## The sorption of benzocaine by nylon 6 (polycaprolactam)

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The sorption of drugs and formulatory adjuvants by plastics can present considerable problems when these materials are used as packaging media. These problems are aggravated by the lack of specific information regarding the individual contributions of the polymer resin and additives such as plasticizers and stabilizers to the product-plastics interaction. Here we report preliminary findings on the interaction of benzocaine in aqueous solution with pure nylon 6 (polycaprolactam) resin.

Powdered nylon 6 (specific surface by krypton adsorption, 7·0 $m^2g^{-1}$) was prepared from nylon chips by a precipitation process. Infrared spectra were consistent with the $\alpha$ form of nylon 6 containing very little monomer. Sorption was determined by shaking the powder with standard benzocaine solutions for one hour at a constant temperature and assaying the supernatant spectrophotometrically.

Uptake of benzocaine by powdered nylon 6 is rapid reaching equilibrium in less than 30 min and follows a $C_1$ type partition isotherm (Giles, MacEwan & others, 1960) which is linear over the concentration range studied (0–6 $\times$ $10^{-3}$M). No plateau was observed. A similar result was obtained for benzoic acid. This contrasts with the finding of Kapadia, Guess & Autian (1964) who reported that the sorption of benzoic acid by commercial nylon 610 film followed a Langmuir isotherm.

The $C_1$ isotherms may be described by the expression, $C_n = KC_w$, where $C_n$ is the uptake by nylon (mol $kg^{-1}$), $C_w$ is the molar concentration in the aqueous phase at equilibrium and K is the equilibrium constant which characterizes the extent of adsorption for the system.

For benzocaine in water at 30°, K = 1·94 $\times$ $10^3$ which increases to 2·53 $\times$ $10^3$ in the presence of 0·5M potassium chloride. K values also vary with temperature and pH.

K decreases with increase in temperature and a plot of log K against $1/T_{abs}$ is linear, leading to a value of $-12{\cdot}3$ KJ $mol^{-1}$ for the standard enthalpy of adsorption.

K values determined in buffer at ionic strength 0·5M and 30° show that benzocaine is only slightly adsorbed at very acid pH (0·69) but as the pH is increased sorption becomes more extensive, rising to a maximum around pH 5 and thereafter remaining constant. The extrapolated K value of 1·40 $\times$ $10^3$ at the $pK_a$ value for benzocaine in 0·5M KCl (2·5) where the drug is 50% ionized is almost exactly midway between the maximum and minimum K values, 2·54 $\times$ $10^3$ and 0·2 $\times$ $10^3$ respectively.

These results are consistent with the adsorption of a monofunctional solute by a polymeric substrate containing regions of varying crystallinity. It seems likely that principal interaction sites are the amide groups of the polymer which probably form weak hydrogen bonds with the amino group of the free benzocaine base.

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## *In vitro* and *in vivo* studies of the metabolism of phenylbutazone in the alloxan rat and rabbit

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In *in vitro* experiments, liver microsomal preparations of normal and alloxan diabetic rats and rabbits were incubated with phenylbutazone in the presence and absence of appropriate cofactors. These preparations were then assayed for unchanged drug and its metabolites at different intervals. In some of these experiments, preformed NADPH and/or a generating system for it were also incorporated in the incubation milieu. In separate experiments microsomal preparations from diabetic animals pretreated with insulin were similarly used.

In *in vivo* experiments the drug was administered to the normal and diabetic animals. Urine was collected periodically and analysed for unchanged drug and its metabolites. The

level of these substances was concurrently determined in the blood. Moreover, the above mentioned determinations were extended to urine and blood samples obtained from animals treated with insulin.

The results of the *in vitro* and *in vivo* experiments indicated that there is a significant difference in the rate of phenylbutazone metabolism in the normal and alloxan diabetic rats and rabbits, being slower in the alloxan-treated group. Because NADPH is involved in drug metabolism by microsomes it was speculated that the nucleotide may be deficient in the diabetic anaimals. To probe this possibility a specific micro assay procedure for NADPH in biological material was developed and applied to livers of normal and alloxan diabetic animals. The results indicated a very sharp drop in hepatic NADPH in the latter group as compared to the controls.

## Metabolism of 5,8,11,14-eicosatetraynoic acid in the rat

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Administration of 5,8,11,14-eicosatetraynoic acid (I) (2g/day for 3 to 4 months) to patients suffering from acne decreased sebum production by up to 40% over control values (Strauss, Pochi & Whitman, 1967), indicating a potential use as an anti-acne agent. The metabolism of this compound is not known, but the disubstituted acetylene group in a number of drugs is apparently biologically stable.

$$CH_3{\cdot}(CH_2)_4{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}(CH_2)_3{\cdot}COOH....I$$

Intravenous administration (0·7 mg/kg) of $\Delta^{5-6}$-$^{14}$C–I to the rat resulted in an initial rapid concentration of radioactivity in the liver (maximum of 40% of dose at 15 min to 1 h). This activity was excreted almost exclusively as metabolized drug via the bile to give about 60% of the radioactivity in the intestinal contents in 6 h. However it was only after 4 to 5 days that this amount of activity was excreted in faeces following i.p. administration of a similar quantity of radiolabelled I. Also, in the bile-duct-cannulated rat about 90% of administered activity was secreted in bile in 24 h, while in the intact animal only 40% appeared in faeces and 3% in urine in 18 h. Thus extensive reabsorption and entrohepatic cycling of this material was occurring. Within 5 days of an i.p. injection most of the radioactivity had been excreted with 65–68% in faeces, 8–17% in urine and 2–3% expired as $^{14}CO_2$. The latter would indicate a minor metabolic route by oxidative attack on the $\Delta^{5-6}$-acetylene bond, probably following initial $\beta$-oxidation. The activity remaining in the body at 5 days (14–22%) was concentrated mainly in skeletal muscle (7·7%), skin (4·3%) and fat (3·8%).

Analysis of bile by radio-t.l.c. indicated exclusive incorporation of the radiolabel in phospholipids. Hydrolysis released a dicarboxylic fatty acid fraction as the main radioactive area. Further analysis indicated the presence of two non-endogenous compounds corresponding (by carbon number correlation on g.l.c.) to C-18 and C-16 dicarboxylic acids. In addition, examination of urine and faeces also indicated the presence of [$^{14}$C]dicarboxylic fatty acids. The finding of these products would suggest that both $\beta$- and $\omega$-oxidative processes are important in the metabolism of I. Corroboration of the $\beta$-oxidation pathway was obtained from a similar study with 1-$^{14}$C-I. Within 5 days of an i.p. injection, 40% of the radioactivity was expired as $^{14}CO_2$ and the activity secreted in bile was associated mainly with the sterol/bile acid fraction, little remaining in the fatty acids.

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