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THE DISSOLUTION OF VERAPAMIL FROM TABLETS PREPARED WITH TWO SODIUM POLYPHOSPHATES.

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ABSTRACT

The ratio of the two polyphosphates, soluble sodium polyphosphate (SPP) and insoluble Maddrell's Phosphate (MPI), will influence the release rate of verapamil from tablets and compressed discs. Dose forms which contain only MPI release the drug constantly for about 8 hours and the inclusion of SPP tends to increase the release rate. Although the tablets containing verapamil and the polyphosphate mixture are harder than similar tablets without the drug, the hardness of the tablets is not influenced by the ratio of the polyphosphates employed and does not cause the variation in release rate observed.

INTRODUCTION

Sodium Polyphosphate (SPP) and Insoluble Maddrell's Phosphate Type II (MPI) are inorganic polyanions which are capable of interacting with suitable cationic drugs by complexation or adsorption respectively. The difference between the SPP and the MPI is the polymer chain-length; the SPP has a chain-length of about 14-17 whereas for MPI the chain-length may be up to 10^3. The structural features of the cations which dictate (a) whether the drug will complex with or adsorb on to the

polyphosphate, and (b) the nature of the resulting complex (soluble, insoluble, liquid or solid) have yet to be ascertained in detail. However, various workers [1-7] have demonstrated that a wide variety of drugs do interact with SPP and MPI.

The release and/or dissolution of adsorbed quinine and propranolol has been studied under acidic conditions [6]. The resulting dissolution profiles were essentially linear for up to 6 hours. More recently, the release of verapamil from a complex and from physical mixtures of the SPP and verapamil HCl has been studied [5]. It was demonstrated (a) that the release was significantly prolonged compared to the pure verapamil HCl powder, (b) the release from the physical mixtures was very similar to release from a preformed complex, (c) the release was not substantially influenced by the percentage of SPP in the tablet (over the range 25-60%w/w), and (d) that the release profiles were nonlinear.

In the previous study, [5], verapamil was chosen as a model drug. Although there may be some therapeutic relevance for a sustained release verapamil dose form, it was primarily chosen for consistency with [5]. The purpose of this research was (a) to study the effect of the inclusion of MPI in the tablet formulation on the release profiles, (b) to improve the flow properties of the ingredients by the production of granules, and (c) to study the effect of granulation on the tablet hardness and release profiles.

EXPERIMENTAL MATERIALS AND METHODS

(a) Materials

Verapamil HCl was obtained from Dr Ian Tucker (Department of Pharmacy, The University of Queensland) while the Insoluble Maddrell's Phosphate (Type II) and Sodium Polyphosphate were purchased from the Sigma Chemical Co. (St. Louis, USA). Povidone USP (PVP) was obtained from GAF (Wayne, USA) and all other materials were of analytical reagent grade. The verapamil HCl and polyphosphates had their identities confirmed by melting point and/or infra-red spectroscopy and were used without further purification.

(b) Analytical procedures

All analyses of verapamil HCl were performed by UV spectroscopy at a wavelength of 276nm, at which linear least squares regression showed that Beer's Law was obeyed over the range of 0-80 micrograms/mL. Neither polyphosphate interfered with the assay of the drug.

(c) Adsorption studies

The adsorption isotherm for verapamil HCl onto 0.25g of MPI at 25^{o}C was established using initial concentrations of drug in the range 6 to 240 mg/10mL. The

adsorption experiments were performed in glass vials (with Teflon lined screw caps) which were sealed with Parafilm (American National Can, USA) and rotated at 20rpm for 4 hours in a controlled temperature water bath. Preliminary experiments showed that equilibrium was reached in this time. The residual concentrations in the vials were determined after appropriate dilution with water.

(d) Tablet formulation

The crystalline SPP was ground in an end-runner mill and the portion which passed through a 250μm sieve was stored over silica gel at 20°C prior to use. The verapamil HCl and MPI were not ground but were similarly stored. The tablet composition was 250mg of verapamil and 250mg of a mixture of polyphosphate powders. The polyphosphate powders were mixtures of SPP and MPI containing 0, 25, 50, 75 and 100%w/w MPI. The combined powders were compressed as simple powder mixtures and after moist granulation of a drug-polyphosphate mixture containing 5%w/w PVP. A minimum volume of absolute ethanol was employed as the granulating fluid. The moist powder was passed through a 16 mesh sieve, dried at 39°C for 24 hours, brushed through a 20 mesh sieve and then stored over silica gel prior to use. Blank granules, without drug, were prepared in the same manner.

Tablets, weighing 500mg, were prepared from blank and drug-loaded granules, with a single punch tablet machine (Manesty E2, England, using a 12.5mm flat punch and die set) which was set to yield maximum compression of the tablets. Discs were prepared from blank and drug-loaded granules and from the corresponding simple physical mixtures of the powders, in a hydraulic press (RIIC, Scotland) with a IR punch and die set (Beckman, Scotland). The compression load was 4 tons for 1 minute. All tablets and discs were stored over silica gel prior to further study.

(e) Tablet and disc properties

The thickness and weight of nine discs or tablets from each of the five different compositions were measured and the compression density calculated. The hardness of 5 tablets of each formulation (both blank and drug-loaded) was determined with a tensile testing apparatus (Instron 1026, Hertsfordshire) with a cross head speed of 60mm/minute. The tablet holder and indenter were custom made in brass and were similar to those on an Erweka Hardness Tester.

(f) Dissolution studies

The dissolution studies were performed in triplicate (in random order) in 900 mL of Simulated Gastric Fluid USP (minus pepsin) in a USP dissolution apparatus with baskets (Prolabo Dissolutest, France) at 37°C and 50rpm. Aliquots of 5mL were taken (and replaced) at various times and assayed for verapamil HCl.

RESULTS AND DISCUSSION

Previous studies with verapamil [5] have shown that the presence of SPP in compressed discs comprising physical mixtures of verapamil and SPP only, caused a significant prolongation of the dissolution time compared to discs of the pure drug. Those studies were performed in Simulated Gastric Fluid USP (minus pepsin). Figure 1 shows the release profiles of verapamil from compressed discs of (non-granulated) physical mixtures which comprised 250mg of drug and 250mg of a mixture of the soluble and insoluble sodium polyphosphates. The discs of the five different polyphosphate compositions released the drug more slowly than was observed in the previous study [5].

This is not likely to be due to the different ratio of total polyphosphate to drug since the previous study showed little effect due to that factor. The main difference between the two studies was that the compression load in the previous study was 10 tons. It is possible that after compression at the higher load, the discs undergo relaxation upon removal of the load and this may have rendered the discs more prone to rapid breakup.

Figure (1a) also shows that the release rates were approximately constant over the first three hours and linear regression of the data over this period was performed to calculate the initial release rate. When the initial release rate is plotted versus the SPP content of the discs (as shown in Figure (1b)), a distinct minimum in the release rate at 50 to 75% w/w SPP is apparent. Therefore, the release rate may be able to be controlled by variation of the polyphosphate composition. However, the powder mixture has very poor flow properties and would not be ammenable to automated tablet production.

Granules bound with 5% w/w PVP were prepared from another set of powder mixtures with the same polyphosphate compositions and were compressed manually on a single punch tablet machine. The dissolution profiles of verapamil from these tablets are shown in Figure (2a) and are less parabolic than those in Figure (1a). The initial release rate from the tablets versus polyphosphate composition is shown in Figure (2b). As the SPP content was increased the release rate increased approximately linearly except for the 25% w/w tablet which displayed a significantly higher release rate.

Since the tablets were produced manually, in a non-instrumented tablet machine, it is possible that the tablets with differing compositions were compressed at significantly different loads. Therefore, another five sets of powder mixtures granulated with 5% w/w PVP were prepared and compressed at a constant load of 4 tons for 1 minute in a laboratory hydraulic press.

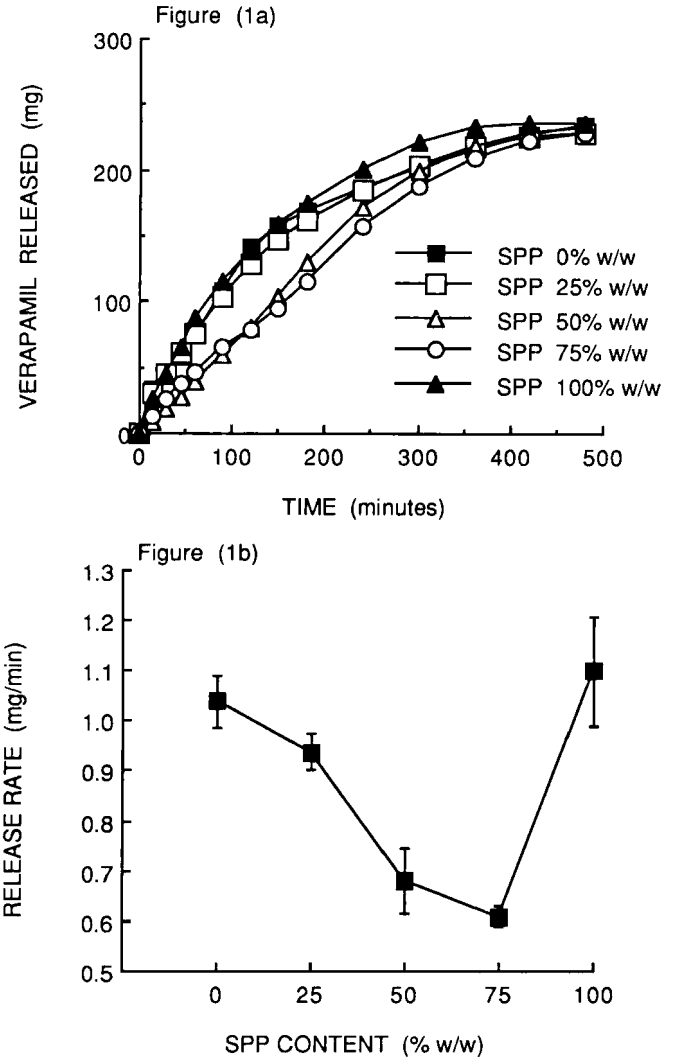

FIGURE 1

(a) The release profiles of verapamil from compressed discs containing SPP and MPI in different ratios. The discs were prepared from physical mixtures of the powders. The point is the mean of triplicated experiments.

(b) The retationship between the initial release rate of verapamil and the polyphosphate composition of the disc.

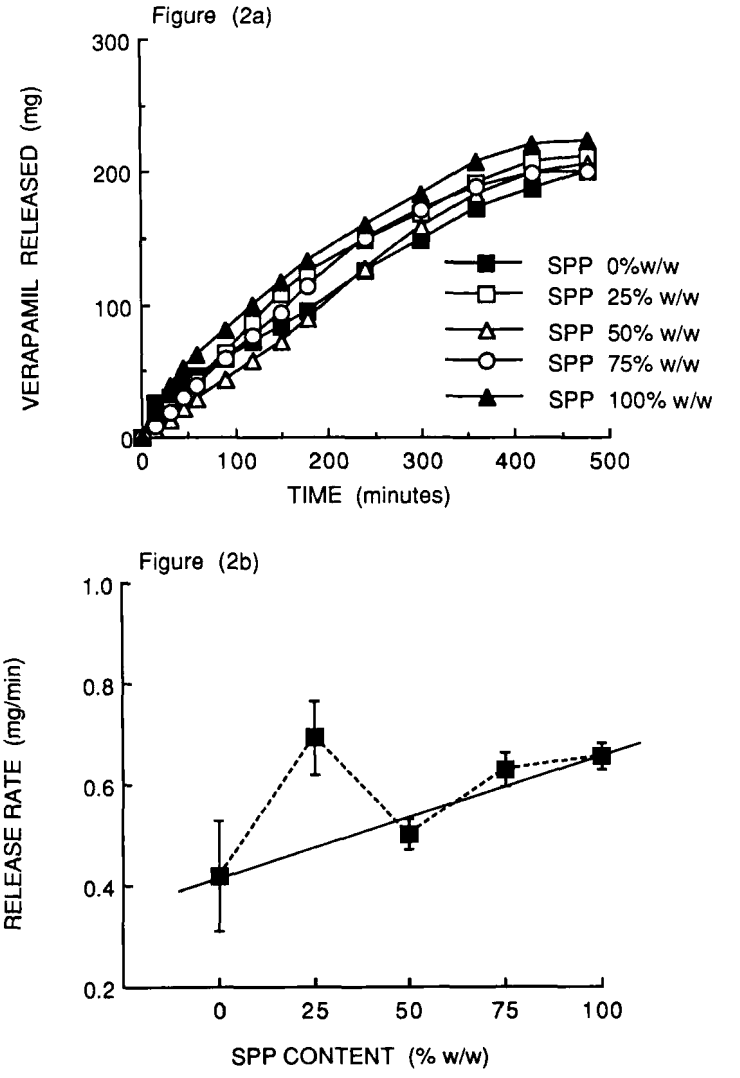

FIGURE 2

(a) The release profiles of verapamil from tablets containing SPP and MPI in different ratios. The tablets were prepared from granulated mixtures of the powders. The point is the mean of triplicated experiments.

(b) The retationship between the initial release rate of verapamil and the polyphosphate composition of the tablet.

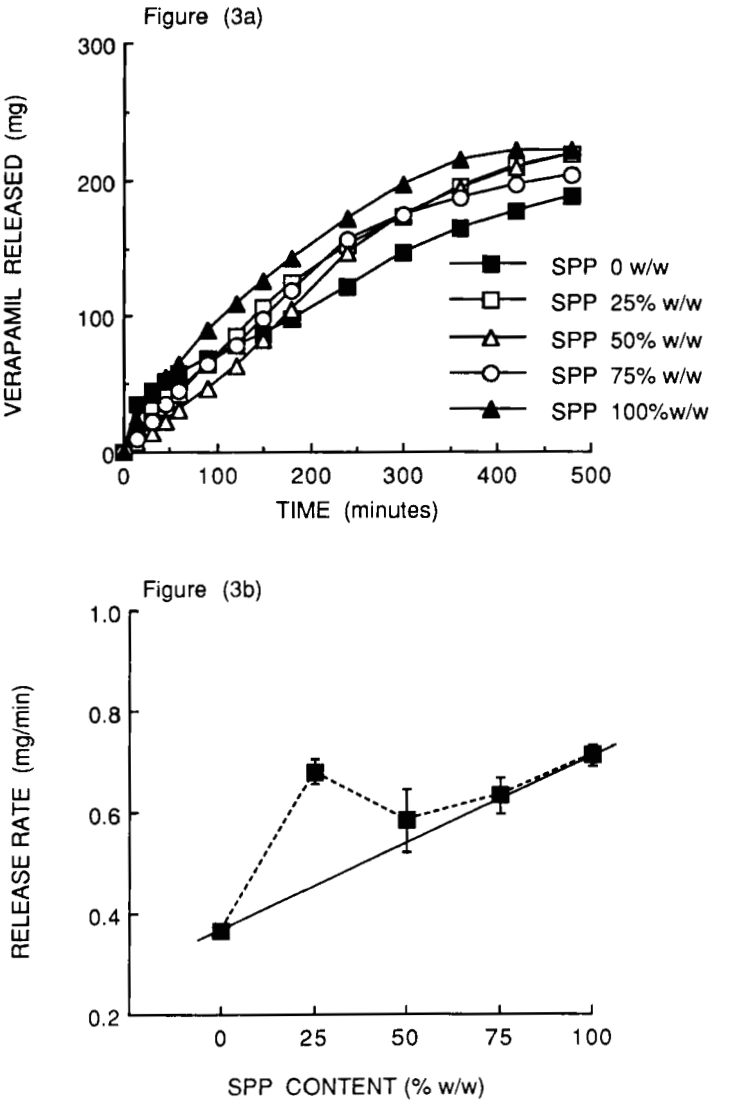

FIGURE 3

(a) The release profiles of verapamil from compressed discs containing SPP and MPI in different ratios. The discs were prepared from granulated I mixtures of the powders. The point is the mean of triplicated experiments.

(b) The retationship between the initial release rate of verapamil and the polyphosphate composition of the disc.

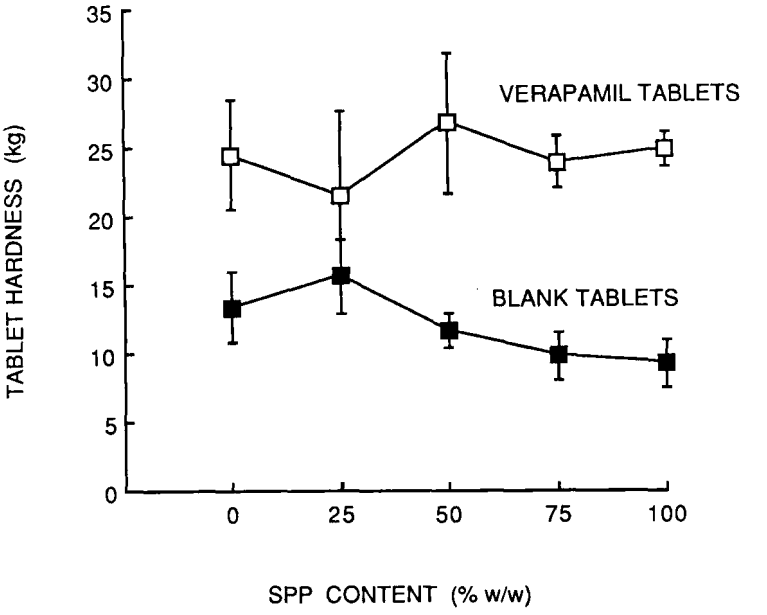

FIGURE 4

The relationship between the hardness of 500mg tablets (with and without verapamil) and the polyphosphate composition of the tablet. The tablets were prepared from granules.

The release profiles for these discs are shown in Figure (3a) and the intital release rates versus SPP content are shown in Figure (3b). The release profiles of verapamil from tablets and discs are very similar. Significantly, the release rate from the 25% w/w SPP discs was again much greater than would be expected. It must be remembered that two different batches of granules were used to prepare the tablets and the discs.

Subjectively, the tablets containing verapamil appeared to be very hard. A previous study [6] on the release of quinine and propranolol adsorbed on to the MPI showed that the hardness of discs of the adsorbed drug is much greater than the hardness of discs of the MPI alone. Consequently, the hardness of 5 tablets of each polyphosphate composition prepared with and without the presence of verapamil HCl, was measured as the maximum strain experienced by the tablets during breaking. The measurements were performed with an Instron 1026 tensile tester.

Figure 4 presents the plot of the hardness of tablets with and without drug as a function of the SPP composition. It is apparent that the tablets containing drug are

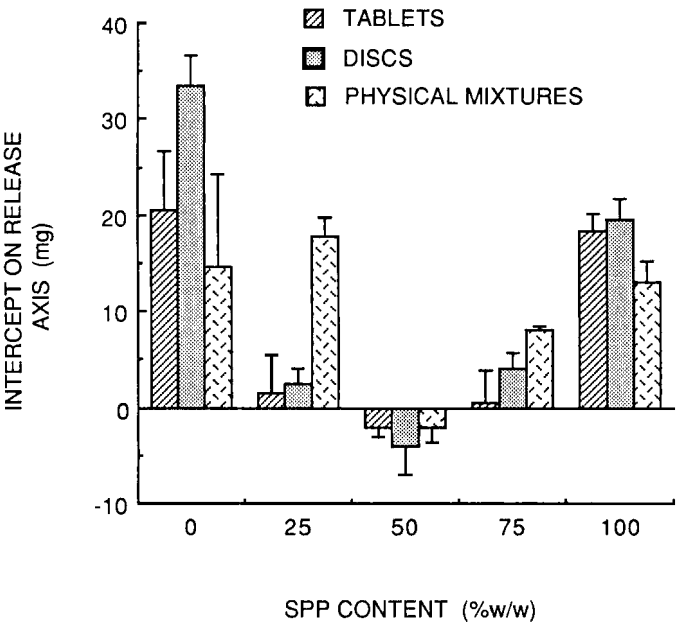

FIGURE 5
The relationship between the intercept on the release axis in Figures 1a, 2a and 3a and the SPP content of the polyphosphate excipient in the compressed dose forms.

significantly harder than those without drug. However, there is no significant variation in the tablet hardness as the SPP content of the tablets is increased. It is unlikely that the minor variation in tablet hardness is the cause of the significant increase in the initial release rate.

An interesting feature of the release profiles shown in Figures (1a), (2a) and (3a) which is not readily apparent, is shown clearly in Figure 5. The intercept of the linear release profile on the ordinate is dependent on the SPP content and the method of manufacture. It appears that in dosage forms containing SPP or MPI only, that there is a significant "burst effect". During this time, it is presumed that there is little control of release attributable to the dose form. While an initial surge of drug release may be beneficial with some drugs, the variability of the data (especially at 0% SPP) suggests that it would be unwise to rely on such behaviour. With the exception of the physical mixes containing 25 and 75% SPP, the dosage forms which contain mixtures of both SPP and MPI produce relatively minor burst effects and these systems may provide more control over the release of the verapamil.

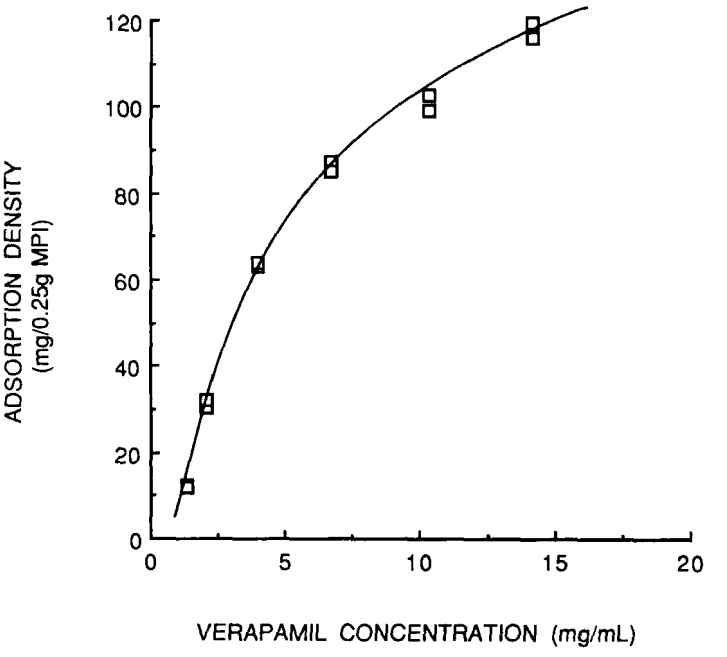

FIGURE 6
The adsorption isotherm for verapamil on to 0.25g of MPI at 25°C.

It is known that verapamil is able to form an insoluble complex with SPP [5] and the results in Figure (6) show that MPI will also adsorb the drug. This isotherm is empirical, since neither the Langmuir nor Freundlich isotherms describe the data. The results show that 250mg of MPI are capable of adsorbing about 120mg of verapamil. Therefore, in systems which contain only MPI, about half of the drug present in the dose form would be adsorbed and the remainder would be available for rapid release.

The complex of SPP and verapamil is very viscous, gel-like and adhesive [5]. It forms very quickly and may act as a binder to maintain dose form integrity, while the MPI acts as reservoir, adsorbing the drug and releasing it slowly in the acidic conditions employed in this study. It is also notable, that despite the relatively large burst of drug release when the tablets or discs are formulated with MPI alone, that the most prolonged release time are obtained.

CONCLUSIONS

The release profiles of verapamil from compressed discs and tablets containing SPP and MPI are dependent on the ratio of the polyphosphates; an increase in release rate accompanies an increase in the SPP content. However, although the tablets containing the drug are significantly harder than blank tablets, the tablet hardness does not significantly vary with changes in the SPP content. These studies have shown that the inclusion of MPI and SPP may control the release rate of drug, and, that granulation provides a simple means by which tablet production may possibly be automated. There are still some problems with hygrscopicity which causes adhesion of the tablets to the tablet punches and this needs to be addressed.

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