Björn Lindman [1]
Anders Carlsson [2, 3]
Kyrre Thalberg [1, 4]
Conny Bogentoft [2, 5]

Polymer-Surfactant Systems and Formulation *

with examples from the use for drug delivery

Polymer-surfactant interactions are discussed with particular reference to structure-forming and solubilisation properties. Novel gels with some interesting properties are described for systems of a nonionic polymer and an ionic surfactant and of a polyelectrolyte and an oppositely charged ionic surfactant, and some possible applications in the pharmaceutical field are discussed. A thermal gelation of a system of a nonionic cellulose ether and an ionic surfactant is found to be useful for in situ *formation of a matrix for local administration of pharmaceuticals.*

Introduction

Polymers and surfactants are extensively employed in a wide range of applications. Frequently they occur together, in particular in complex colloidal systems to achieve colloidal stability, emulsification, flocculation, structuring and suspending properties, rheology control and so forth. Examples of uses are cosmetic products, paints, detergent liquids, foods, polymer synthesis, drug formulations and formulations for mineral flotation.

Against this background, fundamental studies of systems with different combinations of polymer and surfactant are needed [1-3]. Besides experimental studies by different techniques, parallel theoretical work is essential to understand the complex nature of these systems, in particular using the theoretical approaches which have been so successful in describing surfactant and polymer solutions separately [4, 5]. One previously overlooked aspect was that of monitoring the polymer-surfactant interactions via a combined experimental and theoretical study of phase diagrams, an approach which has been instrumental in developing surfactants for various uses [6].

Besides this fundamental approach, which hopefully will be useful in formulations for a wide range of applications, we have more specifically been interested in developing new principles for formulation in the fields of paints and pharmaceuticals. In particular we will in this treatise consider *drug formulation* and describe novel phenomena which may open new ways to improve drug delivery.

Polymers and surfactants in drug formulation

A considerable number of aspects have be taken into account, on introducing novel systems and principles for the formulation of pharmaceuticals. The intended properties of a pharmaceutical formulation have to be unaltered even after storage for long times. It is then preferable to use formulations which represent thermodynamically stable equilibrium states. An often used alternative is that of non-equilibrium disperse systems, which have a long-term kinetic stability.

The rheological properties or consistency are in general also very important to control. Often different properties are desired for different modes of administration and also in other respects the therapeutic use has to be considered in the design of a product. As regards rheology, contradictory demands on a formulation may arise from the administration situation in clinical praxis and the specific requirement of drug release to obtain the intended therapeutic effect ; an oral liquid preparation has for instance to be in an ingestable and easily flowing formulation which may not be able to give the required sustained release properties a highly viscous system may give.

The biopharmaceutical properties of a pharmaceutic product, *i.e.*, the biological effect of the active compound in relation to the composition, design and production process factors is funda-

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[1] *Physical Chemistry 1, Chemical Center, PO Box 124, S-221 00 Lund, Sweden.*
[2] *Kabi Invent AB, Novum, S-141 52 Huddinge, Sweden.*
[3] *Present address : Karlshamns Lipidteknik AB, PO Box 15200, S-10465 Stockholm, Sweden.*
[4] *Present address : Draco AB, PO Box 34, S-221 00 Lund, Sweden.*
[5] *Present address : Astra Research Centre AB, S-15185 Södertälje, Sweden.*

mental for drug formulation. It is well recognized that inactive components of a formulation can influence biopharmaceutical properties such as bioavailability, tolerance and time of duration. One such type of important ingredient that has obtained much attention in recent years is enhancers or absorption promoters. Some types of amphiphilic compounds seem to have the required properties. Another area of biopharmaceutical research has the ambition to develop targeting mechanisms that can improve the delivery of the active compound to the intended biological target.

The surfactant and polymer molecules involved in our research interact *via* weak nonspecific interactions, which are largely determined by molecular shape, size and charge density. Surfactant self-assembly into aggregates of different shapes and sizes, forming isotropic solutions and a large variety of liquid crystalline phases, is in its main features understood in terms of surfactant molecular shape [7], in particular the ratio between headgroup area and hydrocarbon chain volume, and charge. One important feature of surfactant self-assembly, not the least in connection with attempts to use it for formulation, is the compactness of the aggregates. Thus, in surfactant self-assembly in water, the contact between the lipophilic (hydrophobic) parts and the solvent is minimized and there is essentially no penetration of water into micelles and other aggregates. Because of this compactness of the aggregates, there are in general only weak intermicellar interactions at low and moderate concentrations, leading to little long-range structuring and only small effects on rheology. The situation is different for high concentrations, where some phases of interesting rheological properties form, and for systems with very long rod micelles and for some disperse systems. A very important property of amphiphilic systems, like surfactant-water and lipid-water systems is the very good solubilizing properties for essentially all types of substances, of particular significance here being lipophilic and amphiphilic substances and a broad range of macromolecules, including proteins, even of high molecular weight.

Polymer solutions are in important aspects quite different. Thus, a polymer molecule is expanded and occupies a large volume (which depends on the solvent "quality"), which leads to polymer chain contact at low concentrations (c* denoting the concentration of onset of chain overlap). In turn, this leads to influences on rheology at a quite low concentration, and formation of entanglement networks and the possible occurrence of phase separation phenomena. The rheology can be very strongly modified as a result of even quite weak interchain attractions, which can be of electrostatic or hydrophobic origin, as exemplified by the noncovalent (or physical gels) formed by several polysaccharides. Polymer gels and other viscous polymer systems are interesting for drug formulation and have found significant applications. However, because of the low solubility in these gels of most lipophilic and weakly amphiphilic substances they have considerable limitations. We note, however, that block copolymers with hydrophobic and hydrophilic segments may give local association structures providing solubilisation sites for water-insoluble compounds.

In this discussion we should note the generality of the association phenomena described implying that the same phenomena are displayed by biologically occurring lipids and macromolecules and for the synthetic surfactants and polymers, a point which may be significant with respect to the toxicity for certain applications.

For many semisolid drug formulations, one is requiring both good solubilisation properties of the active compound *and* structuring of the vehicles leading to suitable rheological properties. We can see that surfactants and polymers are largely complementary in that surfactants offer a very broad concept of solubilisation, while polymers can be used to obtain the desired rheological properties. It is quite clear that having the complementary solubility and structure-forming properties in a formulation is of interest and is in fact an important incentive for our fundamental studies of polymer-surfactant interactions. Furthermore, the possibility of devising novel structures is another significant motivation behind this interest. In particular, the possibility of modifying the structure-forming, and thus rheological, properties of polymer systems by surfactants appears attractive and, notably, the possibility of physically cross-linking polymer chains by surfactant micelles could offer a novel principle of rheological control.

Polymers and surfactants can be used in many different ways in drug formulation and there are many principles realised in products or in the state of development. For polymers, we may note in particular the use of polymer solutions, gels, solid polymer matrices and coating by polymer films. As regards amphiphilic systems, the most significant are vesicles or liposomes, micellar solutions, microemulsions and liquid crystalline phases ; of the latter, the interesting rheological and solubilization properties of cubic phases have recently attracted considerable interest [8]. In addition, both polymers and surfactants are widely used to stabilize disperse systems, like emulsions and suspensions, as well as the newly developed cubosomes [8].

Polymer-surfactant interactions. Some basic aspects

As regards the general aspects of polymer-surfactant interactions [1-3], a good understanding has developed during the last decade as regards the interactions in dilute systems, while much work remains to clarify the interactions in concentrated systems. There are many elucidating investigations of the binding of a surfactant to a polymer, which demonstrate that association is cooperative and starts at a *critical aggregation concentration*, cac. In this and in other important ways, the concentration dependences of physico-chemical properties resemble the surfactant self-assembly to micelles ; for example, the cac varies in qualitatively the same way as the cmc with the surfactant alkyl chain length. This suggests that as an alternative to consider the association in terms of surfactant "binding" to the polymer, we may consider the effect of the polymer on surfactant micellisation. A nonionic polymer would then, as for low molecular weight molecules, decrease the *critical micelle concentration* (cmc) as a result of the presence of amphiphilic and lipophilic segments, while for a polyelectrolyte simple electrostatic effects would account for the interaction.

Irrespectively of the way of considering the interaction, the picture of the systems emerging from the thermodynamic studies of dilute systems is one of micelle-like clusters of surfactant molecules along the polymer chain. The closeness of the polymer-micelle contact will vary largely between different systems from a rather tight one for polymers containing hydrophobic segments to a quite loose one for certain polyelectrolyte- ionic surfactant systems. The general picture of a "pearl-necklace" type structure [3] is strongly supported by neutron scattering, nuclear magnetic resonance and fluorescence quenching studies.

If we consider the structure-forming and rheological properties, it seems natural to discuss in terms of surfactant binding to the polymer and the effect of this on intra- and interchain interactions, which for the ionic surfactants considered here will be mainly of an electrostatic nature. The effect will obviously depend strongly on the relation between the actual polymer concentration and c*, the concentration where *chain overlap* starts. An ionic surfactant, which binds to a polymer, is expected

to cause expansion for a nonionic polymer and contraction for an oppositely charged polyelectrolyte, with an increase and a decrease in the viscosity, respectively, for dilute solutions. For semi-dilute or concentrated solutions, the effect will be more complex, one factor being that surfactant binding increases or decreases c*. A mechanism that has attracted our interest, is the possibility, for concentrations above c*, of a micelle interacting with more than one polymer chain. Such a novel type of cross-linking could presumably have very important effects on the rheological properties.

Polyelectrolyte-ionic surfactant systems

The cac value is low for the interaction of an ionic surfactant with an oppositely charged polyelectrolyte and it decreases rapidly with the length of the surfactant alkyl chain as well as with the linear charge density of the polymer [1, 2]. A quite general feature of these systems is a phase separation at addition of a certain amount of surfactant, which depends on the surfactant and the polymer as well as the polymer concentration. This *precipitation* can be referred to the reduced charge of the polymer as a result of surfactant binding. Another significant and frequent observation is that at sufficiently high surfactant concentrations a homogeneous single-phase system again results ; such a *redissolution* is facilitated by the presence of added electrolyte and can be brought about also by electrolyte addition alone.

In order to more systematically describe these phase separation phenomena, we have started determinations of *phase diagrams* [9-12]. Since systems of a solvent, an ionic surfactant and an oppositely charged polyelectrolyte are *4-component systems*, a full description requires a rather extensive experimental study as well as (for constant temperature) a three-dimensional representation ; for convenience a *pseudo three-component representation* in a triangular phase diagram is often made. This is illustrated in *Fig. 1* for a system of an anionic polysaccharide, hyaluronan or sodium hyaluronate, and a cationic surfactant, tetradecyltrimethylammonium bromide [9]. The most important feature is that of a separation into one phase which is dilute in the two solutes, and one which is concentrated in both polymer and surfactant. The two phases are both isotropic and belong in fact to the same one-phase region, which completely encircles the two-phase region.

The same type of phase diagram has been obtained for some other polymer-surfactant systems and, although the information is yet far from complete, it appears that the extension of the two-phase region increases with the alkyl chain length of the surfactant [10] and with the charge density of the polymer [12]. Furthermore, it is larger for a polycation than for a polyanion and decreases on addition of electrolyte [12]. The electrolyte effect is illustrated in *Fig. 2* and as can be seen there is in an intermediate range of salt concentrations no phase separation at any conditions. A most conspicuous feature is the reappearance of a two-phase region at sufficiently high salt additions [11]. However, this separation is, as can be inferred from the new direction of the tie-lines, of a completely different nature and results in a separation into one polymer-rich and one surfactant-rich phase.

In *Figure 3*, the phase separation is illustrated in three-dimensional pyramid-shaped phase diagrams [11]. The two-phase region in the absence of added salt is shaped like a sail, which hangs from the water apex of the pyramid *(Fig. 3a)*. For each electrolyte concentration one sail is obtained *(Fig. 3b)*, but the sail shrinks with increasing electrolyte content to completely vanish at a certain point. The two-phase region thus forms a closed three-dimensional body in the phase diagram. At much higher salt contents, there is then another body depicting the novel type of phase separation *(Fig. 3b)*.

The phase behaviour of polyelectrolyte-ionic surfactant systems immediately suggests a number of applications. One, which since decades has found extensive use in the isolation and purification

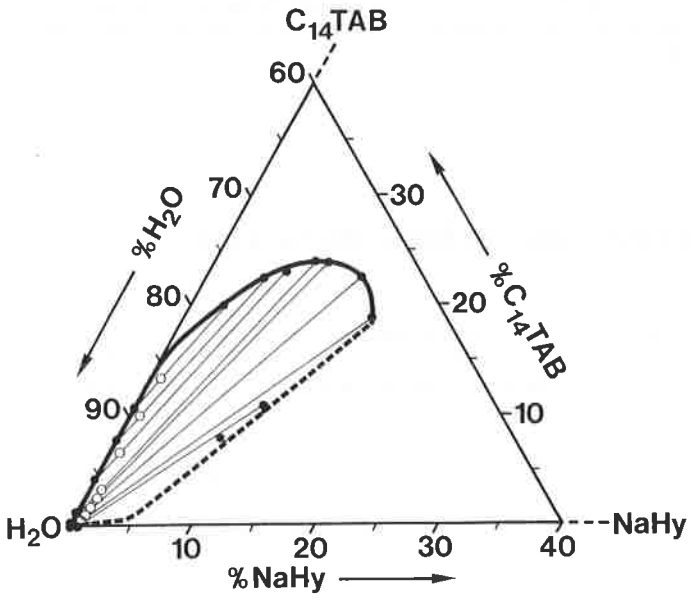

FIGURE 1. - *Pseudo three-component phase diagram for the system sodium hyaluronate (NaHy) - $C_{14}TAB$ - H_2O. Open circles refer to initial sample compositions and filled circles connected by tie lines to the two phases in equilibrium. The dashed part of the phase boundary indicates larger uncertainty.*

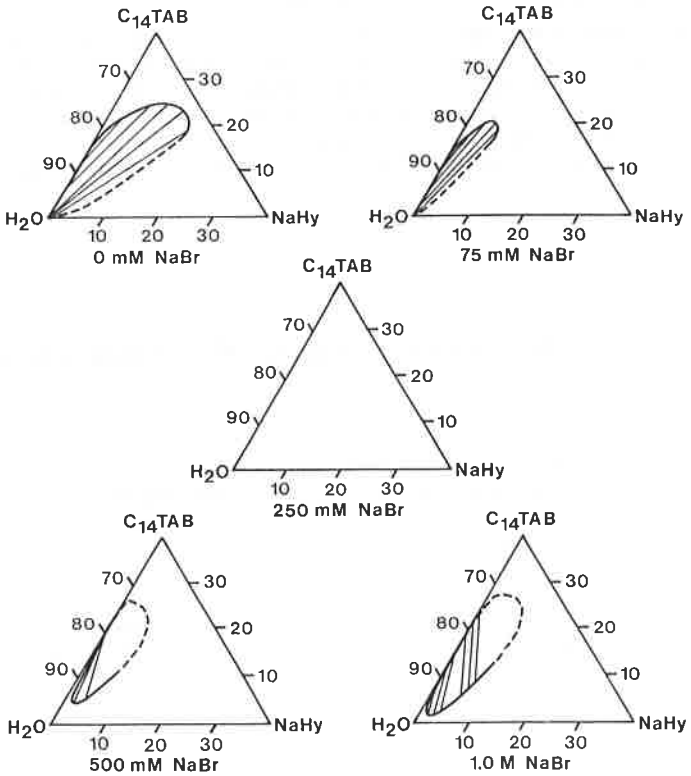

FIGURE 2. - *Pseudo three-component phase diagram for the system NaHy - $C_{14}TAB$ - H_2O at different concentrations of added salt.*

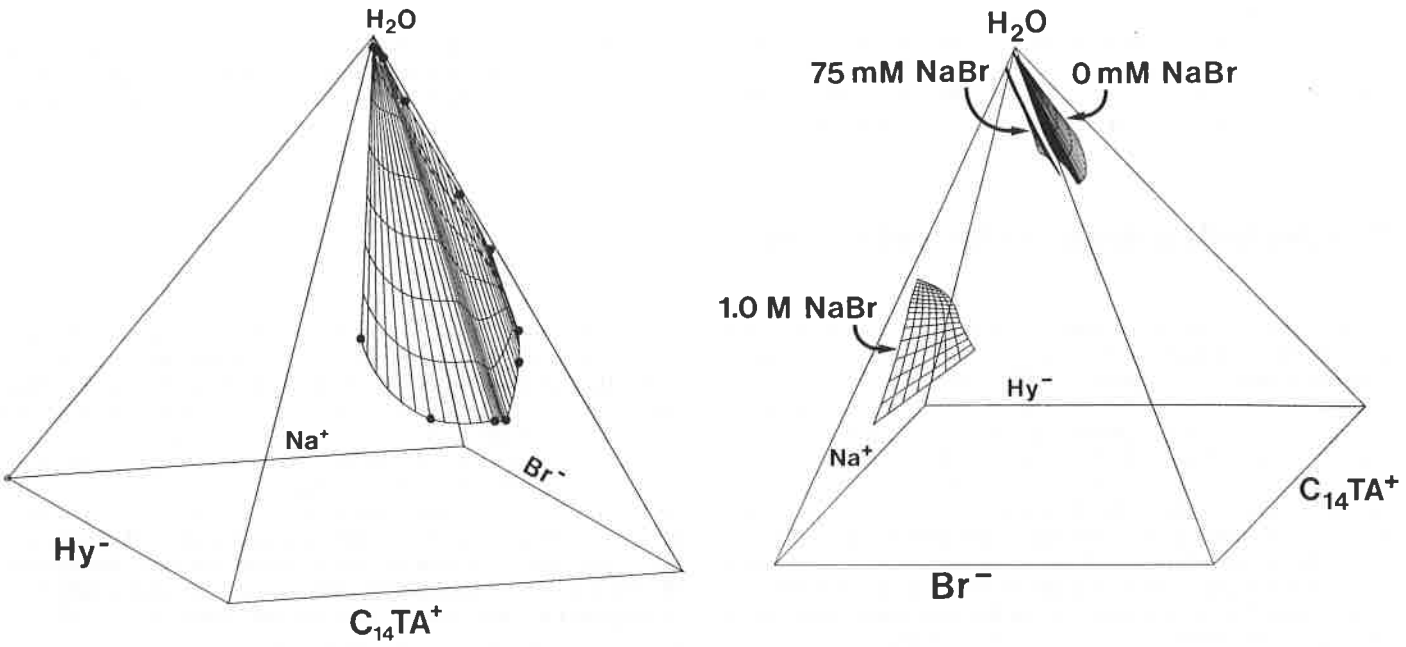

FIGURE 3. - *Pyramid representation for the system of Na^+, Hy^-, $C_{14}TA^+$, Br^- and H_2O, with phase separation surfaces in the absence of added electrolyte (3a) and at 0,75 mM and 1.0 M of added NaBr (3b, from upper right to lower left). The indicated base corresponds to a total ionic concentration of 1.0 M in (a) and 2.5 M in (b).*

of biological macromolecules, is the precipitation by surfactant to concentrate a polymer [13]. By addition of salt, redissolution can be achieved. Both the precipitation and the redissolution will be selective with respect to polymer charge density and, less pronouncedly, to molecular weight. To separate the surfactant from the biological macromolecule, it is common practise to make use of temperature changes, having a surfactant which is sparingly soluble at some lower temperature. The phase diagram work suggests an alternative, and more general, procedure in which polyelectrolyte and surfactant are separated in the novel two-phase region occurring at high salt contents.

The formation of the *concentrated phase* can be referred to the strong attractive interaction between polyelectrolyte and surfactant ; this is weakened by addition of electrolyte. Interestingly, for quite a number of common systems we have investigated, the concentrated phase is an isotropic phase of very high viscosity [14]. This *stiff gel-like phase* has several interesting properties in connection with drug delivery :

– The stiff consistency is suitable for a number of ways of administration and can, furthermore, be modulated at will by varying the surfactant and by addition of electrolyte.

– The gel is thermodynamically stable, forming spontaneously and being infinitely stable.

– The gel coexists with a very dilute solution and is, therefore, stable in the presence of even very large amounts of water.

– The gel contains both hydrophobic and hydrophilic domains and can dissolve both hydrophilic, lipophilic and amphiphilic active substances, low molecular weight compounds or macromolecules.

– The release of active substances can be made very slow and the release rate can be controlled by changing the composition of the gel.

Gel formation in a system of a nonionic polymer and an ionic surfactant

Many practically used nonionic polymers, like cellulose ethers and copolymers of ethylene oxide and propylene oxide, show a phase separation at elevated temperature in aqueous solution [15]. This manifests itself in a strong turbidity of a solution in a certain temperature interval and the phenomenon is usually referred to as *clouding,* and the temperature at which clouding occurs is called the cloud point. This clouding is very significant in connection with products based on these classes of compounds, the occurence of clouding often being a serious problem. The clouding is influenced more or less strongly by different cosolutes. Particularly strong effects result from the addition of ionic surfactants, which cause a dramatic increase of the cloud point even for low concentrations. These nonionic polymers are extensively used in different formulations, such as paints, cosmetics and pharmaceuticals, and often they occur together with ionic surfactants. The resulting inhibition of clouding due to the ionic surfactants can be very significant for many applications, because it allows the use of more hydrophobic and more surface-active polymers without phase separation. However, the approach requires very careful attention since it was discovered that even very small amounts of electrolyte (by themselves having no influence on the clouding), in the presence of ionic surfactant, causes a dramatic lowering of the cloud point [15].

Nonionic polymers are known to interact very generally with ionic surfactants. The systems of nonionic polymer and ionic surfactant were considered to be particularly relevant for the attempt to produce *novel structures* and *formulations with novel rheological properties* since (physical) cross-linking effects can be modulated both by an ionic surfactant and by temperature. Thus, as these polymers become less polar at a higher temperature, they will offer better nuclei for surfactant self-assembly at a higher temperature. In the semi-dilute regime there should be a possibility for the surfactant micelles of cross-linking polymer chains [16].

Our studies have concentrated on a *nonionic cellulose ether,*

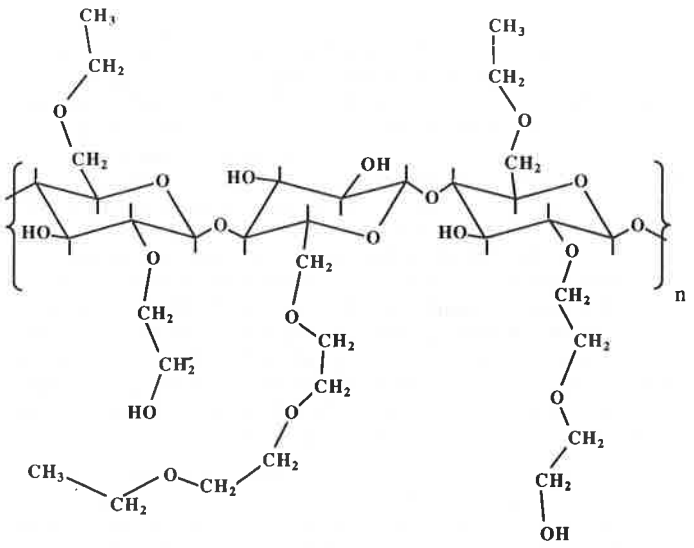

FIGURE 4. - *Structure segment in ethylhydroxyethyl cellulose (EHEC).*

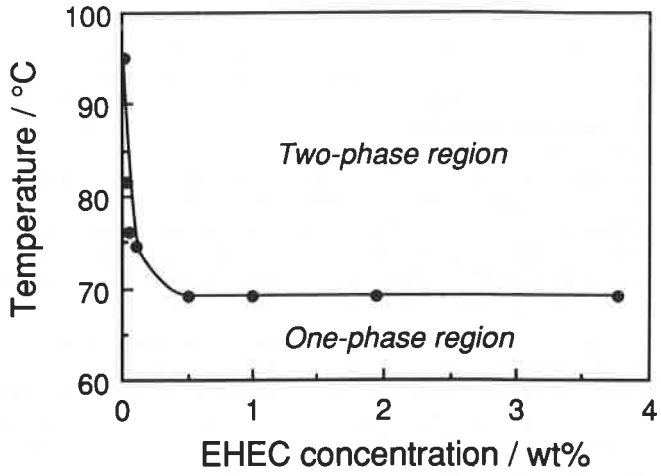

FIGURE 6. - *Part of the phase diagram of an EHEC-water system. The curve dividing the one- and two-phase regions corresponds to the cloud point (CP) curve.*

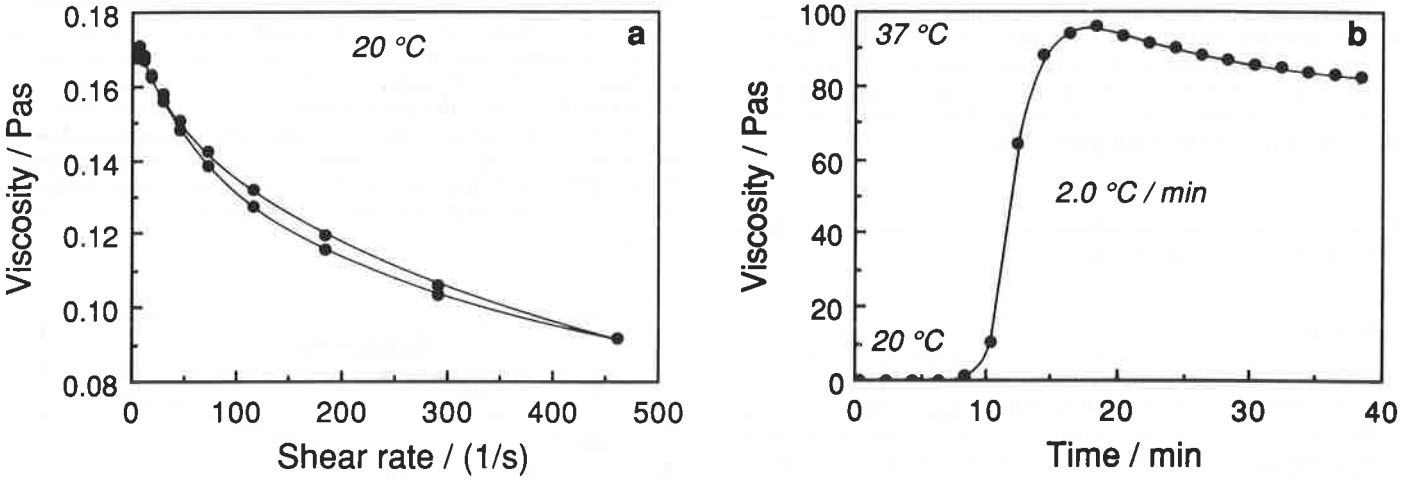

FIGURE 5. - *Typical results from rheological experiments on EHEC-ionic surfactant formulations, here represented by a system consisting of 1.0 wt % EHEC and 3 mmolal SDS in water. At room temperature the system is characterized as a normal polymer solution which flows easily and with a pronounced pseudo-plasticity (a). However, a raise in temperature from 20 to 37 °C leads to gel formation and to a remarkable increase in the steady-flow viscosity (b) - it is not unusual that a 500-fold increase is observed (shear rate 0.2316 s^{-1}). Measured on a Bohlin VOR rheometer (system C14, torque element 4.27 g cm).*

ethylhydroxyethyl cellulose (EHEC), manufactured by Berol Nobel AB, Stenungsund, Sweden. The degree of substitution of ethyl and hydroxyethyl groups can be varied over wide ranges, which provides a means to obtain a polymer with a desired cloud point ; the formula in *Fig. 4* represents a typical substitution with a cloud point of ca. 70 °C. An aqueous solution of ca. 1 % EHEC shows a moderate increase in viscosity compared to neat water ; this decreases on increasing the temperature. In the presence of a small amount of surfactant (0.1-0.5 %), the viscosity is relatively low and the solutions are easily flowing at low temperature. However, on increasing the temperature a dramatic increase in viscosity is observed [16], as illustrated in *Fig. 5*. At low temperature, the solutions are low viscous and the rheological properties are dominated by viscous effects. At higher temperatures, the viscosity increases dramatically and the elastic effects become totally dominating [16]. The system can be characterized as changing with temperature from a viscous solution to a gel, via an entanglement network at intermediate temperature ; the process is reversible and the *gel melts on cooling*. The molecular mechanism is apparently a cross-linking combined with surfactant self-assembly, this being facilitated at a higher temperature, where the polymer is more hydrophobic. The temperature for this gel formation is related to the cloud point of the polymer-water system *(Fig. 6)* and can be varied at will by changing the substitution.

The use of a novel, temperature-induced gel formation for drug delivery

As pharmacologically active, water-soluble substances can be rather generally dissolved in these polymer-surfactant systems, it appeared that these systems, which are low-viscous at room temperature but spontaneously form a stiff gel at body temperature,

can offer improvements in drug administration and drug delivery. The gelling of the nonionic polymer-ionic surfactant system described above is largely independent of the presence of other species in the medium and requires very low concentrations of polymer and surfactant (98-99 % water). Furthermore, the system is compatible with different ways of administration and has a long-term stability. Other aqueous polymer systems known to gel *in situ* require either high salt concentrations (*e.g.* low-acetyl gellan gum [17]), low pH (*e.g.* poly(acrylic acid) [18]) or a high polymer content (poloxamers [19]). Such requirements may not always be possible to fulfil when using the system for delivery of drugs, for example to the eye.

The special EHEC quality showing the gel forming ability has a cloud point (CP) in the range of 30-35 °C and is referred to as EHEC of medical grade by the manufacturer. The gel forming ability *in vitro* has been demonstrated in a number of aqueous solutions (saline, diluted HCl (aq.), simulated gastric and intestinal juices, etc.), provided the temperature is sufficiently high. In *Table I* the behaviour of a number of polymer-surfactant systems in simulated gastric juice is described ; systems A and B are thermally gelling formulations while C-E have either no surfactant or a too high CP.

Systems A-C are based on a relatively hydrophobic EHEC sample with a CP of 34 °C, also referred to as EHEC of medical grade. This polymer is able to form a gel in gastric juice upon a temperature rise provided an ionic surfactant is present in appropriate concentrations, which in the case of SDS means 0.05-0.15 wt %. The more hydrophilic polymers in Systems D and E interact less strongly with the surfactant and no gel formation is observed. Solutions of polymer alone do not exhibit any gelling upon mixing with the warm gastric juice (*cf.* System C).

TABLE I. - *Gel forming ability* in vitro *of polymer-surfactant systems in simulated gastric juice.*

System A
1.0 wt % EHEC (CP = 34 °C ; η = 89 mPas) + 2.6 wt % glycerol + 0.12 wt % sodium dodecyl sulfate (SDS) in water : Gel formation with no appreciable change in size after 1 h. The gel has a somewhat milky appearance due to the high ionic strength of the gastric juice which leads to partial phase separation. Cooling to room temperature leads to a complete mixing and disappearance of the gel.

System B
1.0 wt % EHEC (CP = 34 °C ; η = 89 mPas) + 0.12 wt % SDS in water : Gel formation (white) ; the gel undergoes shrinking due to an unfavourable osmotic balance - after 1 h the size is reduced by ca. 50 %. At any instant, cooling to room temperature leads to a complete mixing and disappearance of the gel.

System C
1.0 wt % EHEC (CP = 34 °C ; η = 89 mPas) : Immediate dilution leading to complete mixing.

System D
1.0 wt % EHEC (CP = 63 °C ; η = 40 mPas) + 0.12 wt % SDS in water : No gel formation - instead the formulation is completely diluted.

System E
1.0 wt % methylcellulose (CP = 37 °C ; η = 40 mPas) + 0.12 wt % SDS in water : No gel formation - instead the formulation is completely diluted.

Data within brackets correspond to 1.0 wt % aqueous solutions. Procedure : 25 mL of the simulated gastric juice (prepared according to USP XXII) was transferred to a container immersed in a thermostat bath (37 °C). 5 mL of the cellulose ether solution to be examined was then gently added to the gastric juice (no stirring) and the fate of resulting system was visually followed over a certain period of time.

The EHEC-ionic surfactant combination, forming a gel in simulated gastric juice, is a drinkable liquid at room temperature. At present the concept of the EHEC-ionic surfactant mixture as a "liquid fibre" is evaluated together with N.W. Read, J. Tomlin, and N.J. Brown at the Centre for Human Nutrition, University of Sheffield. Studies in rats carried out in Sheffield have shown that EHEC-SDS dramatically retards gastric emptying and so may be expected to alter eating patterns in man and to modify the absorption characteristics of other foods. As EHEC is a polysaccharide with a cellulose backbone it will not be broken down by human digestive enzymes and therefore should act on the colon in a similar manner to "dietary fibre" [20]. *In vitro* incubations in Sheffield have confirmed that it would be expected to be an efficient laxative and may even reduce flatulence. Investigations of the effect of EHEC-SDS in normal volunteers (gastric emptying, food intake, small bowel transit, blood glucose absorption and colonic function) are in progress.

The thermoreversible gel based on EHEC and ionic surfactant may have a broad applicability as a "liquid carrier" for delivery of water-soluble drugs. The system has a viscosity that allows spraying, instilling, pouring, drinking, or spreading the dosage form into the intended biological cavity or part of the body. Upon administration the "liquid carrier" will adhere to the mucus or the biological membrane and form a high viscosity or gel layer. It has been shown that it gels in gastric juice (*cf.* above) and that this gel is also retained in intestinal juice. This implies that on oral administration of a drug in the carrier a gel will form in the gastrointestinal tract giving a slow release of the active substance (and the surfactant), see *Fig. 7*, as well as an improved bioavailability. Once the gel is formed it is very resistant to salt and mechanical rupture. The diffusion of the incorporated drug within the gel lump is not restricted (except for drugs having a charge opposite to the surfactant) - instead the border between low salt (gel) and high salt (physiological medium) serves as a diffusion barrier.

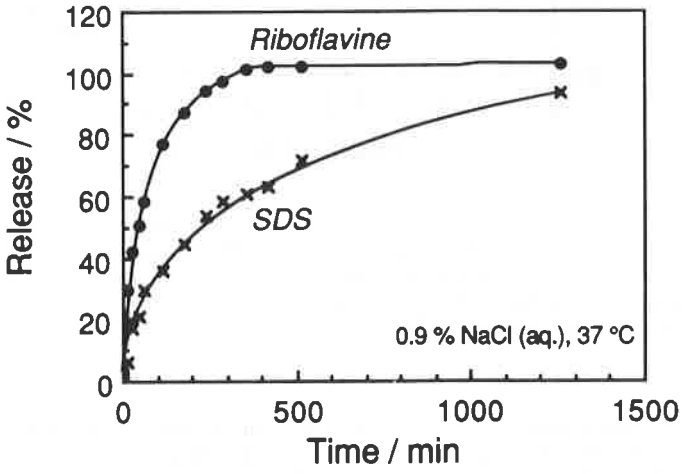

FIGURE 7. - In vitro *diffusion test of riboflavine and SDS from a gel initially containing 1.0 wt % EHEC, 3.0 mmolal SDS and 0.004 wt % riboflavine. The test medium was 0.9 wt % NaCl in water equilibrated at 37 °C. The diffusion cell (a simple steel net basket) containing ca. 8 g gel (preheated to 37 °C) was immersed into a flask of a USP rotating paddle apparatus (Prolabo Dissolutest) with a paddle rotating speed of 100 rpm. Aliquots of medium were withdrawn at selected times and analysed with HPLC by post-column ion-pair extraction with UV detection (SDS) and fluorimetric detection (riboflavine).*

In principle any water-soluble substance can be incorporated in the "liquid carrier" regardless whether it is charged or not. Macromolecules could also be administered by means of the EHEC-SDS vehicle. Here nasal delivery of insulin may serve as

an example which is presently evaluated in a joint project together with L. Rydén and P. Edman at Uppsala University. EHEC-surfactant formulations, containing therapeutic relevant concentrations of insulin, improve the absorption of insulin due to the increased contact time between mucus and the drug. This has been established by measurements of the blood glucose level in rats. Furthermore, release profiles *in vitro* confirm that insulin is efficiently sustained. The role of the surfactant is, besides taking part in the gel structure, to enhance the penetration of the drug through the mucous membrane. The main reason, however, for this system being of interest is the fact that the gel does not undergo phase separation as other thermoreversible polymer systems do. The ability of the EHEC-surfactant gel to maintain its water content after being applied may also facilitate the penetration.

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Formulation et enseignement *

Ce thème a regroupé une conférence principale, une table ronde au cours de laquelle neuf communications ont été exposées et huit communications par affiches.

Les points forts ont montré la nécessité de donner une formation de base à tous les niveaux d'enseignement supérieur. La spécialisation en formulation nécessite en effet une base solide pluri-disciplinaire (description des ingrédients, physico-chimie, notamment des systèmes dispersés, réactivité chimique des composants, physique dans le génie des procédés (D. Reymond, P. Meallier). Une enquête a été conduite auprès d'une trentaine d'établissements supérieurs ; elle démontre que l'enseignement de la formulation relève plutôt des troisièmes cycles des universités (E. Nakache, G. Tersac, J.-P. Gallet).

Au niveau des instituts universitaires de technologie, l'enseignement donne une introduction à la technologie de formulation (P. Meallier et J. Thourey ; J. Fournier).

Un recueil de travaux pratiques regroupe 8 manipulations dans des domaines divers (peinture, adhésifs, pharmacie, phytosanitaire) qui ont été suggérées par différents auteurs (G. Tersac).

Le médicament est un terrain privilégié de la formulation ; la pharmacie galénique constitue un ensemble très élaboré de connaissances et d'enseignement pratique qui conduit en particulier à un DEA de génie pharmaceutique (Y. Pourcelot-Roubeau, C. Jeannin).

Des considérations analogues débouchent dans d'autres domaines sur trois DESS en formulation aux universités de Lille, Besançon et Marseille (Gallet ; Foissy).

La science de la formulation est enseignée en 3e année d'école d'ingénieurs à l'ENSC de Lille (J.M. Aubry), à l'ESCOM (F. Brochard), ainsi qu'à l'ITECH Lyon (J.P. Gallet).

La formation permanente exige, elle aussi, le rappel de connaissances physico-chimiques de base en ouvrant le dialogue avec des praticiens industriels qui apportent leur compréhension des phénomènes liés à des systèmes complexes (F. Brochard).

La rhéologie constitue, par exemple, un outil précieux pour mettre au point les formulations dans la technologie industrielle (P. Fabre).

* *Compte rendu du thème 5 : Formulation et enseignement de Formula II, le 2e Forum international physico-chimie de la formulation et applications qui s'est tenu à Toulouse, les 17-19 octobre 1990.*