Three alternative hypotheses may be formulated to explain the cobalt effect on the vascular permeability: the first, that the effect arose from the hydrogen ion concentration of the unbuffered solution of the salt; the second, an indirect mode of action mediated through the local liberation of histamine; and the third, a direct action of the metal. The first hypothesis seems unlikely since it was demonstrated that pH influences vascular permeability only when it is markedly acid or alkaline (Opie, 1963). Again, the effect does not seem to be mediated through a local histamine liberation, since the action was not inhibited when an antihistamine agent was previously injected and there was demonstrably a lack of action of the metal on the mast cells of the mesentery. The third, and as yet unexplained effect of cobalt in increasing vascular permeability by a direct action of the metal, must now be elucidated.

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Dissolution characteristics of reserpine-polyvinylpyrrolidone co-precipitates

This is a report of a preliminary investigation made to ascertain the dissolution characteristics of a relatively water-insoluble drug reserpine in the form of a co-precipitate or solid dispersion with polyvinylpyrrolidone (PVP). The use of solid dispersions or co-precipitates to facilitate dissolution has been previously reported (Sekiguchi & Obi, 1961; Gibaldi; Feldman & Bates, 1968 & workers there cited; Decato, Malone & others, 1969; Stoll, Bates Nieforth & Swarbrick, to be published).

Reserpine–PVP solid dispersions, in ratios of 1:3 and 1:6, were prepared by dissolving both components in reagent grade chloroform and subsequently removing the solvent by vacuum evaporation. The co-precipitates were dried *in vacuo* to constant weight, screened through standard mesh screens and the 40 to 50-mesh (297–420 μm) fraction collected for use in the dissolution rate studies. Pure reserpine (6–30μm crystals) and a 1:3 reserpine–PVP physical mixture (6–30 μm crystals used) were also subjected to dissolution rate testing.

The dissolution apparatus consisted of a 500 ml three neck round bottom flask containing 350 ml of a 0·005M acetic acid solution (pH 3·65) maintained at 37° $\pm$ 0·1°. The solution was agitated at 60 rev/min by a Teflon stir blade of 70mm diam. connected to a Servodyne-constant torque motor assembly. At time zero, a quantity of reserpine equivalent to 10 mg was introduced into the medium. Periodically 5 ml samples were removed from the flask, subjected to Millipore filtration (0·45 μm pore size) and assayed for drug content using a Beckman DB-G recording spectrophotometer. Reserpine in acetic acid obeys Beer's law at a wavelength of 268 nm. Following the removal of each sample, a 5 ml quantity of fresh dissolution medium was pipetted

into the dissolution flask. The amount of drug in solution at any time during the dissolution run was corrected for this dilution effect (Bates, Gibaldi & Kanig, 1966). PVP in the concentrations present in the assay solutions did not interfere with the determination of reserpine.

A weak acetic acid solution was selected as the dissolution medium because of the extremely low aqueous solubility of reserpine.

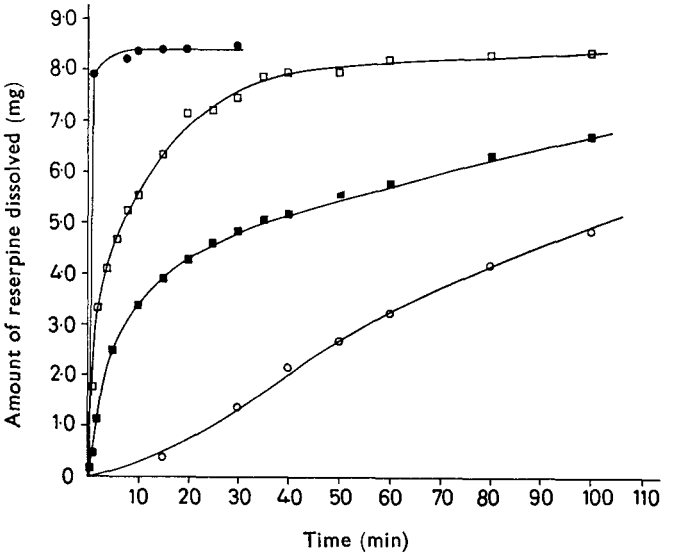

FIG. 1. Dissolution rates of reserpine and reserpine : PVP co-precipitates at 37°. ○ pure reserpine. ■ 1 : 3 physical mixture. □ 1 : 3 co-ppt. ● 1 : 6 co-ppt.

The dissolution behaviour of the four test samples at 37° is shown in Fig. 1. Each curve is drawn through points which represent an average of at least three dissolution runs. It is apparent from an examination of this figure and the dissolution half-lives (reserpine 106 min, 1 : 3 reserpine–PVP mix 35 min, 1 : 3 co-precipitate 7 min, 1 : 6 co-precipitate 0·5 min) that the dissolution rates of the samples decrease in the following order: 1 : 6 co-ppt > 1 : 3 co-ppt > 1 : 3 physical mixture > 1 : 0 pure reserpine. The dissolution half-life data indicate an approximately 15-fold increase in the dissolution rate of reserpine from the 1 : 3 reserpine–PVP co-precipitate and a 200-fold increase for the 1 : 6 co-precipitate over that for the pure reserpine sample. These differences would have been greater had the dissolution rates of the co-precipitates been compared with that for 297–420 μm reserpine particles. However, the 6–30 μm particles were used due to the extremely slow dissolution rate of the former. The marked enhancement in the dissolution characteristics of the co-precipitates most probably reflects a significant reduction in the particle size of reserpine during the preparation of the samples. The reduced particle size and the concomitant increase in the surface area of reserpine exposed to the dissolution medium appears to be the major factor responsible for the observed potentiation. That the dissolution rate of reserpine is particle size dependent is illustrated in Fig. 2 for 6–30 and 297–420 μm reserpine particles. It can be seen from these curves that the finer particles display a significantly greater rate of solution than do the coarser reserpine particles.

Although PVP possesses the ability to form water-soluble complexes with a variety of drugs (Kuramoto & Higuchi, 1954), only about a 20% increase in the equilibrium

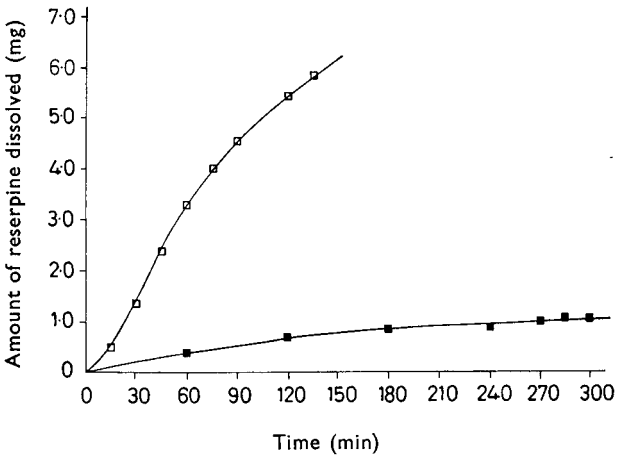

FIG. 2. Effect of particle size on the dissolution rate of reserpine at 37°. □ 6–30 μm particles. ■ 297–420 μm particles.

solubility of reserpine was noted at 37° over a PVP concentration range of 0–1%. This observation, coupled with the fact that the amount of PVP used would yield a maximum concentration of 0·014%, precludes it from functioning to increase the bulk solubility of reserpine and thereby potentiating the dissolution properties of this pharmaceutical. There is, however, a possibility that some complexation could occur in the micro-environment (diffusion layer) immediately surrounding the dissolving solid particles. This mechanism would help to explain the three-fold increase in the dissolution rate of the 1 : 3 reserpine–PVP physical mixture over that for pure reserpine, even though the particle size of the drug in both preparations is comparable (6–30 μm). Nevertheless, it appears that only a change in the physical state of reserpine (i.e., *via* particle size reduction) could account for the five fold increase in the dissolution characteristics of the 1 : 3 co-precipitate compared with the physical mixture of similar composition.

The ability of the water-soluble polymer, PVP, to enhance the *in vitro* dissolution properties of reserpine when the two substances are intimately combined in the form of a co-precipitate or solid dispersion is of importance as it relates to the gastrointestinal absorption of this hydrophobic drug.

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