The use of a gelatin hydrolysate to improve the compressibility of paracetamol and phenacetin

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To overcome the capping which frequently occurs in tablets during compression of phenacetin and paracetamol, Elowe, Higuchi & Busse (1954), formulations incorporating a high concentration of binding agents are used. BYCO (Croda Food Products Ltd.) is obtained from high quality grade gelatin by hydrolysis under controlled conditions. This material comes in various grades. Grade A is recommended as a granulating and binding agent and it has a moisture content of 4 to 7% and average molecular weight of 1000–2000. It exists in the form of a white, spray-dried powder.

A sufficient quantity of the hydrolysate grade A to give 4% concentration based on the dry weight of the materials was added to the dry crystals of phenacetin and paracetamol in a wide mouth jar. Thorough blending was achieved by rolling the closed jars on the roller mill for 1 h. A mixture containing 4% of hydrolysate and 2% moisture was also prepared. Compression was carried out at four machine settings, which gave approximately 45, 90, 140 and 180 MN m^{-2}, on an instrumented single punch tablet machine. The resultant tablets were examined for capping and lamination. Crushing strength was determined by diametral crushing as described by Shotton & Ganderton (1960). Tablets were unsatisfactory if, when removed from the die, they were not sufficiently firm for dimensions to be taken or if capping occurred.

While satisfactory tablets were produced from the formulations containing the hydrolysate, the crystals without additives gave unsatisfactory tablets. The mixtures containing the hydrolysate and moisture however gave the strongest tablets. It was used as a water-soluble binder and the addition of moisture probably activated its binding properties.

Plots of maximum die-wall pressure and residual die-wall pressure as a function of compression pressure, showed significantly greater values for crystals with the hydrolysate than those without. Again, the greatest transmission of pressure to the die wall was recorded for the mixture containing moisture and hydrolysate. The hydrodynamic action of water on the crystal would be expected to result in an increased transmission to the die wall, this is in agreement with the findings of Rees (1967). There is an indication here, also that, where there was capping or lamination the residual die-wall pressure was very low indicating considerable axial relaxation.

The inclusion of this hydrolysate in a formulation appears to be useful for converting a material which is only tableted with difficulty into a directly compressible form. Very similar results were obtained using grade C of the hydrolysate (molecular weight 10 000–12 000).

We are grateful to Croda Food Products Ltd. for a gift of Byco.

REFERENCES

ELOWE, L. N., HIGUCHI, T. & BUSSE, L. W. (1954). *J. Am. Pharm. Assoc. Sci. Ed.*, **43**, 718–721.
REES, J. E. (1967). Ph.D. Thesis, University of London.
SHOTTON, E. & GANDERTON, D. (1960). *J. Pharm. Pharmac.*, **12**, 93T–96T.

The effect of candicidin on exogenous cholesterol absorption in small laboratory animals

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Candicidin is a heptaene macrolide reported to reduce prostatic hyperplasia in dogs (Gordon & Schaffner, 1968), hamsters and as valuable in the symptomatic relief of human benign prostatism, (Keshin, 1973). In the course of study of mechanisms of action, aspects of lipid metabolism are involved, since early work indicated that the cholesterol level in human prostate hypertrophic tissue was elevated (Swyer, 1942) although this was not found to be so by Marks (1974, personal communication), and in the light of the postulated relations be-

tween prostatism and atherosclerosis (Schaffner, 1972). It was also found that plasma cholesterol levels of human volunteers were decreased with daily oral administration of 300–600 mg candicidin.

Method and results: Candicidin has been orally administered to small laboratory animals for up to 15 months. Animals have been allowed normal laboratory diet and water *ad lib* and were maintained under conditions of constant temperature and humidity with a fixed light/dark schedule. Absorption of exogenous cholesterol was monitored by the use of [4–^{14}C] cholesterol. Candicidin and cholesterol were suspended or dissolved in arachis oil and given by stomach tube or into the mouth. Samples of whole blood, plasma, tissue or whole eviscerated animal have been treated with tissue solubiliser and radioactivity counted using a Nuclear Chicago Unilux 3 scintillation counter. All values reported here were obtained on specimens obtained 6 hours after administration of label.

Rat: Analysis of results from 13 experiments involving 120 animals in equal dosed and control groups indicates that cholesterol absorption is reduced to an average value of 23·7% control. In no experiment did absorption exceed a mean value of 39·5% (s.e.m. = 7·0) with dose of candicidin 100 mg kg^{-1}. The effect is similar whether the drug is given as a single dose with the cholesterol, if predosing is employed, or if the animals are dosed with candicidin and the label administered up to 24 h later.

Mouse: Acute studies indicate that absorption of cholesterol is reduced to 8·8% (s.e.m. = 0·54) of control value. Mice predosed for 15 months show cholesterol absorption at a level of 55·0% (s.e.m. = 4·70).

Other animals: Hamster, guinea-pig and rabbit show that similar effects occur in species having widely differing abilities to absorb and excrete exogenous cholesterol.

The effects reported here, of significant reductions in cholesterol absorption related to candicidin administration, are of importance in demonstrating the considerable effects of this substance on lipid metabolism in laboratory animals. Other substances including alternative polyenes and cholestyramine appear much less effective than candicidin by this screening procedure.

REFERENCES

GORDON, H. W. & SCHAFFNER, C. P. (1968). *Proc. Nat. Acad. Sci.*, **60**, 1201–1208.
KESHIN, J. G. (1973). *International Surgery*, **58**, 116–122.
SCHAFFNER, C. P. (1972). *Proc. IV IFS. Ferment. Technol. Today*, 393–399.
SWYER, G. I. M. (1942). *Cancer Research*, **2**, 372–375.

Factors in the experimental evaluation of calcium glycerophosphates in caries

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Dietary calcium glycerophosphate (CaG) reduces the incidence of caries in experimental animals (Federoff, 1965; Bowen, 1972) and is more effective (Grenby, 1973) than the sodium salt (β-isomer). Whilst Bowen (loc. cit.) used the so-called β-isomer in monkeys, Stephen, Bealey & others (1973) using the so-called α-isomer did not find the corresponding expected biochemical changes in plaque in children, although Brook, Gawthorpe & Winter (1973) did so to some extent. The object now is therefore to identify factors which may lead to explanation for these discrepancies.

Two types of CaG were used: 'α-isomer' (BPC 1963: predominantly α-isomer); 'β-isomer' (Sigma-actually DL-α- and β-isomers in roughly equal proportions). Both were tableted (200 mg, plus 700 mg sucrose with or without 10 mg citric acid) under identical physical conditions. Dissolution rate in water was determined using the USP basket (100 rev min^{-1}) in 100 ml water; 5 ml samples were removed at 2 min intervals and the volume restored. For saliva dissolution the subject sucked a tablet, without deglutition, in the washed mouth and saliva was collected over 1 min periods. Calcium was determined flame photometrically (Williams, 1960), employing appropriate controls.