

THE SOLUBILISING PROPERTIES OF LIQUORICE

BY K. C. JAMES AND J. B. STANFORD*

From the Welsh School of Pharmacy, the Welsh College of Advanced Technology, Cardiff

Received February 7, 1962

Conductivity and surface tension measurements have shown that micelle formation occurs in liquorice extracts. A method of determining solubilising power by vapour pressure measurements is described, and results quoted for benzene, chloroform, ethyl acetate, and hexane.

LIQUORICE has been used in pharmacy for many years, principally as a flavouring agent. It is sometimes used for its expectorant properties, and in recent years attention has been drawn to its anti-inflammatory action. Little, however, has been said of its value as an excipient. The production of a stable foam on agitating liquorice extracts is an indication of the existence of at least one amphipathic constituent. This property has been utilised in non-pharmaceutical fields, since liquorice extracts have been used as foam stabilisers (Housemann, 1929), and as dispersing agents for insoluble dyes (Marnon, 1954). A more useful indication of the surface-activity of liquorice is that liquorice extract B.P. will form an apparently homogeneous mixture with considerable quantities of materials which are insoluble in water, such as chloroform and volatile oils. On dilution of these mixtures with water a clear solution is produced. This behaviour is characteristic of solubilisation, and it was the purpose of this investigation to determine if solubilisation does in fact occur and, if so, how efficient a solubiliser liquorice is.

EXPERIMENTAL

Materials

Liquorice was of B.P. quality. The organic liquids were of analytical reagent quality. Each was redistilled before use, and its purity confirmed by boiling point and refractive index.

Preparation of Extracts

Two extracts were prepared, one according to the instructions of the British Pharmacopoeia. In the second extract water was substituted for ethanol. These will be termed "aqueous extract with ethanol" and "aqueous extract" respectively throughout this paper. 0.02 per cent phenyl mercuric nitrate was added to the aqueous extract to prevent fermentation.

Standardisation of Extracts

Since liquorice extracts vary in composition from batch to batch, the extracts were characterised by determining a range of physical and

* Present address: Miles Laboratories Ltd., Bridgend, Glam.

chemical properties. These are summarised in Table I. Physical constants were measured at 20°. Starches and gums were precipitated with ethanol and weighed, and glycyrrhizin determined gravimetrically, after precipitation, with sulphuric acid, from the solution remaining after removal of starches and gums. The experimental procedure described by Housemann (1922) was adopted, except that to completely precipitate the gums and starches it was found necessary to set the mixture aside overnight. Ethanol was determined by the British Pharmacopoeia method.

TABLE I
PHYSICAL AND CHEMICAL PROPERTIES OF LIQUORICE EXTRACTS

Property	Aqueous extract with ethanol	Aqueous extract
Density	1.135	1.154
n_D^{20}	1.416	1.403
pH	5.45	5.23
λ max.	262.5 m μ	262.5 m μ
<i>Chemical composition (per cent):</i>		
Ethanol (v/v)	17.3	—
Starches and gums (w/w)	13.53	12.37
Glycyrrhizin (w/w)	8.26	7.51

Determination of Critical Micelle Concentration

Conductimetric method. The conductances of dilutions of the aqueous extract were measured at 25° using a Cambridge Bridge. The specific conductance first increased with dilution, reaching a maximum at a concentration of 80.7 per cent of extract. A plot of specific conductance divided by the per cent concentration of extract in the dilution (a function of equivalent conductance), against the square root of the per cent concentration of the extract in the dilution is shown in Fig. 1, and gives a

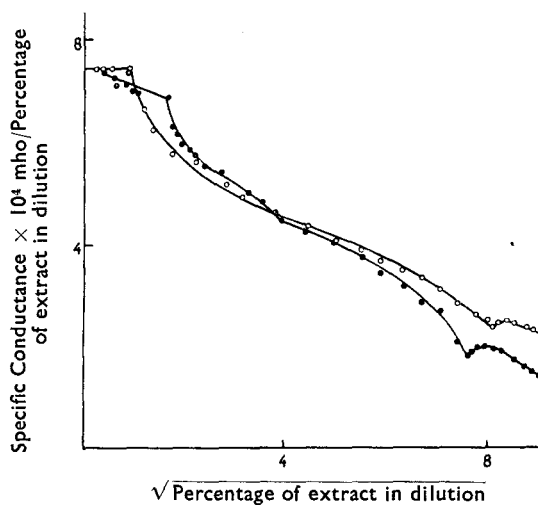


FIG. 1. Concentration-conductance curves for liquorice extracts. ○ Aqueous extract. ● Aqueous extract with ethanol.

SOLUBILISING PROPERTIES OF LIQUORICE

similar inflection, the maximum this time occurring at the lower concentration of 71 per cent. Beyond this the curve continued in a manner characteristic of micelle forming systems, with a critical micelle concentration of 0.9 per cent. The aqueous extract with ethanol gave the same type of curve, with an inflection at 61 per cent, and critical micelle concentration at 2.7 per cent.

A similar curve was obtained with ammoniated glycyrrhizin, but there was no initial maximum in either specific or equivalent conductance. Measurements made with the aqueous extract to which ammoniated glycyrrhizin had been added, showed a maximum in the specific conductance-concentration curve, but this disappeared when equivalent conductances were plotted.

Surface tension method. Surface tensions were determined by measuring with a chainomatic balance the weight necessary to pull a platinum plate out of the surface of the extract. This method has been described fully by Harkins (1930). Measurements were made on aqueous dilutions of the extracts, and surface tension plotted against the per cent concentration of extract in the dilution: the graphs are shown in Fig. 2.

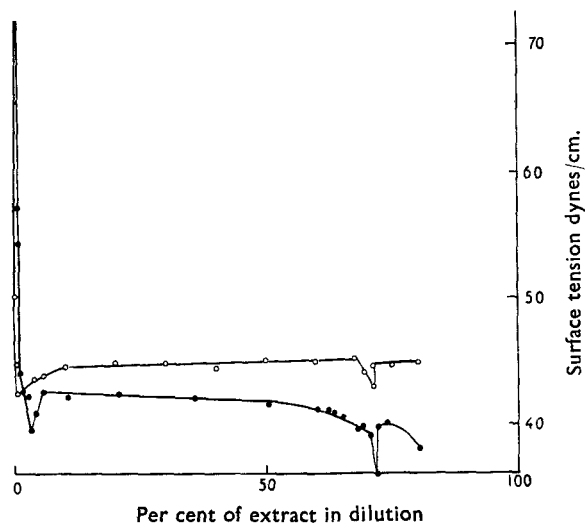


FIG. 2. Concentration-surface tension curves of liquorice extracts. ○ Aqueous extract. ● Aqueous extract with ethanol.

A minimum occurred in the curve for the aqueous extract at 71 per cent, corresponding to the inflection in the conductance curve, but the aqueous extract with ethanol gave a minimum value at 72 per cent, 11 per cent higher than the conductance maximum. Beyond these minima, McBain type III curves were obtained, with critical micelle concentrations at 1 per cent for the aqueous extract, and 3 per cent for the aqueous extract with ethanol. Ammoniated glycyrrhizin gave a similar curve, but without the initial minima shown by the extracts.

The Investigation of Solubilisation

Visual methods cannot be used as liquorice extracts are opaque, and a vapour pressure method similar to that described by McBain (1940, 1941) was therefore adopted. 3.5 g. of extract was weighed into a 100 ml. distilling flask, the side arm of which was fused to a mercury manometer. A rubber bung was used to seal the neck of the flask, and was pierced by a hypodermic needle, through which measured volumes of solubilisate were forced using an Agla micrometer syringe. The apparatus was immersed in a water bath at 25°, and the extract stirred with a magnetic stirrer. The solubilisate was added in increments, and after equilibrium was reached, the manometer level read with a cathetometer. A blank to each determination was carried out using water, or aqueous ethanol of the same strength as the aqueous extract with ethanol.

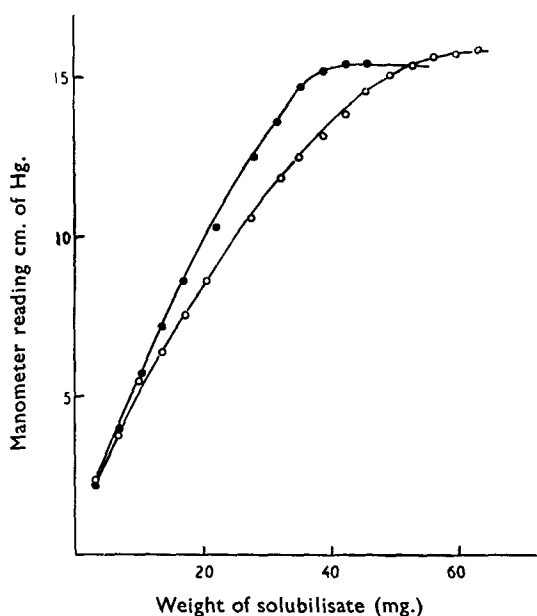


FIG. 3. Vapour pressures of chloroform in aqueous liquorice extract. ● Water. ○ Aqueous extract.

A graph of amount of solubilisate added against vapour pressure is shown in Fig. 3 and is typical of the results obtained. With the blank the vapour pressure rose sharply to a constant limiting value, while with the extract more solubilisate was required to attain the same value. The intersection of the two curves was taken as the limit of solubilisation. After intersection, the vapour pressure curve of the extract rose to a higher limiting value. McBain (1940) has predicted such behaviour when solubilisation gives way to emulsification. Fig. 3 represents the solubilisation of chloroform by the aqueous extract. Other solubilisates examined

SOLUBILISING PROPERTIES OF LIQUORICE

were benzene, ethyl acetate, and hexane. The quantities solubilised are shown in Table II.

TABLE II
SOLUBILISATION BY LIQUORICE EXTRACTS

Solubilisate	Percentage (w/v) solubilised			
	Aqueous extract	Aqueous extract with ethanol	Sodium oleate	
			Vapour pressure	Visual
Chloroform	4.7	6.5	4.2	3.9
Benzene	1.4	1.9	1.9	1.2
Hexane	1.8	2.2	2.4	1.4
Ethyl acetate	0	0	1.0	1.0

Results are corrected for solubility.

As a check on the method, the solubilising power of a 2.76 per cent solution of sodium oleate was examined and compared with results obtained by the visual method. These are given in Table II.

Addition of ammoniated glycyrrhizin to the extracts increased the quantity of insoluble liquid solubilised.

DISCUSSION

The object of this work has been twofold, firstly to determine if the process by which liquorice extracts form clear solutions with materials which are insoluble in water is one of solubilisation, and secondly to investigate the extract's potential in the formulation of mixtures containing insoluble liquids. The first object has been fulfilled by showing that micelles occur in liquorice extracts, and that three liquids which are insoluble in water, namely benzene, chloroform and hexane, are solubilised. Both the conductance and surface tension curves are typical of micelle forming systems, and since the same curves have been produced with solutions of ammoniated glycyrrhizin, glycyrrhizin is a micellating constituent of the extracts. For the second requirement, the quantity of chloroform which can be solubilised by liquorice extract B.P. is given, while the results for benzene and hexane suggest that a volatile oil would be solubilised, probably to the extent of 1 to 2 per cent.

The vapour pressure method described is simpler and more rapid than that used by McBain (1940, 1941) but has the disadvantages that it is probably less accurate, and is limited to those solubilisates having a higher vapour pressure than water. It was for this reason that the number of solubilisates examined was small, and results were not quoted for substances, such as paraldehyde, and volatile oils, which are frequently formulated with liquorice extracts. The aqueous extract with ethanol solubilised more of the three solubilisates examined than the aqueous extract, indicating that ethanol enhances the solubilising power. This is in contrast to the conductance and surface tension results which show that ethanol increases rather than decreases the critical micelle concentration.

The reasons for the initial inflections in the conductance and surface

tension curves is not clear, but the fact that they occur at the same concentration on both aqueous extract curves, and are accompanied by a fall in surface tension indicates that they represent an interfacial change, and could be the critical micelle concentration of another constituent, possibly gum. The effect of ethanol on this point on the conductance curves could be taken as support for the observed effect of ethanol on solubilisation. However, since this did not occur with the surface tensions, and would be contrary to observations on other systems (Ward, 1940; Corrin, 1946; Ralston, 1948) it was assumed to be due to some other phenomenon, probably a change in dielectric of the solvent on dilution with water.

Although examination of the extract makes the results more interesting pharmaceutically, it does present a system which is difficult to work with, and which contains at least two amphipathic substances, namely glycyrrhizin and gum. For this reason work subsequent to this paper is being carried out on the constituents of liquorice.

Acknowledgements. We thank the governors of the Welsh College of Advanced Technology for the award of the John Cory research scholarship to J.B.S., and Mr. R. J. Ingram for his advice and assistance in the preparation of the extracts.

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