ION EXCHANGE*

TECHNICAL APPLICATIONS OF ION EXCHANGE

By Professor J. Büchi

Pharmazeutisches Institut, Zurich

Reaction and Technical Methods of Ion Exchange

If the principle of ion exchange is reviewed it is seen that the exchange reactions have been exploited in many chemical and pharmaceutical procedures. Fig. 1 gives a survey of the various kinds of ionic exchange reactions distinguished according to the types of electrolyte participating[1].

In the first reaction equation, ion exchange is illustrated by the example of cation exchangers. Here, the exchangeable ions are small; the cations of a molecular dispersion are exchanged for the cations held on the cation exchanger. This type is probably the most widely used technically. The second reaction reproduces the conditions prevailing in an exchange system in which filamentary polyions—of, for example, colloidal structure and having a charge of the same sign as the ion exchanger itself—are present in the external solution. In this particular instance the exchangeable ions are able to distribute themselves between the resin and the solution without involving a Donnan effect[2]. The third reaction equation reproduces the conditions in a so-called "contact exchange". This consists of an exchange of ions between solid material containing electrolyte and the ion exchanger, as used by us in, for example, the isolation of the total alkaloids of cinchona bark[3]. The reaction equilibria of the fourth and fifth reactions are usually displaced far to the left because, for steric reasons, no more than a superficial adsorption of the soluble polyelectrolytes occurs and the internal charged particles of the ion exchanger are generally inaccessible to the polyions. As is the case in a mixed bed, nothing more occurs in a cation exchanger of H-form and in an anion exchanger of OH-form, for example, than a superficial adhesion between the two ion exchangers, so that they also can neutralise each other only superficially. The last two reactions have accordingly acquired no great significance in chemical and pharmaceutical elaboration. The use of cation exchangers and anion exchangers in the mixed-bed method is based on the circumstance that the two exchangers exert practically no influence on one another.

As ion exchangers do not act in accordance with the old dictum "Corpora non agunt, nisi soluta," but participate in the solid phase in exchange reactions and, when a desired type of ion has been fixed, can be mechanically separated together with the latter from the solution treated, they can be used for ionic separation.

The techniques of ion exchange at present used industrially do not differ in principle from the method used in the laboratory for analytical

purposes. The following techniques are in use for bringing an ion exchanger into contact with the electrolyte to be treated.

The Batch Technique

After suitable pre-treatment, a specific quantity of the granular ionic exchange resin is agitated with the electrolyte solution until equilibrium of exchange between the ions adsorbable from the solution and the non-adsorbable ions has been established. In the conditions prevailing in the batch method, this process does not take place quantitatively. The extent to which ions from the solution are replaced by the ions fixed in the resin depends on the selectivity of the resin in the prevailing conditions of equilibrium. Where selectivity is not favourable, only a small portion of the ions from the solution can be exchanged for ions from the exchanger resins. When the ionic reaction is completed, the exchanger resin is separated by filtration, washed and processed. This specific technique is used where reactions are required in a closed system and where for technical reasons there is no possibility of supplying new substance to be treated. The batch method is used in the titrimetric determination of exchange capacity, in so-called "contact exchange" and in cases where ion exchangers are used in catalysis.

A. Ordinary ion exchange.

B. Ion exchange without Donnan effect.
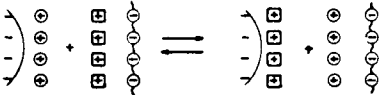
C. Contact exchange.

D. Superficial adsorption of soluble polyelectrolytes.

E. Mixed bed. At most superficial adhesion between the two exchangers.

FIG. 1

The Column Technique

When it is desired to achieve the complete exchange of one ion for another, the batch method is unsuitable. The column method has been developed to achieve this aim. The electrolyte solution to be treated passes down a column charged with the ion exchanger. The upper layers of ion exchanger are thus always brought into contact with fresh, untreated electrolyte solution. As the electrolyte solution passes down through the column, undergoing exchange until a specific equilibrium is established, it comes into contact with fresh ion exchanger, through whose exchange action the equilibrium of the reaction is progressively displaced further to the right, i.e. in the direction of a quantitative ionic exchange.

The effect achieved by the column technique is comparable with that obtained by a large number of successive batch methods.

According to the difference in affinity between two substances to be separated, the column method can be carried out in different ways. The ordinary exchange method is suitable for separating oppositely-charged ions. The ions in the solution flowing through are exchanged for those in the ion exchanger, while foreign ions pass through the column. The elution method enables ions of like charge to be separated. This method combines the chromatographic principles of operation with those of ion exchange on columns[4]. Here the existence of small differences in exchange potential between related ions is exploited. The ions adsorbed at the top of a relatively long ion exchange column are eluted through a continuous interplay of adsorption and desorption and by the fact that a separation of the different ions into more or less clearly separate layers occurs because of slight differences between the equilibria of exchange in the middle and lower parts of the column. If elution is continued, these layers begin to appear in specific fractions of the effluent. A method of separating amino-acids by this principle has been developed by Stein and Moore[5], who were able to recover thirty-eight different amino-acids by this method.

The variants of the elution method include gradient elution, in which the concentration of the eluent is steadily increased and improved separation effects are achieved, and the displacement method, in which the eluent contains an ion whose affinity with the ion exchanger lies between those of the two ions to be separated. Further methods for the use of the ion exchange column will be found in the literature[6,7].

The membrane technique

Ion exchangers can also be regarded as ion filters of selective permeability. Thus in the ideal case a cation exchanger is permeable only to cations, while an anion exchanger is permeable only to anions. These properties were exploited in order to produce semipermeable membranes on the basis of ion exchangers.

$$H_2O + SO_4 \leftarrow SO_4^{--} + 2 Na^+ \rightarrow 2Na + H_2O$$
$$\downarrow \qquad\qquad\qquad\qquad\qquad \downarrow$$
$$O + H_2SO_4 \qquad\qquad\qquad 2NaOH + 2H$$

FIG. 2. Ion exchange membranes.

Figure 2 reproduces schematically a cation and an ion exchanger membrane. Negatively and positively charged groups, respectively, are present on their two outer surfaces. The intermediate cell contains an electrolyte solution (e.g. sodium sulphate). If a potential gradient is
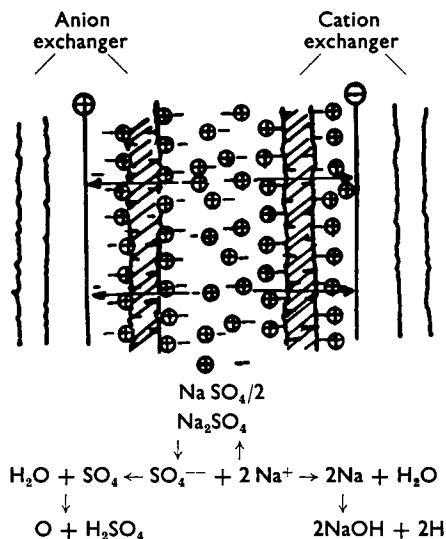
applied to the two sides of the ion exchanger membranes, the cations (Na^+) in the electrolyte cell are able to migrate through the cation exchanger membrane into the cathode chamber. The OH^- occurring at the cathode cannot leave the cathode chamber because the cathode exchanger membranes sealing the chamber are impermeable to anions. Accordingly, soda lye is formed here. The anion (SO_4^{--}) present in the electrolyte cell passes through the anode exchanger membrane enclosing the anode chamber to the anode and there causes the formation of sulphuric acid, because the anode exchanger membranes are impermeable to cations. Thus such cells permit the production of free bases or acids from their salts[8] and also the demineralisation of organic compounds[9]. This principle has made possible the economical demineralisation of sea water for the purpose of producing drinking water, using multiple-cell units[10].

The membrane method, proposed in 1952, has a promising future, especially in electrodialysis.

PROSPECTS FOR THE TECHNICAL UTILISATION OF ION EXCHANGERS

Ionic separation according to the ion exchange principle enables: (a) undesired foreign ions or electrolytes to be removed from a preparation, (b) certain ions or electrolytes to be elaborated as desirable end-products, or (c) certain ions in the form of ion exchangers to be used as catalysers of chemical reactions. These applications will now be discussed by reference to a few examples.

Elimination of undesired foreign ions

If in the course of purifying and elaborating a pharmaceutical preparation it is desired to eliminate contaminating foreign ions, these ions are generally fixed on the ion exchanger by an ion displacement reaction, while the solution of the purified substance is separated from the ion exchanger. The adsorbed product is thus not the desired preparation, but an impurity or by-product originating from accessory substances or produced through side-reactions. A classical example is the softening of hard water, which constitutes the first technical application of ion exchange. The purpose here is to eliminate from the water the hardness-producing ions (Ca^{++}, Mg^{++}, Fe^{++} and Fe^{+++}, Mn^{++}) which are often detrimental. The sodium forms of cation exchangers, such as the permutites and, more recently, the synthetic exchanger resins, are used for this purpose. The hardness-producing cations are exchanged for the Na^+ ions of the cation exchanger according to the following equation (R = exchanger):

$$2[R^-·Na^+] + [Ca^{++}·2Cl^-] \rightarrow [2R^-·Ca^{++}] + 2(Na^+·Cl^-).$$
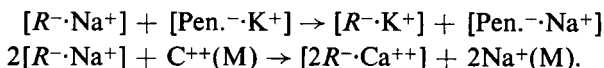
Since the introduction of the new high-capacity exchangers based on polystyrol, the technique of water softening has been further improved. Advantages afforded by these new exchangers are higher capacities, improved utilisation of the regenerating agents, a higher speed of reaction and a longer life of the ion exchangers[6].

In the electro-plating industry, chromic acid baths have to be renewed

from time to time because metallic ions such as Cu^{++}, Fe^{+++}, Mn^{+++} and Al^{+++} accumulate in them. While regeneration of the chromic acid by chemical methods does not pay, it can, after dilution, be passed through a column containing a strongly acidic cation exchanger in the H-form, when the metallic impurities are almost completely held by the exchanger resin, while the chromic acid anion passes without hindrance through the column. Chromic acid solutions so purified can then be returned to the chromium-plating bath. The introduction of cation exchangers of the polystyrol type, which are not attacked by a 10 per cent. chromic acid solution, was necessary before this method of purification could be attempted.

Simple exchange reactions are also used for converting the potassium salt of penicillin into the sodium salt. For this purpose an aqueous solution of the potassium salt is passed through a cation exchanger in the Na-form:

$$[R^-\cdot Na^+] + [Pen.^-\cdot K^+] \rightarrow [R^-\cdot K^+] + [Pen.^-\cdot Na^+]$$
$$2[R^-\cdot Na^+] + C^{++}(M) \rightarrow [2R^-\cdot Ca^{++}] + 2Na^+(M).$$

Similar reactions are also carried out in the elaboration of dietetic milk preparations. For example, calcium can be removed from cow's milk by treating the latter with a cation exchanger in the Na-form. Such low-calcium milk forms a flocculent, readily digestible, coagulated milk in the infant's stomach. In the preparation of another kind of dietetic milk the sodium in cow's milk is replaced by potassium.

The removal of undesired anions is likewise frequently resorted to in industry. According to Christy and Lembcke[11], a formic acid-free formaldehyde can be obtained cheaply by ion exchange. By de-acidifying excessively acid fruit juices and wines by the use of anion exchangers, more pleasant-tasting and better-tolerated beverages can be prepared. In these, a part of the wine is treated with a weakly basic anion exchanger and, after passage through the exchanger, mixed with a sufficient quantity of the untreated wine, since de-acidification, if carried too far, spoils the flavour and adversely affects the keeping properties. The ion exchange method is also industrially used in Switzerland for the partial de-acidification and demineralisation of fruit-juice concentrates[12].

The elimination of cations and anions which are impurities in or harmful ingredients of preparations is known as total demineralisation, and is often done. If the cation exchanger is brought into action in the H-form and the anion exchanger in the OH-form, the electrolyte solution being passed first through the one exchanger and then through the other, complete elimination of the electrolytes is achieved. This de-ionisation or demineralisation of sodium chloride, as a simple example of an electrolyte, may be formulated thus:

$$[R^-\cdot H^+] + [Na^+\cdot Cl^-] \rightarrow [R^-\cdot Na^+] + [H^+\cdot Cl^-]$$
$$[R^+\cdot OH^-] + [H^+\cdot Cl^-] \rightarrow [R^+\cdot Cl^-] + H_2O.$$
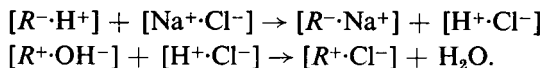
This technique is used for the demineralisation of water and other electrolyte solutions and for purifying colloidal solutions, gels, and so

forth. In many instances the method replaces dialysis and electrodialysis with satisfactory results.

The problem of the production of unobjectionable demineralised water from potable water arose from the needs of pharmaceutical practice. In addition to freedom from chemical and bacteriological contamination, the pharmaceutical industry requires a technique which, while being as cheap as possible, is able to deliver large quantities of purified water at short notice. In view of the rapid deterioration of distilled water through picking up foreign matter from the air, containers and contamination by micro-organisms, the pharmacy ought to have at its disposal a method by which it can itself rapidly manufacture purified water to meet its own requirements.

In the pharmaceutical literature, Harrison, Myers and Herr[13] were the first, in 1943, to consider this question. The first investigations in Europe were carried out by Bütikofer and Ammann[14], and valuable contributions have since been made by Saunders[15], and Fischer[16]. At about the same time Büchi and Soliva[17], at Zurich, reported their experience in the manufacture of demineralised water. These latter investigations were made for the Swiss Federal Pharmacopœia Commission to determine whether "aqua demineralisata" could be accepted on an equal footing with "aqua destillata" for official purposes. To be free from criticism, demineralised water should comply at least with the specifications laid down in the pharmacopœias for distilled water. In the ideal case demineralised water could also, if necessary, subject to certain safety regulations, be used for the preparation of eye-drops, eye lotions and injection solutions.

The experience of Saunders[15], and our own observations[17], have shown that freedom from odour and colour can be satisfied by prepared demineralised water. A complete elimination of mineral substances can be achieved by collecting an effluent water having a specific resistance of not less than 1 million ohms per cm. If the quality of the exchanger resins is as it should be, if they are correctly prepared for ion exchange, and if the deionisation unit is properly operated, it is, as Saunders[15], Fischer[16] and Büchi and Soliva[17] have shown, possible to comply with the requirement that there should be no organic impurities in the demineralised water. Fischer[16] and Büchi and Soliva[17] have confirmed by bacteriological tests of their deionised products that if the exchangers are of suitable quality and the plant is correctly operated, without protracted standby periods, sterile demineralised water can be collected, but there is no guarantee that the effluents will be invariably sterile. The ever-present possibility of a "break-through" of pyrogens in the demineralised water renders the method uncertain. In our opinion, therefore, a demineralised water ought not to be used for the manufacture of collyria or injection solutions unless it has been tested for freedom from pyrogens.

Since the ion exchange process has been technically mastered, it is possible to manufacture unobjectionable purified water which complies with the strict purity specifications prescribed for distilled water in the pharmacopœias, and in view of the fact that increasing quantities of demineralised

water are being used in the pharmaceutical industry, hospital dispensaries and larger pharmaceutical laboratories for preparing medicines, the demineralisation method ought—as Saunders[15] also proposes—to be officially permitted by all pharmacopœias. In both the British and the United States pharmacopœias purified water is now official, and the Swiss Federal Pharmacopœia Commission has also decided to adopt the method while requiring certain safeguards.

Demineralisation is also employed in the sugar industry. The dry residue of molasses from sugar-beet consists of about 91 per cent. sugar, the remainder consisting of inorganic salts and organic impurities which add to the difficulty of crystallisation and reduce the yield of crystalline sugar. By demineralising sugar juices, the yield of crystallisable sugar can be increased by about 10 per cent.

The 10 to 12 per cent. glycerol waters which accumulate in the Twitchell and autoclave processes for hydrolysing fats, contain many inorganic and organic impurities. While the pre-purification and distillation of glycerol by the old methods are very expensive recovery processes, demineralisation by means of ion exchange is much cheaper. By a combined treatment in multiple-bed and mixed-bed plants a glycerol complying with pharma-copœial specifications can be obtained. The product elaborated in this way is cheaper and purer than distilled glycerol[18,19]. A detailed investigation by Rentschler and Tanner[20] shows that faulty brandies can in many cases be elaborated into up-to-standard products by treatment with suitable ion exchangers. Acetic acid, sulphurous acid and mercaptans can be eliminated with anion exchangers, Fe^{+++}, Cu^{++} and Zn^{++} with cation exchangers and excessively high gravities by demineralisation.

Ion exchange is also being used with increasing frequency for purifying high-grade biological preparations. Müller[21], for example, reports the successful elimination of proteolysis products from viruses. In addition, ion exchange is being increasingly resorted to in place of dialysis and electrodialysis for the purification of enzymes.

Isolation of dissociating end-products

In this ionic exchange technique the desired product is adsorbed on a suitable exchanger, there enriched in purified form and, in a final phase, liberated again from the ion exchanger and worked up. This technique is particularly suitable for the extraction of small quantities of substance from very dilute solutions. The desired substance can be concentrated and isolated quickly, without injury, and cheaply without further extraction and evaporation. Due to a high selectivity for specific ions, it is also possible to closely separate related ions through anion exchange. The special properties of the exchanger resins and specific exchange techniques are applicable here.

The recovery of heavy-metal ions from industrial waste liquids is becoming increasingly important. It is not only a question of purifying the waste liquids, some of which are toxic, but also of increasing the economy of the manufacturing processes by recovering accessory substances. The last-mentioned consideration is particularly important in
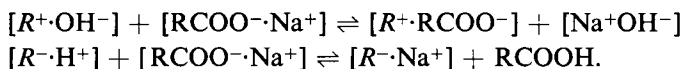
the manufacture of copper-acetate rayon, for example. In order to improve its economy, the practice of recovering copper with the aid of ion exchange has been adopted. The alkaline water from the first wash is passed through a weakly acid cation exchanger, such as Amberlite IRC-50, the copper being almost quantitatively retained on the exchanger resin. Regeneration is made with sulphuric acid and the copper recovered by electrolysis. In the rayon industry zinc is also now being successfully recovered from the washing water. The wash water containing zinc and sodium is passed through a strongly acid cation exchanger in the H-form. The zinc held on the exchanger is liberated by the use of sulphuric acid as a regenerating agent. The resultant zinc sulphate solution can, after concentration, be returned to the manufacturing cycle[12].

Large quantities of chromic acid are apt to be lost with the washing water in electroplating shops. The practice has recently been adopted in many places of collecting this water and treating it with a strongly basic anion exchanger, such as Amberlite IRA-410 or, better still, IRA-401. After passage through the exchanger column, the column is regenerated with sodium sulphate. The regenerating fluid must subsequently be passed through a strong cation exchanger for the recovery of the free chromic acid.

The preparative extraction of organic bases and the manufacture of their salts have been studied at length by many authors. We shall refer later in detail to the use of ion exchange for the isolation and elaboration of alkaloids.

A very important application of ion exchange in pharmaceutical chemistry is in the elaboration of free organic acids and their salts. Strongly contaminated acids which accumulate as dissolved salts in a chemical or biochemical reaction can be passed over suitable anion exchangers in the hydroxyl form and fixed on the exchangers. The elution of the free acids from the column is effected with a mineral acid.

$$[R^+ \cdot OH^-] + [RCOO^- \cdot Na^+] \rightleftharpoons [R^+ \cdot RCOO^-] + [Na^+ OH^-]$$
$$[R^- \cdot H^+] + [RCOO^- \cdot Na^+] \rightleftharpoons [R^- \cdot Na^+] + RCOOH.$$

The salts of organic acids can also be passed over a cation exchanger in the H form, whereupon the solution of the free organic acid will appear in the effluent. This acid may have to be eluted with an organic solvent if it is insufficiently soluble in water. Carbonic acids, amino-acids, oxycarbonic acids and the like can be elaborated in this way. This technique is also used, for example, in the manufacture of complexones.

A procedure of the utmost importance in pharmacy is the isolation of alkaloids from drug extracts and the like for the purpose of determining the vegetable base content or of extracting the vegetable bases for purposes of elaboration. The underlying principle is that the alkaloidal salts dissociate in aqueous solution, alkaloidal cations being formed. Ion exchange in the case of alkaloidal salts can, in principle, be carried out by two different techniques, i.e. either by the use of cation or anion exchangers.

In the technique I (Fig. 3) a cation exchanger in the H-form is used. The alkaloidal cation displaces the H^+ from the exchanger and is fixed on the cation exchanger like a salt. In the favourable case the colouring matters and other ballast substances of the drug extract pass through the column without being adsorbed on the exchanger, and can be separated with the effluent. The alkaloid base can then be liberated from the resin through the treatment of the latter with an alkali; ammonia is most suitable for this purpose. The poorly soluble alkaloid base which separates is then dissolved in an organic solvent such as ethanol, which is used as an eluent.
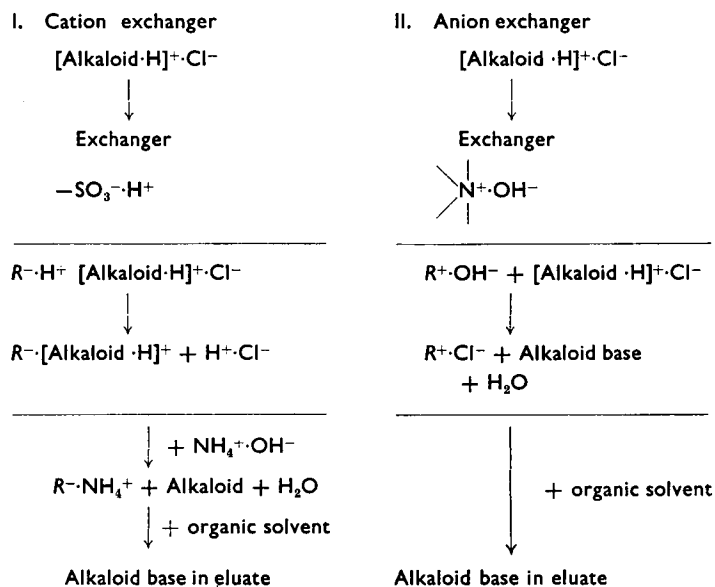
I. Cation exchanger

$$[\text{Alkaloid·H}]^+ \cdot Cl^-$$

$$\downarrow$$

Exchanger

$$-SO_3^- \cdot H^+$$

$$R^- \cdot H^+ \quad [\text{Alkaloid·H}]^+ \cdot Cl^-$$

$$\downarrow$$

$$R^- \cdot [\text{Alkaloid ·H}]^+ + H^+ \cdot Cl^-$$

$$\downarrow + NH_4^+ \cdot OH^-$$

$$R^- \cdot NH_4^+ + \text{Alkaloid} + H_2O$$

$$\downarrow + \text{organic solvent}$$

Alkaloid base in eluate

II. Anion exchanger

$$[\text{Alkaloid ·H}]^+ \cdot Cl^-$$

$$\downarrow$$

Exchanger

$$\diagdown \overset{|}{\underset{|}{N}}{}^+ \cdot OH^- \diagup$$

$$R^+ \cdot OH^- + [\text{Alkaloid ·H}]^+ \cdot Cl^-$$

$$\downarrow$$

$$R^+ \cdot Cl^- + \text{Alkaloid base} + H_2O$$

$$\downarrow + \text{organic solvent}$$

Alkaloid base in eluate

FIG. 3. Isolation of alkaloids. R = exchanger.

The liberation and elution of the alkaloid base can be carried out in one operation if separation and elution are performed with an ammoniacal ethanol.

In the technique II an anion exchanger in its OH-form is used. The exchanger extracts the salt formed from the alkaloid salt and the poorly-soluble alkaloid bases are precipitated in the column. The base is then eluted from the column with the aid of an organic solvent.

Technique I has been successfully used preparatively by Applezweig[22] for the isolation of the alkaloids of cinchona and solanaceæ. Many other authors have since attempted isolation with permutites, carboxylic and sulpho-acid resins. Nicotine can be obtained from tobacco juices and scopolamine concentrated from highly diluted fluid extracts by this technique, which is suitable both for elaborating the pure total alkaloids of a drug and for extracting individual alkaloids in the pure state.

Technique II has been proposed by Jindra[23] for determining the content of alkaloidal drug preparations. It has, however, the great drawback

that the separation of the bases from the vegetable colouring matters is inadequate, with the result that the eluates are usually strongly coloured and in many cases can be titrated only electrometrically. If in addition other salts, such as sodium chloride, are present in the alkaloid solution, they appear as alkalis in the eluate and prevent direct titration.

Ion exchangers were early applied to preparative elaboration from drug extracts. In particular, the development of ion exchangers on a resin basis gave impetus to this pharmaceutical application. Nachod[24] and Applezweig[22,25] were the first to institute experiments with a view to the incorporation of ion exchangers in the process of extracting alkaloids. It is to them that we owe the first studies on the extraction of cinchona alkaloids, and atropine. Stimulated by our earlier experience in the percolation of cinchona bark and the manufacture of cinchona dry extracts[26], in which field, as is commonly known, the problem of the quantitative extraction of the alkaloids and the elimination of the ballast substances without loss of alkaloids has not yet been solved, we set ourselves the task of studying the isolation of the total alkaloids of cinchona bark and their elaboration into totaquine-like preparations on a laboratory scale by the use of a suitable cation exchanger. We were able to base our work on our own analytical studies[3] of cinchona bark and extract. Those studies elicited the fact that, among cation exchangers of different degrees of acidity, Duolite C–10 ($-SO_3^-\cdot H^+$ and $-O^-\cdot H^+$) is best suited to the purpose of adsorbing quinine quantitatively from an acid ethanolic solution such as is available after drug extraction. We knew, moreover, that it was preferable to use a cation exchanger rather than an anion exchanger because the colouring matter of cinchona bark can be much better separated by the former method. A part of the coloured accompanying substances is adsorbed and a part passes through. The colouring matter retained in the column can be dissolved with 10 per cent. ammonia, while the alkaloids remain held in the resin. The alkaloid bases are then liberated with 10 per cent. spirit of ammonia and can be eluted quantitatively.

It seemed logical to us to apply this principle of exchange and elution to the continuous percolation method, the menstruum then being used continuously in the circulation process, thereby achieving an economy. The alkaloid yields in Table I show that if these yields are compared, for example, with the figures obtained in the manufacture of cinchona extract according to Ph. Helv. V (88 per cent. of the alkaloids are yielded to the percolates, 55 per cent. appear in the finished dry extract), the results achieved by ion exchange can be regarded as very satisfactory. There are practically no alkaloid losses, during ion exchange and elution, and the total yield achieved, i.e. 85 per cent. of the alkaloids, is very favourable.

Ion exchange has also been successfully resorted to in the extraction of vitamins. B_1 and B_2, for example, can be easily and perfectly separated by this method. The procedure used in the case of these B-complex vitamins is that yeast is extracted with dilute acidic ethanol and the weakly basic aneurine is adsorbed from this solution with the help of a strongly

acid cation exchanger. Riboflavine is retained in the solution and is recovered therefrom. Aneurine is then separated from the exchanger resin with a strong acid, and processed[27]. Since with this method there is a danger of the decomposition of aneurine, isolation is preferably carried out with a weakly acid ion exchanger such as Amberlite IRC-50, as elution then takes place much more gently. Ascorbic acid, folic acid and vitamin B_{12} have also been extracted and purified by ion exchange[28].

TABLE I

ALKALOID YIELDS OF CINCHONA BARK USING EXCHANGE AND ELUTION

Working phases	Bark I 11·75 per cent.	Bark II 4·21 per cent.
(a) Extracted by percolation with 0·1N sulphuric acid ..	88·9　　,,	86·25　,,
Loss during extraction　..　..　..　..	11·1　　,,	13·75　,,
(b) Adsorbed on Dowex C-10 from the percolate by ionic exchange without loss　..　..　..　..	0　　,,	0　　,,
(c) (i) Lost in the elution of the colouring matter and ballast substances　..　..　..　..	0·05　,,	0·05　,,
(ii) Lost in the elution of the alkaloids (readsorption, etc.)　..　..　..　..　..	1·34　,,	0·95　,,
Total losses determined　..　..　..	12·6　,,	14·75　,,
(d) The following were obtained on crystallisation of the alkaloids		
1st crystallisation　..　..　..　..	43·05　,,	43·0　,,
2nd crystallisation　..　..　..　..	34·5　,,	32·8　,,
3rd crystallisation (or mother liquid)　..	9·95　,,	9·4　,,
Total yields of alkaloids　..　..　..	87·5　,,	84·2　,,

Suitable exchange techniques are being used in the manufacture of antibiotics. Through its adsorption on anion exchangers, penicillin can be separated from raw culture filtrates and freed from accompanying toxic matter. These latter substances pass through the exchanger column together with other impurities, and the penicillin is subsequently liberated from the exchanger column in the form of the sodium or potassium salt. Streptomycin was formerly isolated from the culture filtrates through adsorption on animal charcoal and other adsorption agents. The yields achieved by this means were, however, unsatisfactory, amounting to only about 30 per cent. Streptomycin can be much more successfully adsorbed from the filtered culture liquid directly on a weakly acid carboxyl exchanger such as IRC-50. When the exchanger column charged with streptomycin is regenerated with mineral acids, the antibiotic is quantitatively liberated and processed. Various other antibiotics are now being elaborated and purified by ion exchange[29-32].

Ion exchange has also proved serviceable in the separation of chemical compounds which are relatively closely related. The basis of this application is that, while the selectivity of the exchangeable ions differs widely according to the sign of their charge, their size, form, charge and specific structure, very slight changes in the structure and in the constitution of the exchanger (particle size and shape, chemical constitution of the ionogenic groups, degree of wetting, exchange capacity, etc.) are able to greatly modify the pattern of selectivity. If it is further borne in mind that

external factors also (nature of the solvent, nature and quantity of additives such as chelate formers, reaction temperature and reaction time) play a part, it will be appreciated that there must be possibilities of selectively separating dissociating substances which are closely related chemically. Accordingly, it was possible to simplify very considerably the separation of the amino-acids, after the hydrolytic cleavage of the proteins, by the use of exchange resins. It is principally to Kunin and Winters[33] that credit is due for having exploited the high efficiency of the synthetic exchanger resins for the preparative separation of the amino-acids into the principal groups of the acid, neutral and basic representatives, and in the case of the latter group into arginine, lysine and histidine.

Application of ion exchangers as catalysers in elaborative chemistry

A large number of chemical reactions in the fluid phase are catalysed by H^+, OH^- and other ions. The necessary ions were formerly added to the reaction system exclusively in the form of soluble electrolytes. Shortly before the last World War a systematic investigation was undertaken for the first time to ascertain whether exchange resins could also be used for this purpose. In principle, an ion exchanger is suitable for catalytic reactions if it contains the catalytically active ion as the opposed ion. The catalysed reactions take place mainly in the pores of the exchanger compound. No exchange of ions takes place so that it is not necessary to regenerate the resins. The catalytic power of an ionic exchange resin depends fundamentally on the number of active groups, which in their turn condition the exchange capacity. Given equal capacity, a carboxylic acid exchanger is substantially less effective than a sulphonic acid exchanger for the purposes of a reaction catalysed by H^+. Ion exchangers saturated with H^+, OH^-, CN^-, CH_3COO^- or Hg^{++} have already been used with great success in the catalysis of many reactions, such as hydrolysis and saponification, condensation, addition, dehydration, alcoholysis, interchange of ester radicals and so forth. The following processes have been performed technically on a considerable scale: the hydrolysis of ethyl acetate, galacturonic acid ethyl ester, cane sugar, maltose, polyvinyl acetate, esterification of acetic acid, oxalic acid and benzoic acid with methanol, butanol and even with higher alcohols[34]. The advantage of the exchanger catalysers resides in the fact that they are readily separated from the reaction product because they are solid and the catalytically active ions are fixed on the resin. Interfering side-reactions can also often be avoided, which may lead to improved yields and purer products than those obtained by the conventional methods. Thus the hydrolysis of proteins, such as casein, can be effected without the formation of humic acids[35]. Many condensations with aldehydes can be performed without the formation of resinous polymerisation products[36]. Deuel[37] was able to show, moreover, that with the aid of ion exchange catalysers it is possible to hydrolyse substances selectively. Maltose, for example, can be decomposed in the presence of glycogen without the glycogen being attacked. The macromolecules of the glycogen cannot

penetrate the fine-pored ion exchangers that are suitable for this reaction, and are therefore practically not attacked.

I trust that my remarks will have given a useful survey of the technical application of ionic exchange. In view of the wide range of possible applications, it has been necessary to mention only a few processes, which are of significance primarily in the pharmaceutical field. Nevertheless, these examples show that ion exchange has now achieved the importance of such classic techniques as adsorption, extraction, filtration and distillation. There can be no doubt that the opportunities for development, which it affords, will continue to be fruitfully exploited in the improvement of pharmaceutical working methods.

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