A second explanation is that the total amount of insulin absorbed was increased in diabetic dogs. In recent years, Olsen & Rosenberg (1970) and Younoszai & Schedl (1972) demonstrated that total absorption of glucose, amino acids, lipid, etc, from the intestine was increased in diabetic animals compared with that in normal animals. The mechanisms of the increased absorption of insulin from the rectum in dabetic state require clarification.

Eighty U kg^{-1} (Patel & Ryman, 1975) and 25 U kg^{-1} (Shichiri & others, 1974) of oral insulin preparations were required to lower the blood glucose concentrations of alloxan rats and of normal rabbits, respectively. These results indicate the insulin suppository to be more effective than oral insulin preparations.

REFERENCES

BAKTH, S., MAY, P., AKGUN, S. & ERTEL, N. (1976). *Clin. Res.*, **24**, 636A.
INOUYE, W. Y. & VARS, H. M. (1962). *Surg. Forum.*, **13**, 316–317.
HALES, C. N. & RANDLE, P. J. (1963). *Biochem. J.*, **88**, 137–146.
HOFFMAN, W. S. (1937). *J. biol. Chem.*, **120**, 51–55.
OLSEN, W. A. & ROSENBERG, I. H. (1970). *J. clin. Invest.*, **49**, 96–105.
PATEL, H. M. & RYMAN, B. E. (1975). *FEBS Letters*, **62**, 60–63.
SHICHIRI, M., SHIMIZU, Y., YOSHIDA, M., KAWAMORI, R., FUKUCHI, M., SHIGETA, Y. & ABE, H. (1974). *Diabetologia*, **10**, 317–321.
SHICHIRI, M., KAWAMORI, R., YOSHIDA, M., ETANI, N., HOSHI, M., IZUMI, K., SHIGETA, Y. & ABE, H. (1975) *Diabetes*, **24**, 971–976.
SHIGETA, Y., SHICHIRI, M., OKADA, A. & KARASAKI, K. (1972). *Endocrinology*, **91**, 320–322.
STIMMLER, L. (1967). *Diabetes*, **16**, 652–655.
YOUNOSZAI, M. K. & SCHEDL, H. P. (1972). *Am. J. Physiol.*, **223**, 828–831.

Solubility studies on ethyl cellulose used in film coating

D. J. KENT, R. C. ROWE*, *ICI Pharmaceuticals Division, Alderley Park, Cheshire, SK10 2TG, U.K.*

It has long been recognized that the properties of films are dependent on the solvent used for coating and as a general rule it can be said that maximum coating solvation and polymer chain extension will produce the most superior films showing the greatest cohesion (Banker, 1966). A knowledge of the solubility of polymers is of great importance, therefore, and in this respect polymer chemists have tended to use the solubility parameter approach. This is based on the regular solution theory of Hildebrand & Scott (1950) who proposed that the heat of mixing (ΔH in the Gibb's free energy equation) is given by:

$$\Delta H = Vm \left[\left(\frac{\Delta E_1}{V_1} \right)^{\frac{1}{2}} - \left(\frac{\Delta E_2}{V_2} \right)^{\frac{1}{2}} \right]^2 \phi_1 \phi_2$$

where Vm is the total volume of the mixture, ΔE is the energy of vaporization of component 1 or 2, V is the molar volume of component 1 or 2 and ϕ is the volume fraction of component 1 or 2. The expression $\Delta E/V$ is usually described as the cohesive energy density and the square root of this has been given the symbol δ-the solubility parameter. It can be seen that the heat of mixing of two substances is thus dependent on $(\delta_1 - \delta_2)^2$

* Correspondence.

and that if $\delta_1 = \delta_2$ complete solubility and miscibility is assured.

This means that each polymer or solvent can be characterized by its solubility parameter which should define its compatibility with every other solvent. For solvents, the solubility parameter can be readily calculated from heat of vaporization and extensive lists are now available (Burrell, 1975). For polymers the solubility parameter is often determined from studies of polymer/solvent interactions (as measured by swelling or intrinsic viscosity) which are assumed to be at a maximum when the solubility parameter of the polymer is equal to the solubility parameter of the solvent. However, it has been argued by several authors (Crowley & others, 1966; Hansen, 1967) that a single parameter is not enough for solvents possessing a significant dipole moment (e.g. alcohols, esters, ketones, aldehydes, etc.) and they have suggested the use of three component parameters. These are difficult to apply practically, and for most purposes the technique described by Burrell (1975) is more commonly used. This involves determining the solubility parameter range of a polymer in three classes of solvents (capable of poor, moderate or strong hydrogen bonding) by mixing a known weight of the polymer in a selected

solvent and observing the resultant mixture. If it is single phase and free from gel particles, the polymer is 'judged' soluble. The mid-point of the solubility parameters of the range of solvents in which the polymer is soluble is usually taken as its solubility parameter. This method suffers from the disadvantage in that it does not quantify the degree of polymer/solvent interaction in each of the solvent classes and this is of importance when predicting the properties of films cast from solvent mixtures. During research work on ethyl cellulose, a polymer used widely in the preparation of delayed release films (Shah & Sheth, 1972), it was found necessary to define the optimum solvent for this polymer and this study reports work to that end.

Three batches of ethyl cellulose (Hercules Powder Co. Ltd., U.S.A.) were used: two were grade N7 each with a viscosity value of 7·5 mPas (U.S.N.F. XIV 1975) but with ethoxyl contents of 47·9 and 49·9% (U.S.N.F. XIV 1975) respectively; the other was grade N50 with a viscosity value of 45·5 mPas and ethoxyl content of 47·9%. The solvents used together with their molar volumes and solubility parameters are given in Table 1.

Intrinsic viscosities were determined by measuring the viscosities of the solvent and a solution of known concentration of the polymer (usually between 0·1 and 0·5% w/w) using a U tube viscometer and substituting these values in the equations derived by Rudin & Wagner (1975). All measurements were made at 25°C.
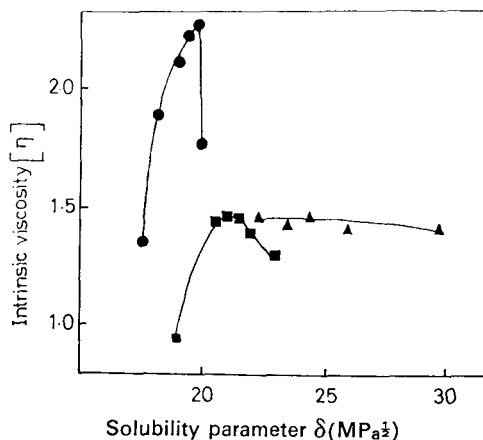
The solubility profile for the N50 grade of ethyl

FIG. 1. The solubility profile of N50 grade ethyl cellulose in:—● Poorly hydrogen bonding solvents. ■ Moderately hydrogen bonding solvents. ▲ Strongly hydrogen bonding solvents.

cellulose is shown in Fig. 1. Similar results were found for the N7 grade with the same ethoxyl content except that the intrinsic viscosities were much lower. While there are distinct maxima in the curves for the poorly and moderately hydrogen bonding solvents, there is little or no difference over the solubility parameter range 20–30 MPa$^{\frac{1}{2}}$ for the strongly hydrogen bonding solvents. The highest intrinsic viscosity values occur in the poorly hydrogen bonding solvents indicating that these are the better solvents for ethyl cellulose. The maxima in the curve at solubility parameter 19·7 MPa$^{\frac{1}{2}}$ for the poorly hydrogen bonding solvents is very similar to that predicted from the mid-point of the solubility parameter range given by (Burrell, 1975) but for the other two solvent classes the results vary, although the single solubility parameter value for ethyl cellulose in the literature of 21·1 MPa$^{\frac{1}{2}}$ (Burrell, 1975) is very close to the maxima for the moderately hydrogen bonding solvents.

These results make no correction for the molar volume of the solvent. This can be done using the equation (Huglin & Pass, 1968):

$$\left[\frac{1}{V_S} \ln \left(\frac{[\eta]_{max}}{[\eta]} \right) \right]^{\frac{1}{2}} = k^{\frac{1}{2}}(\delta s - \delta p)$$

where Vs is the molar volume of the solvent, $[\eta]$ and $[\eta]_{max}$ are the intrinsic viscosities in the solvent and the maximum obtainable for that class of solvent (estimated from graphical plots similar to Fig. 1), k is a constant and δp and δs are the solubility parameters of the polymer and solvent respectively. A plot of the left hand side of this equation (ordinate) vs δs (abscissa) yields a straight line intersecting the abscissa axis at a value δs which equals the solubility parameter of the polymer. Data for all three batches of ethyl cellulose in

Table 1. *Properties of the solvents used for solubility studies.*

	Solubility parameter MPa$^{\frac{1}{2}}$	Molar volume cm³ mol^{-1}
Solvents capable of poor hydrogen bonding		
Carbon tetrachloride	17·6	97·1
Toluene	18·2	106·8
Chloroform	19·0	80·7
Chlorobenzene	19·4	102·1
Dichloromethane	19·8	63·9
Ethylene dichloride	20·0	79·4
Solvents capable of moderate hydrogen bonding		
Dibutyl phthalate	19·0	266
Diethyl phthalate	20·5	198
Methyl formate	20·9	61·6
Ethylene glycol monoethyl ether	21·5	97·8
Dimethyl phthalate	21·9	163·0
Ethylene glycol monomethyl ether	23·3	79·1
Solvents capable of strong hydrogen bonding		
2-Butanol	22·1	92·0
Isopropanol	23·5	76·8
n-Propanol	24·3	75·2
Ethanol	26·0	58·5
Methanol	29·7	40·7

the poorly hydrogen bonding class of solvents was analysed in this way and the resultant regression lines are shown in Fig. 2. It can be seen that the solubility parameter of ethyl cellulose in this class of solvent varies with the ethoxyl content of the polymer, the batch with the highest ethoxyl content (49·9 %) having the lowest solubility parameter (19.0 MPa$^{\frac{1}{2}}$). The two batches with the same ethoxyl content but different molecular weights have a higher solubility parameter (19·4 MPa$^{\frac{1}{2}}$).

The authors of one of the first published papers on ethyl cellulose films (Haas & others, 1952) found that for all the film properties studied—density, tensile strength, modulus of elasticity and elongation—the
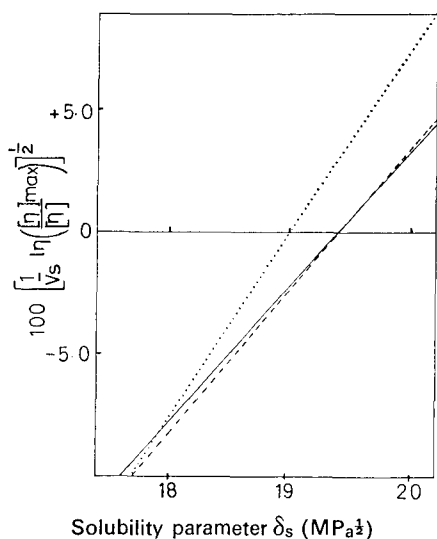
order of solvents was benzene > chlorobenzene > 2-nitropropane. This illustrates the potential of the solubility parameter approach since from the data reported here, this could have been predicted since 2-nitropropane has a solubility parameter of 20·3 MPa$^{\frac{1}{2}}$ as compared to 19·4 MPa$^{\frac{1}{2}}$ for chlorobenzene and 18·8 MPa$^{\frac{1}{2}}$ for benzene.

The data has also implications in:—

(a) The choice of mixed solvent systems. In the film coating of solid dosage forms mixtures of chlorinated hydrocarbons and alcohols are often used. For ethyl cellulose a good solvent mixture would be one in which the alcohol (in which it is relatively poorly soluble—Fig. 1) evaporates at a faster rate than the chlorinated hydrocarbon so that at the point of gelling the solvent system is rich in the poorly hydrogen bonding solvent.

(b) The prediction of film/substrate adhesion. It has been found that film/substrate adhesion is greatest when the polymer is cast from a solvent with a solubility parameter close to that of the polymer (Engle & Fitzwater, 1962; Nadkarni & others 1975).

(c) The choice of plasticizers. It has been suggested that the optimum plasticizer for a polymer will be one that has a solubility parameter close to that of the polymer (Bernardo & Burrell, 1972). For ethyl cellulose this would mean that diethyl phthalate ($\delta = 20·5$ MPa$^{\frac{1}{2}}$) would be a better plasticizer than dioctyl phthalate ($\delta = 16·2$ MPa$^{\frac{1}{2}}$). This hypothesis is being tested.

While it must be realized that, at best, the solubility parameter alone is no more than a useful guide to predicting solubility, the results illustrate the potential of a combined approach of solubility parameter and a quantitative measure of the polymer/solvent interaction by intrinsic viscosity measurements. Data on other polymers used in the film coating of solid dosage forms would be invaluable to the formulator in the optimisation of formulations for both sustained release and enteric coatings.

May 10, 1978

FIG. 2. Regression lines (calculated by the method of least squares) for ethyl cellulose . . . . . N7 grade (ethoxyl content 49·9 %) – – – N7 grade (ethoxyl content 47·9 %) —— N50 grade (ethoxyl content 47·9 %).

REFERENCES

BANKER, G. S. (1966). *J. pharm. Sci.*, **55**, 81–89.
BERNARDO, J. J. & BURRELL, H. (1972). In: *Polymer Science*, pp. 538–578. Editor: Jenkins, A. D., North Holland Publishing Co.
BURRELL, H. (1975). In: *Polymer Handbook*. 2nd Edition, pp. IV. 337–360. Editors: Bandrup, J. and Immergut, E. H., Wiley Intersci.
CROWLEY, J. D., TEAGUE, G. S. & LOWE, J. W. (1966). *J. Paint Technol.*, **38**, 269–280.
ENGLE, J. S. & FITZWATER, R. N. (1962). In: *Adhesion and Cohesion*, pp. 89–100. Editor: Weiss, P. N. Y.: Elsevier.
HAAS, H. C. FARNEY, L. & VALLE, C. (1952). *J. Colloid. Sci.*, **1**, 584–599.
HANSEN, C. M. (1967). *J. Paint. Technol.*, **39**, 104–117.
HILDEBRAND, J. H. & SCOTT, R. L. (1950). *Solubility of Non-Electrolytes*. 3rd Edition. N.Y.: Reinhold.
HUGLIN, M. B. & PASS, D. J. (1968). *J. Appl. Polym. Sci.*, **12**, 473–485.
NADKARNI, P. D., KILDSIG, D. O., KRAMER, P. A. & BANKER, G. S. (1975). *J. pharm. Sci.*, **64**, 1554–1557.
RUDIN, A. & WAGNER, R. A. (1975). *J. Appl. Polym. Sci.*, **19**, 3361–3367.
SHAH, N. B. & SHETH, B. B. (1972). *J. pharm. Sci.*, **61**, 412–415.