

DEMINERALISED WATER FOR PHARMACEUTICAL PURPOSES

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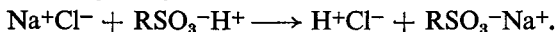
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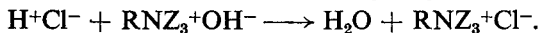
THE process of purifying water by means of ion exchange resins has been known for 20 years. In the last few years, the technique has been so improved that it can be used for the large-scale preparation of water. It is a matter of some importance to decide whether this "demineralised" water, as water purified by ion exchange resins is generally called, is of sufficient purity to replace distilled water of the British Pharmacopœia, for some pharmaceutical purposes. Demineralised water is considerably cheaper than distilled water and it has the great advantage that large volumes can be rapidly prepared from tap-water. Its value to the manufacturing pharmacist should be considerable.

The two resins of principal interest in the purification of water are the strong cation exchanger, containing sulphonic acid functional groups (RSO_3^-H^+ , where R stands for the resin structure) and the strong anion exchanger containing quaternary ammonium groups ($\text{R.NZ}_3^+\text{OH}^-$, where Z stands for an aliphatic group). These ion exchange resins consist of hard organic polymer particles, each containing ionised, functional groups of a single type distributed throughout the mass of the resin. The ionised groups fixed in the resin structure, have oppositely charged ions held loosely to them and it is these loosely-held ions which are able to exchange with similarly charged ions in a solution in contact with the resin. The resins are insoluble in water, but the dry materials swell up when wetted.

If a dilute solution of sodium chloride is passed through a column of the above cation exchange resin in the hydrogen form, the sodium ions from the solution are exchanged with hydrogen ions from the resin giving an effluent consisting of hydrochloric acid.



The exchange is in fact, reversible, but by the use of a column and an excess of resin, it can be driven completely in the direction shown. If the effluent from this column is passed through a column of the second type of exchanger, the chloride ions are removed giving a pure water effluent.



If the original solution consists of ordinary tap-water, the two columns remove the dissolved salts, giving a water of sufficient purity for many industrial purposes. The efficiency of the salt removal is most conveniently assessed by measuring the specific electrical resistance of the effluent. This decreases when the water is allowed to stand, owing to carbon dioxide absorption from the atmosphere.

If the two resins are mixed together in a single column, a considerable improvement in demineralising efficiency is obtained. Water of specific resistance of 10 megohm. cm. is readily prepared, comparable only with

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conductivity water prepared by repeated distillation in a quartz still. Until recently, the mixed resin column method has been unsuitable for large-scale work owing to the difficulty of regenerating the resins, when spent. However, with the development of the quaternary ammonium anion exchangers, regeneration has become possible because this exchanger is considerably less dense than the cation exchanger. If a rapid backflush of water is passed up through the mixed resin column, the two resins separate and a sharp line of demarcation appears between them. They can then be regenerated separately with sodium hydroxide for the upper layer of anion exchanger and hydrochloric acid for the lower layer of cation exchanger. After washing, the resins can be remixed by blowing air up through the column.

The chief disadvantage of demineralised water is that although it is almost completely free from salts, it may contain non-ionic and colloidal impurities, incompletely removed from the feed water by the resins.

The suitability of demineralised water for pharmaceutical purposes was examined by Harrison, Myers and Herr¹. In 1943, they reported that their product, obtained from New Brunswick tap-water by treatment with cation and anion exchangers contained in separate columns, was within the specification of distilled water of the United States Pharmacopoeia. They also showed that the resin treatment did not enhance the pyrogenic effect of the feed-water although they pointed out that it should not be presumed that strongly pyrogenic water would be purified by treatment with the exchangers.

Reents and Kahler² showed that water from a mixed resin ion exchange column, collected only when its specific resistance exceeded 1 megohm cm. contained 0.02 parts per million (p.p.m.) or less of calcium, magnesium, sodium, chloride and silica; sulphate, nitrate and iron were undetectable.

Bütikofer and Ammann³ in 1952 concluded that demineralised water was not suitable for use in place of aqua destillata of the Pharmacopoea Helvetica V. They used the resins in both separate and mixed columns and found that it was not always possible to obtain a product which passed the permanganate test (a less exacting test than that imposed by the British Pharmacopoeia, the Swiss requiring only 3 minutes of boiling). They also stated that the treated water had a disagreeable taste, that it often failed the chloride test and that the residue after evaporation exceeded the limit of 1 mg. per 100 ml. A detailed examination of this paper reveals that the authors do not appear to have had any criterion of electrical resistance for acceptance or rejection of the demineralised water, they only mention that commercial equipment gives a warning when the resistance (specific resistance?) of the water drops below 50,000 to 100,000 ohms. This rejection figure is too low for demineralised water, the limit should be at least 1 megohm. cm. Lack of resistance control of the effluent would account for their positive chloride and residue results. The presence of detectable amounts of chloride in mixed resin, demineralised water is a good indication that the process is not being carried out correctly. Their permanganate reaction is due partly to the same cause and partly to the

fact that they carried out only 6 regenerations of the resins. They noted that the quality of the water improved as the number of regenerations increased. There is no doubt that fresh resins do contain organic impurities which are only slowly eliminated with use. This problem is overcome by some manufacturers by cycling the resins between active and inactive forms several times, before marketing them. The work of Bütikofer and Amman is a good example of the way in which a poor quality product results from the use of a faulty demineralising technique. The results they obtained with the mixed resin column were better than those with the separated resin columns.

Eisman, Kull and Mayer⁴ have described some bacteriological experiments with demineralised water. They used two demineralising plants, each having separate columns for anion and cation exchangers. The first plant was kept in continuous operation and was regenerated at least every 4 days. The output from this plant was substantially sterile, a bacterial count gave an average figure of 1 organism/ml., the feed water having an average count of 50 organisms/ml. The second plant was used infrequently and was only regenerated every 20 days. Immediately after regeneration the demineralised water had a low count, but after standing without use for a few days, the count rose to 1500 or more organisms/ml., much higher than the feed water. The organisms present in the contaminated water were of the type normally present in fresh water, mainly *Pseudomonas*. From this work it appears that a resin bed which is allowed to stand without regeneration can form a culture medium, from which bacteria are flushed out when the unit is set in operation. A demineralised water of very low bacterial count can be obtained if the ion exchangers are used daily and are frequently regenerated. Assuming that *Pseudomonas* is the only impurity present in the water, that each organism occupies a mean volume of $1.3\mu^3$ and has a loss of 90 per cent. on drying with a 10 per cent. nitrogen and 50 per cent. carbon content (dry weight basis), then the following numbers of organisms/ml. will cause the water to fail the chemical tests.

100 million/ml. for the residue test (BP. 1953).

30 million/ml. for the oxidisable matter test (B.P. 1953).

5 million/ml. for the albuminoid nitrogen test (p. 1019).

Other workers⁵ have reported that freshly regenerated resins can have a sterilising effect on slightly contaminated waters.

Cruickshank and Braithwaite⁶ have examined bacterial growth on ion exchange resin columns and have studied methods suitable for sterilising them. They concluded that there is no evidence that bacteria use the resins as a nutrient and they consider that the growth is due to a filtering effect, both bacteria and suspended organic matter being filtered off from the feed water, the latter providing the food for the former to grow on the column. They considered that the most suitable sterilising agent for a contaminated cation exchanger column was formaldehyde. 3 to 5 hours contact of a 0.25 per cent. solution with the resin gave complete sterilisation without damage to the resin. Subsequent washing gave a complete removal of the formaldehyde.

Experimental

Demineralised water was prepared by treatment with mixed exchange resins contained in a Pyrex tube, 120 cm. long and 7.5 cm. in diameter (see Fig. 1). The resins rested on a stainless-steel gauze A; below this there was a reducing adaptor B and the bottom outlet tube C was closed with a seasoned rubber tube and a screw clip. The upper end of the Pyrex tube was closed by means of a bung through which tubes for the feed water and regenerating liquids passed, these tubes were closed at their lower ends by distributors consisting of sintered glass discs, 3 cm. in diameter.

The large Pyrex tube was two-thirds filled with a mixture of one part of Zeo-Karb 225 (cation exchanger) and two parts of De-Acidite FF (anion exchanger) these being equivalent proportions of the two materials. The resin bed volume was approximately 2 l.

To activate the resins and to regenerate them when spent, a fairly rapid stream of water was passed up through the outlet tube C and run to waste through D, after a few minutes a sharp line of separation E appeared between the two resins. The water flow was then stopped, the top of the large Pyrex tube being left full of water. The upper, anion exchange layer was then treated with 2 l. of 5 per cent. sodium hydroxide solution which was introduced through tube D and withdrawn through tube F whose distributor was placed about 2 cm. above the line of separation of the resins, E. The upper layer was then washed with demineralised water. The lower, cation exchange layer was similarly regenerated with 9 l. of 1.5 per cent. sulphuric acid introduced through F and withdrawn from C. After washing this lower layer, most of the water above the resin bed was allowed to flow away and the resins were remixed by blowing a current of air up through C for about 5 minutes. The remaining liquid above the resins was drained rapidly away and the column was allowed to stand for several hours before use. The regeneration could be completed in about 1½ hours.

To prepare demineralised water, London Metropolitan Water Board tap-water was run in at the top of the resin column and the purified water was removed through the tube C. This effluent passed through a conductivity cell fitted with platinum electrodes whose resistance measured directly the specific electrical resistance of the treated water.

The first runnings from the column after regeneration or after standing had a low specific resistance. The effluent was rejected until the value of

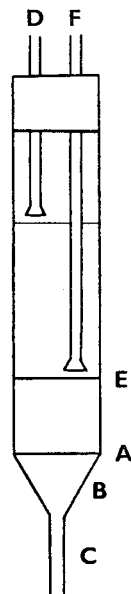


FIG. 1. Demineralising column ready for regeneration.

this property rose to 1 megohm cm., usually about 20 l. of water were rejected in this way. After collection was started, the specific resistance often rose to about 15 megohm cm. before declining again. When it had fallen to 1 megohm cm., collection of demineralised water was stopped and the resins were regenerated. The rate of flow of water through the column was adjusted to 20 to 30 l./hr., but much higher rates could be used.

With a moderately hard tap-water feed, the sulphuric acid regenerant for the cation exchanger was found to be unsatisfactory, fine precipitates of calcium sulphate formed in the column being carried through by the feed water. 2 l. of 5 per cent. hydrochloric acid was therefore used for most of the cation exchanger regenerations. After about 15 regenerations, the volume of acceptable demineralised water obtained between regenerations decreased quite considerably. To overcome this, the resin bed was washed through completely with 18 l. of 5 per cent. hydrochloric acid solution. A vigorous evolution of carbon dioxide from the anion exchanger occurred, suggesting that the loss of de-ionising efficiency was mainly due to the high affinity of this resin for carbonate ions, these ions not being completely removed by regeneration with sodium hydroxide.

Over a 5-month period, an average volume of 90 l. of acceptable, demineralised water was obtained between regenerations. Initially the column was run to exhaustion and regenerated 6 times before samples were collected for examination by the British Pharmacopoeia, 1953 tests for distilled water.

The results of these tests are summarised below.

Description

The demineralised water was invariably clear and colourless. The accepted water was also tasteless, but the early runnings from the column which had been standing for some time in contact with the resins, had a slight unpleasant taste. This water was, however, rejected by the specific resistance test.

Copper, Iron and Lead. Not detected in any samples.

Chloride. Not detected in any of the samples examined.

Sulphate. Not detected.

Ammonia. No colouration with Nessler's reagent.

Oxidisable Matter. All samples of specific resistance above one megohm cm. passed this test. Some early runnings from the column, of unacceptable specific resistance, were at the limits of the B.P. test (note that this requires 10 minutes boiling with permanganate, whereas the Pharmacopœa Helvetica test used by Bütikofer and Ammann, requires only 3 minutes boiling).

Non-Volatile Matter. This is probably the most critical of the B.P. tests in relation to demineralised water. Accepted samples of demineralised water passed the test, but water of specific resistance of 0.5 megohm cm. gave a residue of 2 mg./100 ml., well above the prescribed limit of 0.001 per cent.

After the column had had about 30 regenerations, a sample of water was taken at a specific resistance of just over 1 megohm cm. This was analysed

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according to the "Approved Methods for the Physical and Chemical Examination of Water," published by the Institution of Water Engineers, 1949. The following results were obtained.

Heavy metals. At the limits of detection ; 0.1 parts per million (p.p.m.) of zinc ; 0.05 p.p.m. of copper, iron and lead.

Free ammonia. 0.01 p.p.m. as nitrogen. This is similar to the value obtained for "ammonia-free" water and is very much lower than the usual value for ordinary distilled water which is 0.2 p.p.m.

Albuminoid nitrogen. This is an important analytical result for demineralised water since it measures the amount of colloidal, nitrogenous material which passes through the resin column. With this sample of demineralised water the low value of 0.02 p.p.m. of albuminoid nitrogen, was obtained. The feed water had an average value of 0.07 p.p.m. so it seems that the resins have removed some of the albuminous colloids from the tap water. Albuminoid nitrogen is not usually detectable in distilled water.

Oxygen absorption. In this test a sample of water is heated for 4 hours at 27° C. with dilute potassium permanganate solution. The amount of permanganate used up by the reducing materials in the water is determined and the result is expressed as p.p.m. of oxygen. The demineralised water gave a figure of 0.04 p.p.m. of oxygen compared with an average value of 0.8 p.p.m. for the feed water. This test therefore also indicates that the resins do remove some organic matter from tap water. The average oxygen absorption for distilled water is much the same as that for the demineralised water.

A Suggested Amendment to the Monograph on Distilled Water in the the British Pharmacopoeia

The use of demineralised water is rapidly growing and it can be prepared in a state of purity equal to that of distilled water. It therefore seems desirable that demineralisation should be officially permitted as a method for purifying water for pharmaceutical purposes. To effect this, the author suggests that the present monograph in the British Pharmacopoeia dealing with distilled water should be modified as follows:—

- (1) The title of the monograph should be changed to "Purified Water."
- (2) The method of preparation should be altered to "Purified Water is prepared from a potable water either by distillation or by treatment with ion exchange resins." (With a specification for suitable resins in an Appendix.)
- (3) All the existing tests should be retained with the following addition.

Albuminoid Nitrogen

To a 500 ml. sample of water contained in a 1 l. distillation flask, add 0.2 g. of magnesium carbonate and distil 200 ml. of the water. Add 25 ml. of alkaline permanganate solution (8 g. of potassium permanganate and 200 g. of sodium hydroxide are dissolved in 1 l. of ammonia free water ; before use the solution is mixed with an equal volume of water and evaporated down to its original volume). Distil 100 ml. of water and to

this add 4 ml. of alkaline solution of potassium mercuri-iodide. The colour is not more intense than that given by 100 ml. of ammonia-free water containing 4 ml. of dilute solution of ammonium chloride (Nessler's). (This corresponds roughly to 0.06 p.p.m. of albuminoid nitrogen.)

This new test would guard against the inclusion of undesirable amounts of albuminous colloidal matter in the demineralised water.

The ion exchange method of water purification is unlikely to be suitable for the preparation of water for injection. Pyrogens are almost certainly colloidal in nature and although freshly regenerated resins may remove them almost completely from the feed water, as the resins become spent, they will pass increasing quantities of colloids.

SUMMARY

1. Demineralised water, prepared from tap-water by treatment with mixed anion and cation exchange resins, has been examined by means of the tests of the British Pharmacopœia for distilled water. It has also been subjected to a more detailed analysis.

2. The results show that providing a correct demineralising technique is used and that only water of specific resistance greater than 1 megohm cm., is collected, the purity of the product is at least equal to that of distilled water, B.P.

3. It is suggested that the monograph on distilled water in the British Pharmacopœia should be amended so that demineralised water of suitable purity can be included within it.

The author thanks Mr. J. P. Vokes for carrying out much of the experimental work, the Permutit Co., Ltd., for the loan of the demineralising equipment and Professors H. Berry and W. H. Linnell for their interest and support.

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DISCUSSION

The paper was presented by THE AUTHOR.

MR. J. H. OAKLEY (London) said that he agreed in general with Dr. Saunders's findings. He would reserve judgment on the proposed limits for albuminoid nitrogen until the test had been worked over a longer period. The Swiss findings only emphasised how important it was to let the resins settle down and have many regenerations before using the water. He had met a difficulty with a new resin at an early stage when a Nessler ammonia test had indicated heavy contamination with ammonia. This was later found to be aldehyde derived from the resin. The author stated that the carbon dioxide content would increase on storage, but he

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thought it would decrease. Toxicity tests had shown that there were no toxic materials added to the water. He agreed that the plant must be used frequently, preferably daily, and should not be allowed to lie stagnant for long periods. In this way the bacterial content of the water tended to be reduced. One difficulty arose through channelling, since this reduced the efficiency of demineralisation. The resins tended to act as a filter, and material was trapped in the upper parts of the resin, but this could be removed by backwashing, which also disturbed the bed and prevented channelling. If the plant were in the same building and near to a distilled water plant, sulphuric acid rather than hydrochloric acid should be used for regeneration.

MR. W. TRILLWOOD (Oxford) asked how the resins behaved if the water used were not of a good potable standard?

MR. D. N. GORE (Dorking) remarked that demineralised water was used in the laboratories with which he was associated, except for microbiological work.

MR. T. D. WHITTET (London) said that the American workers, Reid and Jones, had claimed that ion exchange resins would quantitatively remove pyrogens from tap water. He had tested demineralised water for pyrogens, and even when the feed water was strongly pyrogenic the treated water was apyrogenic. On the other hand, using the resins as columns, as suggested by the Americans, he had had no success in removing pyrogens. With bead resins he had been unable to remove pyrogens using columns, but with granular resins the pyrogenicity of the tap water was reduced. He had used a column 10 to 12 cm. long, and the amount of water passed through the column was very small compared with that used by Reid and Jones. There was need for many more experiments in connection with the removal of pyrogens. Demineralised water would be useful in a hospital pharmacy, for example, for washing ampoules.

MR. G. SYKES (Nottingham) asked whether the water obtained was bacteriologically satisfactory if the columns were used continuously. Was the bacterial content lower than that of the initial water? Was the bacterial content high if the column had not been used for a time?

DR. G. E. FOSTER (Dartford) observed that demineralised water might be cheaper than distilled water if prepared in a laboratory, but in a factory condensed waste steam produced water which was quite satisfactory for many purposes.

DR. R. E. STUCKEY (London) said that it was necessary to watch for organic materials, which were not removed by the normal deionisation mechanism of the columns but were removed by simple adsorption processes. Had the author any experience of putting water through with a high organic content? It was essential that the process should operate continuously in order to get a bacteria- and mould spore-free water. Had Dr. Saunders any suggestions to make regarding a specification for the resins?

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DR. SAUNDERS, in reply, said the carbon dioxide content would not increase if the material were sealed, but if it were stored in contact with air it was possible to watch the conductivity rise as carbon dioxide was absorbed. It was essential to keep the plant in frequent use, so that the method was unsuitable for small-scale work. If all the water needed was run off after regeneration and the column left standing it could be sterilised, by running dilute formaldehyde solution through it and washing thoroughly before the next regeneration. He had done no work with water heavily contaminated with colloidal material, but the B.P. tests would give an adequate safeguard if the water were very bad. He had carried out no bacteriological tests, but other workers had confirmed that as long as the columns were kept in continuous operation the bacterial count of the water coming out was very low indeed. He had not drawn up specifications for the resins, but it would not be difficult to do so.