[^3H]*Mepyramine* (N-[4-*methoxyphenyl*)*methyl*]-N-2-[5-^3H]*pyridinyl*-1,2-*ethanediamine*)-Bromomepyramine (II) (10 mg) in 95% ethanol–triethylamine (5:2 v/v) with 10% Pd/C as catalyst was stirred at room temperature in an atmosphere of tritium gas (reaction carried out by The Radiochemical Centre, Amersham). The catalyst was removed by filtration, the solvent evaporated under vacuum and the residue taken up in chloroform and extracted with 0·5M NaOH. The organic phase was washed twice with distilled water, the solvent removed under vacuum and the residue taken up in 10% maleic acid in ethanol (2 ml). The product was purified by thin-layer chromatography on silica gel G (Merck) in two stages. A preliminary purification was achieved using the solvent systems ethanol–acetic acid (9:1, v/v), chloroform–triethylamine (9:1, v/v) and light petroleum (b.p. 80–100)–ether–triethylamine (9:9:1, v/v/v) and the product from this step, stored at −10° as the maleate, further purified by running in ethanol–acetic acid–water (8:1:2, v/v/v) and, finally, chloroform–triethylamine (9:1, v/v). The final product was eluted with ethanol, acidified with acetic acid to give a 5% solution and stored at −10°. The concentration of [^{3}H]mepyramine was determined from the ultraviolet absorbance at 310 nm, using non-radioactive mepyramine as standard (the equimolar amount of maleate or the excess acetic acid does not interfere at 310 nm). The specific activity was 20 Ci mmol^{-1}.

The radiochemical purity of the product was established (a) by thin-layer chromatography (Prepared Polygram silica gel layers with fluorescent indicator, Machery & Nagel), from the coincidence of the R_F value for the single peak of radioactivity in [^{3}H]-mepyramine (run with added non-radioactive mepyramine as carrier) with that for authentic mepyramine run concurrently, in three solvent systems: ethanol–acetic acid–water (8:1:2, v/v/v), benzene–triethylamine (9:1, v/v) and chloroform–triethylamine (9:1, v/v) and (b) by high voltage electrophoresis (Shandon Southern, model L24) on Whatman No 1 paper in 0·1 M citric acid-phosphate buffer, pH 3·05, at 40 V cm^{-1} for 45 min, where the peak of radioactivity migrated towards the anode at the same rate as authentic mepyramine. The high-voltage electrophoresis achieved a better separation between mepyramine (I) and bromomepyramine (II) than any of the t.l.c. systems.

The chemical purity of the [^{3}H]mepyramine was established by bioassay, using the inhibition of the contractile response of longitudinal muscle strips from guinea-pig small intestine to histamine. The affinity constant, deduced from 3 measurements of the extent of the shift of the dose-response curve to histamine, was $1{\cdot}6 \pm 0{\cdot}4 \times 10^9$ M^{-1}, in excellent agreement with the value of $1{\cdot}6 \pm 0{\cdot}3 \times 10^9$ M^{-1} obtained for non-radioactive meypramine (Table 1).

The synthetic approach described above provides a convenient and easy route to high-specific activity [^{3}H]-mepyramine, the chemical and radiochemical purity of which is borne out by its successful use in labelling histamine H_1 receptors in guinea-pig intestine (Hill & others, 1977) and brain (Hill & Young, 1978; Hill & others, 1978).

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New hydrophilic vehicle enabling rectal and vaginal absorption of insulin, heparin, phenol red and gentamicin

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Drugs that are poorly absorbed or decomposed in the gastrointestinal tract, such as insulin, heparin and certain amino-glycoside antibiotics, require to be administered parenterally for effective systemic action. The use of the rectal or vaginal routes for these drugs has failed to accomplish significant absorption or clinical effects. Preparations of heparin are available for topical use, but there is no evidence of systemic action.

We have developed a hydrophilic vehicle from which systemic action is obtained after rectal or vaginal administration of drugs not normally active via the gastrointestinal tract. The base comprised the non-ionic surface-active agent Cetomacrogol 1000 (polyethylene glycol 1000 monocetyl ether) in combination with various concentrations of polyethylene glycols. Con-

* Correspondence.

centrations of the components and molecular weights of the polyethylene glycols varied according to the consistency required to obtain dosage forms ranging from solid suppositories to semi-solid micro-enemas or vaginal applications.

The cetomacrogol base was tested *in vivo* in rats using phenol red, insulin, heparin and gentamicin. The base comprised 0·53 g cetomacrogol 1000, 0·14 g polyethylene glycol 400 and 0·33 ml water for 1 ml semi-solid micro-enema. Polyethylene glycol 400 was incorporated in order to obtain the semi-solid consistency. The ingredients of the base were melted and the drug solution was added maintaining the mixture at about 45° after which syringes were filled with 1 ml of this preparation. Phenol red, which is used as an intestinal marker and renal function test agent, is known to be poorly absorbed. Schanker & others (1957, 1958) reported that less than 2% is absorbed from the rat stomach in 1 h or the rat intestine in 3 h. McLeod & others (1968) found the absorption of an oral dose from the entire gastrointestinal tract to be 1% or less h^{-1}. It was therefore chosen for the proposed formulation. Rectal absorption was measured in 5 rats using 1 ml of a semi-solid micro-enema containing 2 mg phenol red. Spectrophotometric determination of the phenol red, recovered from urine collected over the 1½ h after administration, was 77% ± 9·6 (s.e.m.) of the dose given. This established that the cetomacrogol base could effect absorption of a strongly acidic substance which is fully ionized, has a very high water-oil partition coefficient and, according to the accepted theory of passive diffusion, should not be able to penetrate the gastrointestinal or rectal membranes in significant amounts (Schanker, 1959).

Insulin (neutral) was administered in the cetomacrogol base at a dose of 27 i.u. rectally in 1 ml of a semi-solid micro-enema to rats (230–270 g, Male Hebrew University 'Sabra' strain) fed on a pelleted chow diet, in which diabetes had been induced by streptozocin (50 mg kg^{-1}) injection (Patel, 1974). Blood glucose content, measured by the GOD-Perid method (Werner & others, 1970) was reduced after 1,2 and 4 h to 33·2 ± 6·5, 30·1 ± 3·5 and 37·4 ± 3·0% (s.e.m.) of the initial value. The corresponding reduction in blood glucose on injection of 4 i.u. insulin intraperitoneally was 36·1 ± 2·2, 28·7 ± 1·0 and 39·4 ± 3·6% at 1, 2 and 4 h, respectively. Thus the time dependence patterns of the hypoglycaemic effect were similar using the cetomacrogol base rectally and the neutral insulin solution intraperitoneally, a strong effect being observed at 1 and 4 h, with the maximum effect in the 2 h blood sample. The significance level was $P < 0{\cdot}001$ using 25 rats and independently prepared batches of the micro-enema. No hypoglycaemic effect was observed in controls in which insulin was administered rectally in a classic polyethylene glycol base.

Vaginal administration of insulin 27 i.u. in the cetomacrogol base to 5 diabetic female rats also gave a blood glucose content reduction to 66·3 ± 4·6, 50·7 ± 3·2 and 48·9 ± 11·2% of the intial value at 1, 2 and 4 h. This base also effected rectal absorption of heparin and gentamycin. The former was measured by its anticoagulant effect, and the application of 5000 units of heparin in the base extended the mean blood coagulation time of normal rats by about tenfold. The antibiotic concentration was measured directly by bacteriological assay of blood and urine and, on application of 10 mg of gentamycin in the base, therapeutic blood concentrations were obtained and a substantial proportion of the antibiotic was recovered from the urine (unpublished results). Controls containing the respective drugs in a PEG base gave negligible absorption or clinical effects.

The cetomacrogol base is evidently effective in introducing the drugs systemically by the rectal or vaginal route. Its use* may possibly open a way to the development of alternative routes of administration of drugs hitherto given parenterally and causing patient compliance or other problems. Other related non-ionic surfactants have been studied (to be published).

Whilst non-ionic surfactants have relatively low LD 50 and chronic toxicity values (Swisher, 1968), toxicity tests on the base applied by these routes have still to be made.

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