

PATENT SPECIFICATION

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(54) ENRICHMENT AND/OR SEPARATION OF AN ORGANIC
 COMPOUND BY ADSORPTION PROCESSES

(71) We, ROHM AND HAAS COMPANY, a corporation organised under the laws of the State of Delaware, United States of America, of Independence Mall West, Philadelphia, Pennsylvania 19105, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:

This invention is concerned with adsorption processes for the concentration of one or more components of aqueous solutions.

For the purposes of this specification and claims the term "concentration" means to separate one or more components in substantially pure form or condition from a mixture thereof or to isolate fractions which are enriched in one or other component, that is, the fractions contain one or more components in higher concentration.

Our copending U.K. Patent Application No. 6145/66 (Serial No. 1,129,125) describes and claims a process for the concentration of a substance having in its molecule a hydrophobic portion and a hydrophilic portion, from an aqueous medium containing it, wherein the medium containing the substance is contacted with particles of a substantially non-ionogenic macroreticular cross-linked synthetic resin having a porosity of at least 10%, a specific surface area of at least 10 sq.m. per gram and which is not swollen by the medium, so that the substance is adsorbed on to the surface of the resin. Generally the process involves the additional step of desorbing the substance from the resin.

In accordance with the present invention, the above process is applied to the concentration of vitamin B-12, tetracycline hydrochloride or oxytetracycline hydrochloride.

The macroreticular resin used in the process of the invention is preferably of 16 to 100 mesh (U.S. Standard Screen Series) in particle size, but for some special purposes the resin particles

may be as small as about 400 mesh (37 microns).

Macroreticular resins are characterized by the presence, throughout the polymeric matrix, of a network of "extra-gelular" micro channels or pores. While these micro channels are very small, they are large in comparison with the pores in conventional homogeneous cross-linked gels. Macroreticular resins suitable for use in the invention may have specific surface areas of up to 2,000 sq. m. per gram or more.

In general, since the macroreticular resins find their greatest value in the processing of aqueous solutions, they are preferably not extremely hydrophobic or water-repellent. The preferred resins are cross-linked resins which have solubility parameters (expressed in the

units $\sqrt{\frac{\text{calories}}{\text{cubic centimeter}}}$) of at least 8.5 and

those having such parameters up to 15 or more are satisfactory for use in aqueous systems.

The macroreticular resins employed as the adsorbents herein are more fully described in specification No. 1,129,125. Preferred resins are polymers of divinyl benzene or copolymers thereof with monovinyl aryl monomers, particularly styrene and/or ethylvinylbenzene, with or without up to 5% of other mono-ethylenically unsaturated monomers such as acrylonitrile.

The adsorbents used in the process of the invention may also be employed to effect the slow, sustained release of the adsorbed drugs when the adsorbent is administered internally or externally to a patient.

For details as to the manner of contracting the resin adsorbent and the aqueous solution of the aforesaid pharmaceutical substance which is to be concentrated, reference should be made to said Specification No. 1,129,125. Specification and illustrative embodiments of the invention are presented in the following examples in which parts and percentages are

on a weight basis and temperature are in degrees C. unless otherwise noted.

EXAMPLE 1.

In a chromatographic column having a diameter of approximately 0.5 inches, there is placed 50 ml. of the resin beads composed of a copolymer of 50 percent divinylbenzene, 41 percent ethylvinylbenzene and 9 percent styrene, the copolymer having a surface area of 330m.²/g., a porosity of 0.44 ml./ml. and a solubility parameter of about 9.1. In another identical column, there is likewise placed 50 ml. of a cation exchange resin of the carboxylic type, and more specifically a resin which is commercially available as Amberlite IRC-50 from the Rohm and Haas Company, Philadelphia Pennsylvania. (Amberlite is a registered trade mark). A concentrate of vitamin B-12 is diluted with water to 15 ppm and passed through each column at a flow rate

of 1 gal./cu. ft./minute. The capacity of each resin to take up the vitamin B-12 is measured at two different points. The first is designated as breakthrough, that is, the point at which there is leakage from the column of vitamin B-12 at a 50% concentration. A second point of measurement is designated as the saturation point which is that point wherein the resin no longer takes up any more of the material being separated from the aqueous solution, which in this case is vitamin B-12. Thereafter, each of the column is eluted with methanol at a flow rate of 0.5 gal./cu. ft./minute and the maximum or peak concentration of the vitamin B-12 during the elution is observed and noted. All of the above observations are shown in Table I which clearly indicates the superiority of the non-ionogenic polymer resin over the carboxylic resin for separating vitamin B-12.

TABLE I

Resin Type	Resin Capacity		Elution	
	Break-through (mg./ml.)	Saturation (mg./ml.)	Peak Concentration (ppm)	Volume (bed. vol.)
Carboxylic	0.03	0.14	150	5
non-ionogenic	3.5	5.2	7200	2

EXAMPLE 2.

A 1000 ppm aqueous solution of tetracycline hydrochloride is passed at a flow rate of 1.0 gal./cu. ft./minute through a chromatographic column approximately 0.5 inches in diameter and containing 50 ml. of the non-ionogenic resin employed in Example 1. At the saturation point, 44 mg. of tetracycline hydrochloride is adsorbed per ml. of resin. After elution of the resin with five bed volumes of methanol, the effluent shows an elution peak of 30,000 ppm of tetracycline hydrochloride. In a similar manner, an influent having 100 ppm of tetracycline hydrochloride is passed through an identical column and resin at the same flow rate. In this situation, the saturation capacity is 7.4 mg. per ml. of resin. Likewise, an elution peak of 16,000 ppm is observed during elution with three bed volumes of methanol.

EXAMPLE 3.

An aqueous solution of oxytetracycline hydrochloride at a concentration of 100 ppm is passed through a column and non-ionogenic resin identical to that employed in Example 1 at a flow rate of 1.0 gal./cu.ft./minute. At the saturation point, 7.6 mg. of oxytetracycline hydrochloride is adsorbed per ml. of resin

Upon elution with two bed volumes of methanol, an elution peak of 17,600 ppm is observed.

WHAT WE CLAIM IS:—

1. A process for the concentration of a substance having, in its molecule a hydrophobic portion and a hydrophilic portion, from an aqueous medium containing it wherein the medium containing the substance is contacted with particles of a substantially non-ionogenic microreticular cross-linked synthetic resin having a porosity of at least 10%, a specific surface area of at least 10 sq. m. per gram and which is not swollen by the medium, so that the substance is adsorbed on to the surface of the resin, wherein the substance is vitamin B-12, tetracycline hydrochloride or oxytetracycline hydrochloride.

2. A process according to claim 1 in which the resin is a copolymer of divinyl benzene, styrene and ethylvinylbenzene.

3. A process according to Claim 1 or 2 including the additional step of desorbing the adsorbed substance from the resin.

4. A process according to Claim 1 substantially as hereinbefore described with reference to any one of the foregoing examples.

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3. A process according to Claim 1 or 2 including the additional step of desorbing the adsorbed substance from the resin.

4. A process according to Claim 1 substantially as hereinbefore described with reference to any one of the foregoing examples.



5. Vitamin B—12, tetracycline hydrochloride or oxytetracycline hydrochloride when concentrated by a process according to any one of the previous claims.

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