the two parameters is, therefore, recommended when considering rigid polymers like cellulose ethers.

Mixtures between a poorly hydrogen bonding solvent and a strongly hydrogen bonding solvent, e.g. methylene chloride/ethanol 60/40% (w/w), have been shown to be suitable solvent systems for ethyl cellulose 10 cps when considering $[\eta]$ and k'.

Addition of up to 10% of water to the mixture of methylene chloride and ethanol is advantageous for the solvent power for ethyl cellulose 10 cps. However, since the polymer precipitates at approximately 13% water content in the solvent mixture, problems may occur during the evaporation of the more volatile organic components at a coating operation even at relatively low original water concentrations. Thus, even a low water content should be avoided in the organic solvent systems intended for coating with ethylcellulose.

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