currents measured at —1·5 V; drop time, 3 s; current density, 5×10^{-3} A mm^{-2}. The diffusion currents were expressed as pen response in mm. The difficulty of the methyl nitrate being reduced at approximately the same potential as the glyceryl trinitrate was overcome as follows. The response, i_1, of 1 ml standard methyl nitrate solution was measured; the response, i_2, for the mixture of 1 ml of internal standard and 1 ml unknown trinitrate solution was then corrected for i_1 giving

$$\text{Glyceryl trinitrate concentration} = \frac{(i_2 - i_1)c}{i_1 A}, \text{ mg ml}^{-1}$$

where c = concentration of internal standard,

$$A = \frac{\text{1 mg glyceryl trinitrate}}{\text{1 mg methyl nitrate response}} \text{ ratio.}$$

A series of three glyceryl trinitrate and three methyl nitrate solutions (0·2, 0·4 and 0·9 mg ml^{-1}) was assayed in a Latin square sequence and the response for 1 mg of both substances thus calculated from a mean of 18 readings. The results are given below with their fiducial limits ($P = 0{\cdot}05$).

1 mg glyceryl trinitrate response = 17·32 ± 0·53 mm.

1 mg methyl nitrate response = 46·12 ± 0·74 mm.

(1 mg glyceryl trinitrate/1 mg methyl nitrate) response ratio = A = 0·358—*0·376*—0·393

A re-determination 3 months later showed that the 1 mg glyceryl trinitrate response had changed significantly to 16·58 ± 0·67 mm, whereas the ratio, A was almost unchanged at 0·345—*0·365*—0·385, thus vindicating the internal standardization.

1 ml aliquots of methyl nitrate solution (approximately 0·3 mg $MeNO_3$) were mixed with 1 ml samples of a series of glyceryl trinitrate solutions of concentrations 0·1, 0·2, 0·4, 0·8, 1·6 mg ml^{-1}. The response was linear with respect to glyceryl trinitrate concentration and the gradient was 17·14 mm mg^{-1}, indicating no interference between the compounds.

An assay was performed on 6 samples taken from a powdered mass of 100 tablets. A weight of powder containing about 5 mg glyceryl trinitrate was mixed with 10 ml acetone on a 'Whirlimixer' for 3 min. The suspension was clarified by centrifugation and 1 ml supernatant liquid mixed with 1 ml methyl nitrate solution, 3 ml polarographic solvent and analysed. The glyceryl trinitrate content per mean tablet weight was 0·478 ± 0·004 mg ($P = 0{\cdot}05$).

Six samples analysed by the B.P. method gave a mean tablet content of 0·476 ± 0·005 mg ($P = 0{\cdot}05$). A variance ratio test showed that the proposed method and the B.P. method showed no significant difference in their precision (variance ratio = 1·80; F = 5·05 for $P = 0{\cdot}05$, 5 × 5 degrees of freedom), and a *t*-test showed that the means were not significantly different ($t = 1{\cdot}11$, tabulated value 2·23 at $P = 0{\cdot}05$, 10 degrees of freedom.

Single tablet assays were performed by placing one tablet in the polarographic cell, powdering with a glass rod, adding 2 ml of half strength methyl nitrate solution and 3 ml polarographic solvent. Results for 6 tablets of nominal strength 0·5 mg were 0·478, 0·492, 0·477, 0·465, 0·480, 0·480 mg; mean = 0·478 ± 0·009 mg ($P = 0{\cdot}05$). 6 tablets assayed by the B.P. method gave the results 0·476, 0·482, 0·481, 0·460, 0·487, 0·475, mean = 0·477 ± 0·010 mg ($P = 0{\cdot}05$), in good agreement with the results of the polarographic method.

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Potentially biodegradable microcapsules with poly (alkyl 2-cyanoacrylate) membranes

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The poly (alkyl 2-cyanoacrylates) are used as biodegradable tissue adhesives in surgery. The methyl ester in solid form degrades most rapidly yielding formaldehyde which is believed to be responsible for its histotoxicity. The butyl ester, with a slower degradation rate, is well-tolerated in vivo (Leonard 1970). In a previous paper, Florence et al (1976) showed that methyl 2-cyanoacrylate and butyl 2-cyanoacrylate dissolved in an oil phase formed polymeric films in contact with an aqueous phase and suggested that these monomers could be used in the preparation of microcapsules which would degrade in vivo. The present paper describes the preparation of microcapsules formed from butyl 2-cyanoacrylate monomer. The reaction involves a base catalysed anionic mechanism (Coover et al 1959) with the monomer dissolved in the oil phase of a water-in-oil emulsion and in situ polymerization occurring at the interface of the aqueous disperse phase. Aqueous protein solutions have been used as the microcapsule core materials; the protein is believed to act as an

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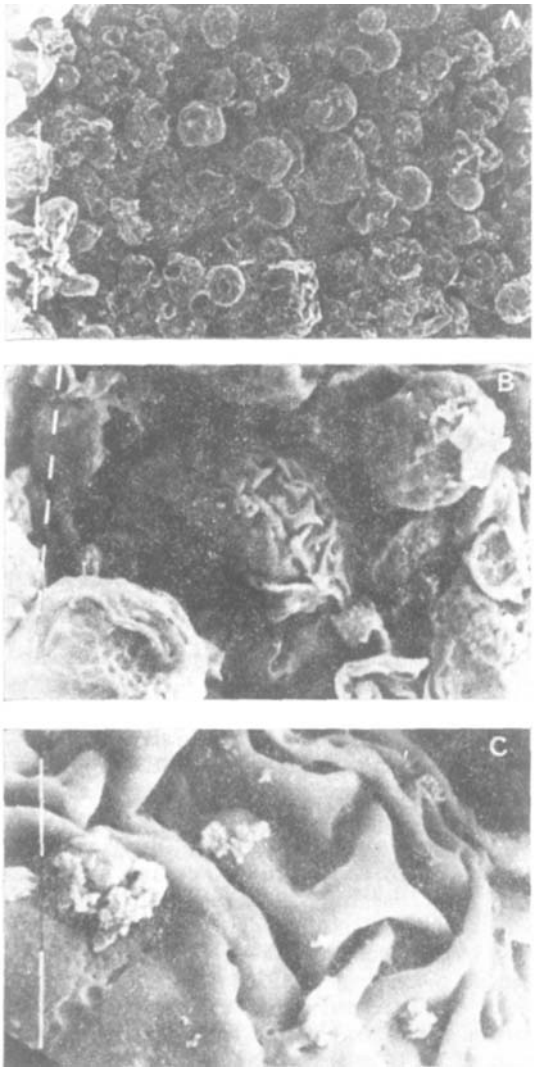

FIG. 1. Scanning electron micrographs of poly (butyl-2-cyanoacrylate) microcapsules at various magnifications. The markers on each photograph represent the following values (A) 100 μm (B) 10 μm and (C) 10 μm.

initiator and therefore to become a cross-linking agent on the inner wall surface. When aqueous solutions of I-125 labelled albumin are encapsulated, 30–40% of the albumin becomes incorporated into the microcapsule membrane.

This described method of microencapsulation does not require the presence of reactive monomers in the core material, a disadvantage of microencapsulation using interfacial polycondensation, as developed by Chang (1972, 1977) for the microencapsulation of enzyme replacement therapy and other applications. Recently Couvreur et al (1978) described the formation of poly (methyl 2-cyanoacrylate) and poly (ethyl 2-cyanoacrylate) microspheres (around 0·2 μm in diameter) which are probably of a solid rather than capsular nature as are our microcapsules. A typical procedure used in the preparation of poly (butyl-2-cyanoacrylate) microcapsules is detailed here: an aqueous solution (2 ml) of the material to be microencapsulated is emulsified in an organic solution (10 ml) (e.g. chloroform: cyclohexane 1 : 4, containing 5% v/v Span 85 (sorbitan trioleate)). Organic phase (10 ml) containing butyl 2-alkyl cyanoacrylate monomer (0·25 ml) is added whilst stirring is continued for 3 min. Cyclohexane (20 ml) is added to quench the reaction and reduce the possibility of polymerization occurring between the formed microcapsules. The microcapsules sediment in a few minutes and the organic phase is decanted. Polysorbate 20 (30% v/v, 20 ml) is added and the suspension well stirred; water (20 ml) is added, followed by ethanol (40 ml). After the microcapsules have sedimented they are repeatedly washed by centrifugation and finally resuspended in an aqueous buffer solution.

Microcapsules of controlled size can be prepared from a few micrometres to several hundred micrometres in diameter.

Fig. 1 shows scanning electron micrographs of the microcapsules prepared as above, dried and coated with gold. A Philips P SEM instrument was used. The capsule walls do not appear to be porous but the polymer film is convoluted in many of the capsules. The nature of the surface bears little resemblance to the films produced at macroscopic oil-water interfaces using different oil phases (Florence et al 1976), underlining the importance of the organic phase in determining the morphology of the interfacial film. The properties of the microcapsules produced are thus influenced by the organic phase and it is therefore difficult to generalize about their behaviour without reference to the mode of preparation.

The most interesting feature of poly (alkyl cyanoacrylate) microcapsules is their potential biodegradability. Although it is known that the poly alkyl 2-cyanoacrylates degrade in vitro (Leonard et al 1966) and in vivo (Leonard 1970) and that the length of the alkyl substituent controls the rate of degradation, such experiments have been conducted on polymers of different morphology (e.g. solid chips) (Vezin & Florence 1978). There is thus no guarantee of microcapsule biodegradation. We have no quantitative data on the question at present but have evidence that degradation occurs with the production of formaldehyde. The degradation reaction is, however, rapidly inhibited by the presence of degradation products and polybutyl 2-cyanoacrylate microcapsules have been stored for 18 months as an aqueous dispersion in a sealed container. Thus one of the problems of degradable systems, that of storage before use, is overcome. On injection in vivo the formaldehyde is kept at sink levels and this allows the breakdown of the polymer to proceed.

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Specific binding of [^{3}H]sulpiride to rat striatal preparations

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Sulpiride is an antipsychotic agent belonging to the substituted benzamide group of compounds (Justin-Besancon et al 1967). Sulpiride also is an anti-emetic (Corsini et al 1976) and increases serum prolactin concentrations in man (Mancini et al 1976). All these effects are associated with dopamine receptor antagonism, so sulpiride appears to act like neuroleptics of the phenothiazine, butyrophenone and thioxanthene classes.

Animal experiments support this hypothesis. Sulpiride blocks locomotor activity induced by apomorphine, inhibits apomorphine- and amphetamine-induced circling behaviour and increases both striatal and mesolimbic dopamine turnover (Elliott et al 1977). However, sulpiride has little cataleptic activity, does not inhibit stereotyped behaviour induced by apomorphine and does not inhibit dopamine-stimulated adenylate cyclase activity either in vitro or in vivo (Laville 1972; Trabucchi et al 1975; Elliott et al 1977; Jenner et al 1978a). In addition, sulpiride only weakly inhibits [^{3}H]haloperidol or [^{3}H]spiperone receptor binding in striatal preparations (Jenner et al 1978a; Jenner et al 1978b) despite being equivalent in activity to haloperidol or fluphenazine on direct intracerebral injection (Hondo et al 1977; Costall et al 1978).

These differences in the mode of action of sulpiride (and other benzamide drugs in general) has formed one of the essential pieces of data taken by some workers to indicate the presence of multiple dopamine receptors in brain (see Kebabian & Calne 1979 and references therein). Two major classes of dopamine receptors are currently conceived, namely those dependent on adenylate cyclase for impulse transmission and those which are not. Substituted benzamide drugs are thought to act as specific antagonists on this latter receptor population.

It is of obvious importance to be able to specifically characterize each of these receptor sub-populations. *cis*-Flupenthixol provides a means of examining adenylate cyclase-dependent receptors. There is a correlation between the ability of neuroleptics to displace [^{3}H]*cis*-flupenthixol from its striatal binding sites and their ability to inhibit dopamine stimulation of striatal adenylate cyclase (Hyttel 1978). However, no means of examining the adenylate cyclase-independent dopamine receptor population has been available until now. We report the specific binding of [^{3}H]-sulpiride to rat striatal preparations.

(±)-[^{3}H]Sulpiride (26·2 Ci mmol^{-1}) was custom synthesized by The Radiochemical Centre, Amersham by the catalytic dehydrogenation of the brominated derivative *N*-1-ethyl-2-pyrrolidyl-methyl-2-methoxy-4-bromo-5-sulphamoylbenzamide (SESIF, France). Purity was 98% as judged by thin layer and paper chromatography.

Female Wistar rats (150 ± 10 g; Olac International) were killed by cervical dislocation and decapitation. The brain was rapidly removed onto ice and the striata dissected into ice-cold 50 mM Tris-HCl buffer (pH 7·7). Striatal tissue was prepared according to the method of Leysen et al (1978). Aliquots of the final ice-cold tissue preparation (1 ml containing 12·5 mg striatal tissue) were placed in small glass tubes and 0·05 ml 0·1% ascorbic acid solution or displacing drugs dissolved in this volume of ascorbic acid solution was added. (±)-Sulpiride or its enantiomers, (+)- and (—)-sultopride (SESIF, France), (+)- and (−)-butaclamol hydrochloride (Ayerst Laboratories), *cis*- and *trans*-flupenthixol hydrochloride (Lundbeck, Copenhagen), dopamine hydrochloride, noradrenaline hydrochloride or 5-hydroxytryptamine creatinine sulphate (Sigma Chemical Co.) all at concentrations between $10^{-10} - 5 \times 10^{-3}$ M, or 0·05 ml 0·1% ascorbic acid solution were added to the incubates in displacement experiments. Incubations were started by the addition of [^{3}H]sulpiride (5–40 nM) in 0·05 ml 0·1% ascorbic acid solution. Incubation was carried out at 37 °C for 1 h after which the incubates were immediately transferred to plastic micro-centrifuge tubes (capacity 1·5 ml; Alpha Laboratories) and centrifuged in a Beckmann Microfuge B at approximately 8000 *g* for 1 min. Samples were placed in ice, the supernatant

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