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AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner, acting for the Comptroller General, dated the sixteenth day of May, 1962, under Section 14, of the Patents Act, 1949.

PATENT SPECIFICATION

NO DRAWINGS

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857,193

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International Classification:—A61k.

COMPLETE SPECIFICATION

Resin-Drug Compounds

We, CLINICAL PRODUCTS LIMITED, a Body Corporate organised under the Laws of Great Britain, of 225, Bath Road, Slough, Buckinghamshire, formerly of 2, The Green, Richmond, Surrey, 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 relates to therapeutic compositions, its object being to provide compositions suitable for oral administration and adapted to be acted upon by the natural contents of the gastro-intestinal tract to give a sustained release of an ionisable therapeutic agent.

According to the present invention, a therapeutic composition consists in a derivative of barbituric acid adsorbed in ion-exchange relationship on a polystyrene anion-exchange resin, the resin having a degree of cross-linkage in the ranges of 1—5% or 7—9%, or of 12% or 20% and a particle size between −16 and +200 mesh B.S.S.

The derivative resin product may be mixed with uncombined resin.

Suitable ion-exchange resins are available commercially and may be divided into two types according to the functional groups associated with the synthetic, insoluble, macromolecular compound known as the resin matrix.

In the resin matrix the amount of cross-linking may be varied and the functional group may be for example, a quaternary ammonium group (strong anion exchange) or a primary amino group (weak anion exchange).

The resin may be cross-linked with divinyl benzene.

A suitable resin for use in the invention is produced by The Permutit Company Limited under their Registered Trade Mark "DeAcidite," and "DeAcidite FF" is a strongly basic quaternary ammonium polystyrene resin in either the chloride form or the hydroxide form with a range of particle size of −16 +200 B.S.S. mesh with degrees of cross-linking in the range of 1—5%, 7—9%, 12% and 20%.

Two suitable therapeutic agents of an acidic character are amylobarbitone and phenobarbitone.

FORMATION.

THE REACTION

Resin (in chloride form) + a sodium barbiturate e.g. sodium amylobarbitone. → Resin-barbiturate + sodium chloride

RELEASE OF THERAPEUTIC AGENT

resin barbiturate + HCl → Resin in chloride form + a barbiturate

resin barbiturate + NaCl → Resin in chloride form + a sodium barbiturate

[*Price 4s. 6d.*]

The rate of release of the therapeutic agent may be varied by:—

(a) utilising different types of resin, particularly according to the percentages of cross-linkages present.
(b) varying the amount of therapeutic agent combined with the resin, or adding pure resin to the saturated compound.
(c) varying the ionic concentration of the therapeutic agent.
(d) varying the temperature.
(e) varying certain other physical properties of the resin such as particle size.

The resin may be saturated with the therapeutic agent by passing a solution of the drug, in alcohol or water, through a column of the resin until the composition of the liquid issuing from the column is the same as that entering. Alternatively varying amounts of the therapeutic agent may be combined with the resin by agitating the resin with a solution of the therapeutic agent for varying periods of time.

If the resin is saturated with the therapeutic agent a maximum amount of the agent is released on elutriation with slightly acidic or neutral or slightly alkaline elutriant (e.g. N/10 hydrochloric acid or sodium hydroxide potassium dihydrogen phosphate solution buffered at pH 7.5) during the initial stages of elutriation but an equilibrium is eventually set up.

If the resin is combined with an amount of therapeutic agent less than that required to saturate, the amount of the agent released in the initial stages is less than that released when the resin is saturated but eventually the same equilibrium is reached.

The normal contents of the stomach may be taken as being of an acidic nature (approximately equivalent to N/10 HCl) whilst those of the intestine are neutral or slightly alkaline. On being taken by mouth the resin salt may be expected to move from the stomach to the intestine in about two hours and then remain in the intestine for a longer period. The rate of release of the therapeutic agent from the resin-agent compound is not influenced by the changes of ionic concentration likely to occur in the gastro-intestinal tract.

These conditions may be approached approximately by using in the elutriation experiments designed to produce a curve relating the amount of agent released with time, in the first two hours N/10 aqueous solution of hydrogen chloride and thereafter a sodium hydroxide-potassium dihydrogen phosphate medium buffered at pH 7.5.

Examples of Formation of the Resin-agent Salt.

EXAMPLE I.

A quantity of a highly basic anion exchange resin formed from a polystyrene polymer 8% cross-linked with divinylbenzene and containing quaternary ammonium groups is placed in a tube and a solution of a sodium barbiturate, for example, sodium phenobarbitone, is passed through the column at room temperature until the solution issuing from the column has the same composition as that entering the column.

EXAMPLE II.

1 gram of a highly basic anion exchange resin formed from a polystyrene polymer 8% cross-linked with divinylbenzene and containing quaternary ammonium groups combined with 0.702 gram of phenobarbitone on agitating with a 10 per cent aqueous solution of sodium phenobarbitone, at room temperature in about 24 hours. Complete saturation is obtained by continuing contact with the sodium phenobarbitone for a longer period of time when 1 gram of the resin combines with about 0.80 gram of phenobarbitone.

WHAT WE CLAIM IS:—

1. A therapeutic composition, suitable for oral administration and adapted to be acted upon by the normal contents of the gastro-intestinal tract to give a sustained release of an ionisable therapeutic agent consisting in a derivative of barbituric acid adsorbed in ion-exchange relationship on a polystyrene anion-exchange resin, the resin having a degree of cross-linkage in the ranges of 1—5%, or 7—9%, or of 12% or 20%, and a particle size between −16 and +200 mesh B.S.S.

2. A therapeutic composition, as claimed in claim 1, wherein the derivative resin product is mixed with uncombined resin.

3. A therapeutic composition, as claimed in either of claims 1 and 2, wherein the resin is a cross-linked polystyrene-type resin containing quaternary ammonium groups.

4. A therapeutic composition, as claimed in claim 3, wherein the resin is cross-linked with divinyl benzene.

5. A therapeutic composition, as claimed in any one of claims 1 to 4, wherein the derivative of barbituric acid is amylobarbitone or phenobarbitone.

6. The therapeutic compositions particularly described herein.

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Acting For Comptroller.
The Patent Office, 25, Southampton Buildings, LONDON, W. C. 2.

The rate of release of the therapeutic agent may be varied by:—

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(b) varying the amount of therapeutic agent combined with the resin, or adding pure resin to the saturated compound.
(c) varying the ionic concentration of the therapeutic agent.
(d) varying the temperature.
(e) varying certain other physical properties of the resin such as particle size.

The resin may be saturated with the therapeutic agent by passing a solution of the drug, in alcohol or water, through a column of the resin until the composition of the liquid issuing from the column is the same as that entering. Alternatively varying amounts of the therapeutic agent may be combined with the resin by agitating the resin with a solution of the therapeutic agent for varying periods of time.

If the resin is saturated with the therapeutic agent a maximum amount of the agent is released on elutriation with slightly acidic or neutral or slightly alkaline elutriant (e.g. N/10 hydrochloric acid or sodium hydroxide potassium dihydrogen phosphate solution buffered at pH 7.5) during the initial stages of elutriation but an equilibrium is eventually set up.

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