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STUDIES ON THE COMPLEXATION OF SOME DRUGS WITH SODIUM POLYPHOSPHATE.

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ABSTRACT

This report presents the results from the three phases of a study on the complexation of some drugs by sodium polyphosphate (SPP); firstly, the complexation studies which attempted to determine the complex stoichiometry, secondly the preparation of a quantity of verapamil polyphosphate complex and finally some dissolution studies. The complexation results show that amitriptyline, amethocaine, propranolol and verapamil form insoluble complexes with SPP. Under the same conditions of preparation, the stoichiometries of the complexes are approximately one, but are not equal. The dissolution profiles of the verapamil complex and also physical mixtures of verapamil and SPP were determined in an acidic medium. Under both of these conditions the release of the drug was significantly prolonged compared to pure verapamil.

INTRODUCTION

For many drugs and for various reasons, some form of controlled, prolonged release oral dosage form is considered ideal. Many formulation techniques have been employed to achieve this goal, and the production of poorly soluble derivatives is just one such technique.

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In the case of ionized drug molecules it is possible to form complex salts through the interaction of the active drug with a ligand of opposite charge. A great variety of inorganic and organic salts have been employed [1]. The ligands chosen are often naturally occurring macromolecules such as alginic acid [2], pectin [3-5] and tannic acid [6-8]. The processes of molecular entrapment [9,10] and complexation [11] with Carbopol 934 are typical of the employment of synthetic polyanions. However, inorganic ligands have received somewhat less attention.

SPP is a soluble inorganic polyanion which is capable of interacting with some organic cations. Lach and various co-workers [12-14] have demonstrated that papaverine, quinine, quinidine, chlorpromazine and other drugs form poorly soluble complex salts with inorganic SPP. Studies on the canine bioavailability of polyphosphate complexes have yielded variable results; Soo [13] found no effect on quinidine, whereas Patel et al. [14] showed an increase of up to 25% in the bioavailability of papaverine. Kaplan and Buckwalter [15] have produced a complex with tetracycline, while Bunn and Cronk [16] reported higher blood levels of tetracycline from administration of the complex than from administration of the hydrochloride.

Previous studies by one of the present authors [17], have focussed on the adsorption interaction between eight organic cations and another SPP which is, in fact, insoluble. In particular, for example, an adsorbed system of quinine on the insoluble polyphosphate was prepared, compressed into tablet-like discs and the release of the active drug was monitored in acidic and neutral media. In an acidic medium, release of the quinine was constant for 3-5 hours and was inversely related to the concentration of sodium chloride added to the dissolution fluid.

The primary disadvantages of the adsorbed systems are the tedious procedure required to prepare them, the poor flow properties of the powdered adsorbed system and the low drug content of the tablet. On a weight in weight basis, the loading of a tablet with active drug, was at best, 25%w/w. However, if we achieve a stoichiometry of unity, then, depending on the molecular weight

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of the drug a loading of about 80-90%w/w can be achieved. Therefore, complexation offers a means to eliminate the loading limitation. However, this study was necessary to begin to appreciate what other problems may occur and to discover if complexes held any promise as sustained release systems.

The choice of verapamil as the primary focus of our attention was not made in order to address an urgent therapeutic need, but simply since it was a convenient model drug. However, a recent comprehensive review on the pharmacokinetics of verapamil has been published [18]. They reported results which show that a once daily dose of 240 to 480mg verapamil in a sustained release tablet, markedly reduced both the systolic and diastolic blood pressures of 3900 patients.

MATERIALS AND METHODS

Materials

Verapamil HCl was obtained from Dr Ian G. Tucker (Pharmacy Department, The University of Queensland), propranolol HCl and amitriptyline HCl were generously donated by Dr S. Cheng (Alphapharm, Brisbane) and Dr D. Kingston (Roche, Sydney) respectively, while atropine sulphate, ephedrine HCl and procaine HCl were purchased from the Sigma Chemical Company (St Louis, USA). The SPP was also obtained from the Sigma Chemical Company. All materials were used as obtained but their identities were confirmed by melting point analysis and infra-red spectroscopy. All solvents and electrolytes were of analytical grade.

Analytical Procedures

The SPP was potentiometrically titrated using a model 620 Metrohm pH meter and 0.5M sodium hydroxide which had been standardized against hydrochloric acid (Volucon, BDH). The method [19] is well established and is briefly outlined. Approximately 2.5g of SSP was accurately weighed, dissolved in distilled water and made up to 50mL. Aliquots (25mL) had their pH rapidly adjusted to about 3 and then were titrated with the 0.5M sodium hydroxide until a pH of about 11 was reached. A similar, accurately weighed quantity of SPP was hydrolysed by an accepted modification [20] of the method above. The SPP and about 4g of potassium chloride were dissolved in 20mL of distilled water and

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20mL of Hydrochloric Acid and then the solution was boiled dry. The crystalline solids were redissolved in distilled water and made up to 100mL. Aliquots of 25mL were titrated as before.

The concentration of total phosphorous was also determined by an Inductively Coupled Plasma (ICP) emission spectrometer (Labtan, Australia) at a wavelength of 178.287nm, using 50, 100 and 200ppm aqueous solutions of potassium dihydrogen orthophosphate as the standards. This analysis was performed on the pure SPP and also on the complex, whose preparation is described below.

The concentrations of all drugs were determined by UV spectroscopy (Pye Unicam PU8600) at the maximum wavelength for each drug. Beer's Law calibration curves were prepared and subjected to linear regression. The presence of the SPP did not interfere with the UV analysis.

Determination of Complex Stoichiometry

Fixed initial concentrations of the drugs (either 35mM or 70mM) with various concentrations of SPP up to 35mM were equilibrated in an agitating water bath, for 4 hours or 24 hours at 25°C or 37°C. These experiments were performed in triplicate. After equilibration, the glass vials containing the viscous oily complex were centrifuged isothermally and the residual drug concentrations determined by UV analysis.

Complex Preparation

A quantity of a verapamil-polyphosphate complex (VPPC) was prepared by assuming that the average chain-length of the SPP was 14. This figure was determined from potentiometric titration analysis and its calculation is discussed below. The complex was produced by equilibration at 25°C for 24 hours. The viscous oily VPPC sedimented and the aqueous solution was decanted. The VPPC was gently washed with water, before being dissolved in acetone. The bulk of the acetone was then evaporated by gentle heat, after which the VPPC was dried by vacuum desication. The dried VPPC was crystalline but hygroscopic and was stored under vacuum.

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Dissolution Studies

The dissolution studies were performed on discs of pure drug, VPPC or various physical mixtures of verapamil and SPP which were compressed under 10 tons load in a Beckman IR die with an RIIC hydraulic press. The USP basket method was employed at a temperature of 37°C and at 50 rpm using a Prolabo Dissolutest apparatus. The dissolution medium was Simulated Gastric Fluid USP (minus pepsin). Drug dissolution was monitored by UV analysis.

RESULTS AND DISCUSSION

Polyphosphoric acid has two types of protons; the terminal groups each have one weakly dissociating proton, while each phosphate group (including the terminal groups) has a strongly dissociating proton. The volume of alkali consumed between the end-points at 4.5 and 9 is a measure of the number of weakly dissociating protons. Since each orthophosphate molecule contains one of the weakly dissociating protons, complete hydrolysis of SPP will enable the estimation of the total orthophosphate content via the total number of weakly dissociating protons. Therefore, the number average chain-length (n) of the SPP is calculated from the relationship [19] shown in the equation below.

$$n = 2V_H/V_{NH}$$

The symbols V_H and V_{NH} are the titration volumes of sodium hydroxide consumed by the hydrolysed and non-hydrolysed samples respectively. The number average chain length so calculated was 13.95 which may be rounded to 14 and which is in reasonable agreement with the average of 15 claimed by the manufacturer. The results from the ICP analysis of the SPP do not yield an average chain length, but rather, estimate the total phosphate content of the SPP as 9.297mmole/gram.

The lower graph in Figure 1 shows the complexation diagram at 25°C for verapamil with an initial concentration of about 35mM after 4 hours equilibration. It is apparent from the agreement between the data that good experimental precision was obtained. The stoichiometry predicted from the initial slope is 0.863. At the higher concentrations of phosphate, the efficiency of the complexation process is decreased, as shown by the deviation from

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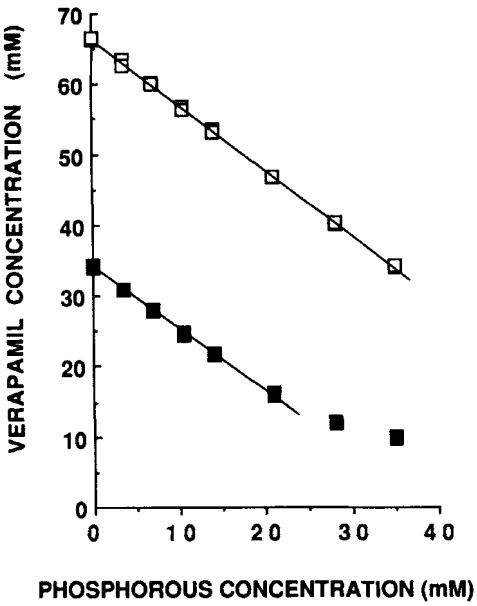

FIGURE 1

The complexation diagrams for verapamil and sodium polyphosphate at 25°C with initial concentrations of 35mM and 70mM for the verapamil. All of the data from triplicated determinations are shown.

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linearity. The upper graph in Figure 1 is a complexation diagram obtained under the same conditions, except that the initial concentration of verapamil was about 70mM. The stoichiometry is slightly increased at 0.936, and the efficiency of complexation has been improved at the high phosphate concentrations.

Table 1 summarizes the stoichiometry results for verapamil and illustrates some important findings. There is excellent agreement between the stoichiometries predicted by linear regression of the individual sets of data. Analysis of variance of the data at 25°C, demonstrates that at a level of $p<0.01$, doubling the initial drug concentration to 70mM causes a small but significant increase in the stoichiometry. However, increasing the equilibration time to 24 hours did not cause significant changes. Furthermore there was no significant

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TABLE 1

Summary of stoichiometries determined for the verapamil-polyphosphate complex determined at various initial concentrations of verapamil, equilibration temperatures and equilibration times. At 25°C the individual estimates and the mean from triplicated experiments are shown.

Equilibration temperature and initial verapamil concentration		Complex stoichiometry after specified equilibration time. (hrs) 4	24
25°C	35mM	0.867	0.855
		0.866	0.863
		0.857	0.841
		0.863	0.853
	70mM	0.944	0.925
		0.926	0.934
		0.939	0.933
		0.936	0.931
	35mM		0.856
37°C	70mM		0.899

interaction between the effects. After 24 hours equilibration at 37°C, there appeared to be a very slight decrease in the stoichiometry at the higher initial concentration.

The complexation of three other drugs was also briefly investigated and the results are shown in Figure 2. At an initial concentration of 35mM, and after 24 hours equilibration at 25°C, the predicted mean stoichiometries from duplicated experiments for amethocaine, propranolol and amitriptyline are 0.837, 0.914 and 0.988 respectively. Since values very close to unity can be

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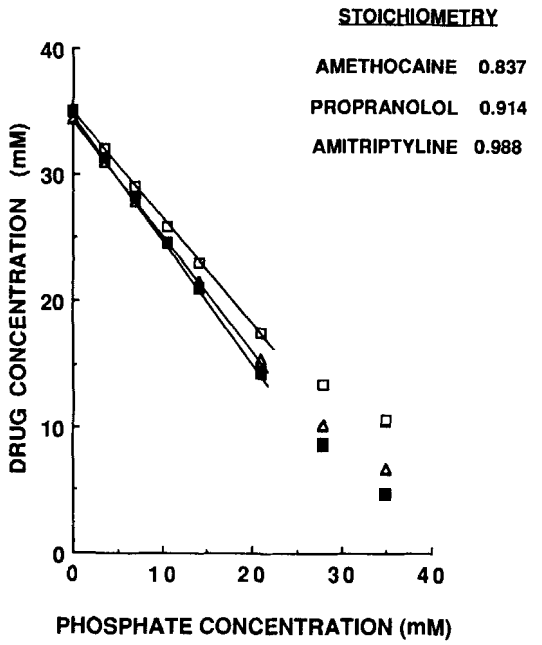

FIGURE 2

The complexation diagrams for amethocaine, propranolol and amitriptyline with sodium polyphosphate at 25°C. All of the data from duplicated determinations are shown.

obtained, it is suggested that the values which differ from unity do not reflect adversely on the experimental methods, but show that structurally diverse drugs have different affinities for the SPP. This suggests that the interaction mechanism is not solely coulombic. Furthermore, it was found that some cations, such as ephedrine, procaine and atropine do not form insoluble complexes.

The composition of the VPPC was determined by dissolving a weighed quantity in dilute acid and then analysing the solution for drug and phosphorous content by UV and ICP respectively. The total concentrations of phosphate and verapamil were determined to be 1.825 and 1.858 mmole per gram of VPPC dry weight. Therefore, the drug loading in the VPPC is 91%w/w. Furthermore, the

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TABLE 2

Solubility data for pure verapamil and verapamil-polyphosphate complex at 37°C. "Acid" refers to Simulated Gastric Fluid USP (minus pepsin).

Dissolution Medium	Solubility (mg/mL) of complex at 37°C	
	4 hours	24 hours
Acid	22.99	23.99
Distilled Water	14.40	14.35
Aqueous NaCl (50mM)	16.92	16.68
Aqueous NaCl (100mM)	17.97	18.28
Pure Verapamil/Acid		485.35

close agreement between the two components indicates a stoichiometry of 1 for the complex. This value approximates the estimates obtained graphically, and is in agreement with the values previously reported [12,13].

The equilibrium solubility of the VPPC at 37°C was determined in Simulated Gastric Fluid USP (minus pepsin), distilled water and 50mM and l00mM aqueous solutions of sodium chloride. The results, presented in Table 2, show that the solubility of pure verapamil in the acid medium at 37°C is 485.4 mg/mL. The VPPC is much less soluble in the same acid medium and even less soluble in distilled water. The addition of sodium chloride brought about an increase in VPPC solubility. A concentration of 50mM sodium chloride approximates the average concentration in the human stomach. It is important to assess the effect of sodium ions since they may contribute, by ion-exchange, to drug release. As can be seen, an increase in the dissolution time from 4 to 24 hours, causes a small increase in the amount of VPPC dissolved in the acidic medium.

Figure 3 shows that dissolution of the VPPC was slow relative to pure verapamil which dissolved within 20 minutes. The VPPC became a hydrated viscous mass during the dissolution process and some of the VPPC fell through

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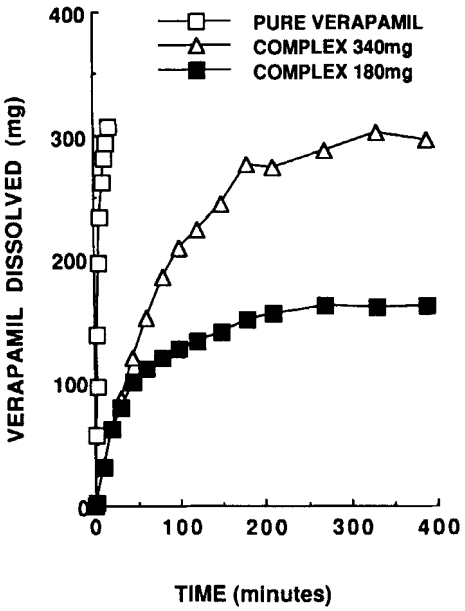

FIGURE 3

The dissolution profiles of pure verapamil (300mg) and 340 or 180mg of the verapamil-sodium polyphosphate complex in Simulated Gastric Fluid (minus pepsin) at 37°C. The means of triplicated determinations are shown.

the basket mesh. This may have contributed to the erratic dissolution profiles. Because of their hygroscopicity, manufactured tablets of the VPPC would be difficult to process and store. Physical mixtures of the drug and the SPP offered an improvement to these adverse features. Therefore, mixtures of a constant weight of verapamil and various weights of SPP were prepared and their dissolution profiles determined under the same conditions.

The dissolution profiles of discs containing 150 or 300mg of verapamil and enough SPP to give a 40% w/w content of SPP are shown in Figure 4. The bars represent the range of data obtained from the dissolution of three discs. In both systems there appeared to be progressive conversion of the opaque solid white disc to a gel-surrounded dry central core. The release from the discs with the higher drug loading was more erratic; which is to be expected since these discs tended to break up irregularly during dissolution.

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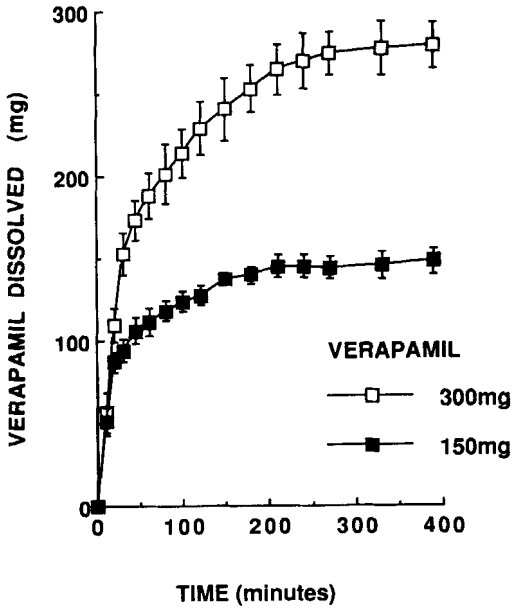

FIGURE 4

The dissolution profiles of physical mixtures of 40%w/w sodium polyphosphate and 150 or 300mg of verapamil in Simulated Gastric Fluid (minus pepsin) at 37°C. The means of triplicated determinations are plotted and the bars show the total range of the data.

Figure 5 shows that there is not a great difference between the release profiles of physical mixtures comprising 25%, 40% or 60%w/w SPP and a constant 300mg of verapamil. This is probably due to the fact that, based upon the measured total phosphate content of the SPP, there is more than sufficient phosphate in the disc with 25%w/w loading to cause complete complexation of the drug present. The dissolution profiles of 340mg of complex (equivalent to about 300mg of drug) and 300mg of pure drug are shown again for comparison. A similar pattern was displayed for the same drug / SPP ratios but with l50mg of drug.

The lower portion of Figure 6 schematically represents a possible mechanism to explain the release of drug from the complex in an acidic environment. It is speculated that water and protons are able to penetrate into

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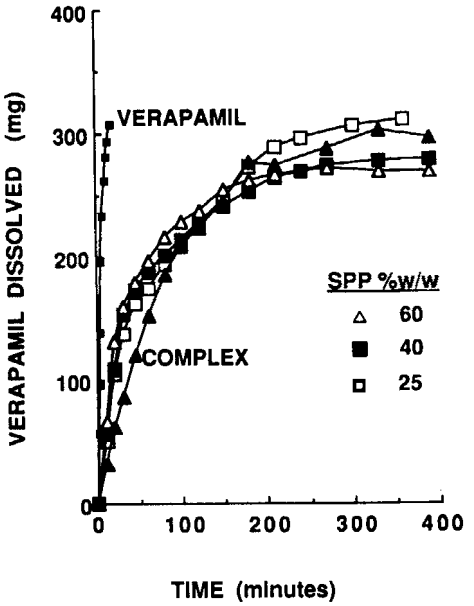

FIGURE 5

The dissolution profiles of physical mixtures of 300mg of verapamil and sufficient amounts of sodium polyphosphate (SPP) to yield 25%, 40% and 60%w/w loadings of SPP. The profiles of pure verapamil (300mg) and verapamil- sodium polyphosphate complex (340mg) are shown for comparison. The means of triplicated determinations in Simulated Gastric Fluid (minus pepsin) at 37°C are shown.

the matrix of the compressed discs of VPPC and that either the SPP chain is hydrolysed and the drug is then released as an undissociated (poly)phosphate complex fragment or that ion-exchange causes the liberation of drug from intact or hydrolysed complex prior to release of the free drug. If release as undissociated (poly)phosphate fragments occurs, presumably these would also undergo hydrolysis and/or ion-exchange in the solution phase before releasing free drug. As the process of drug release from the compressed disc of VPPC occurs, a very adhesive gel-like layer accumulates on the disc surface. This viscous surface layer probably superimposes a diffusion step in the overall release process and may partially account for the decreasing rate of release

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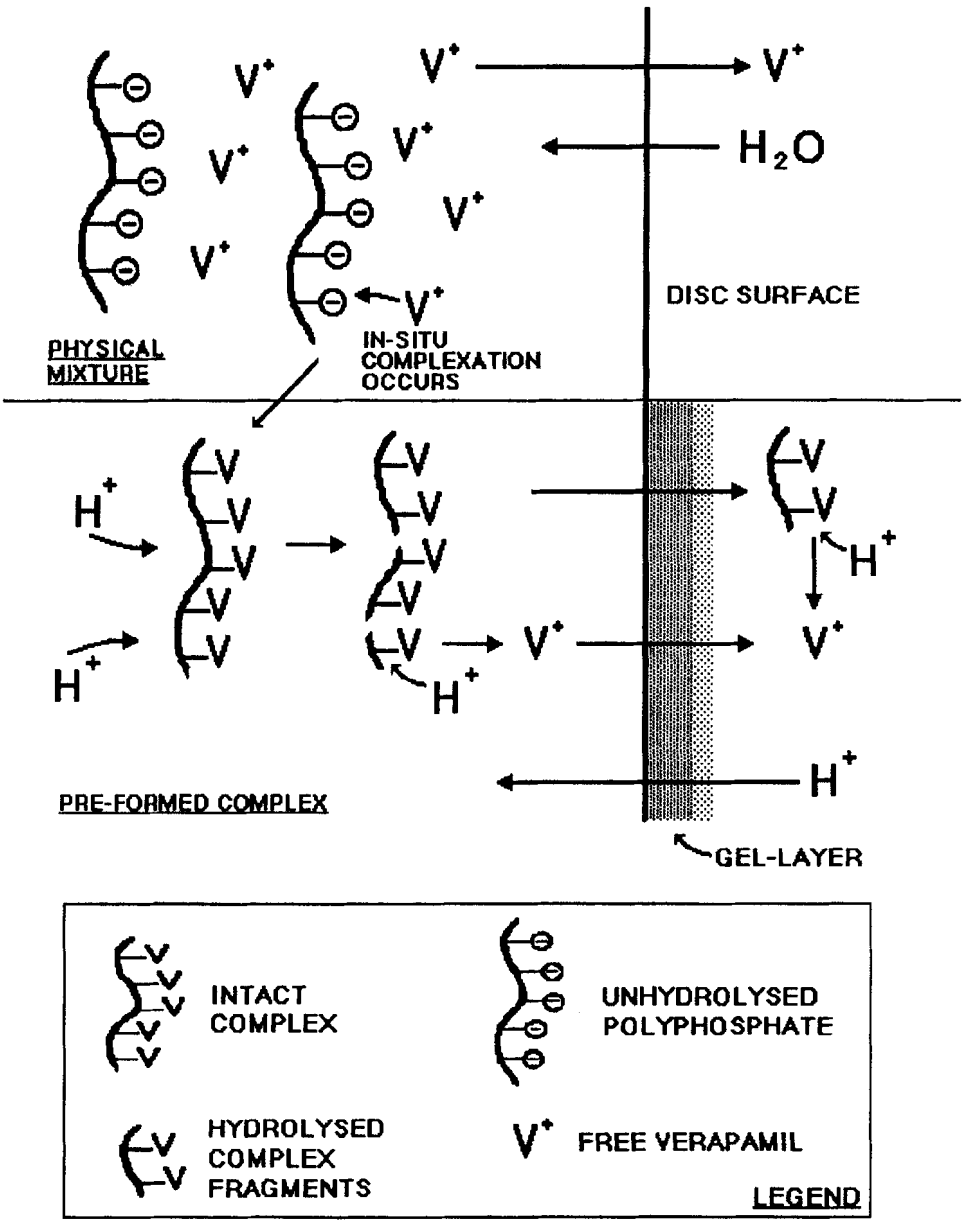

FIGURE 6

A schematic representation of the proposed mechanism of release of verapamil from physical mixtures of verapamil and sodium polyphosphate (upper sketch) and from the verapamil-sodium polyphosphate complex.

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observed in Figure 3. It is presumed that this layer would be most compact at the disc surface.

In the case of physical mixtures of drug and SPP, it is suggested that both components dissolve simultaneously, and that complexation occurs in-situ. The likely course of events is shown in the upper portion of Figure 6. A fraction of the drug would be released from the mixture immediately, but the remainder would undergo complexation in-situ. The release of drug complexed would follow the mechanism outlined above. The immediate release of uncomplexed drug may explain the faster release from the mixtures than from preformed VPPC over the first 75 minutes. It appears (from Figure 5) that as the quantity of SPP in the physical mixtures is increased, the release of drug is slightly increased. This may be due to the fact that, since there is sufficient SPP in the lowest loading to cause complete complexation of the available drug, any excess SPP will simply act to physically disrupt the integrity of the disc matrix. As in the release from compressed discs of preformed complex, an adhesive gel-layer developed on the surface during the release process.

CONCLUSIONS

It appears that sodium polyphosphate is able to form insoluble complexes with amethocaine, amitriptyline, propranolol and verapamil, but not with atropine, ephedrine and procaine. The stoichiometry of all of these complexes is close to unity. A larger quantity of a verapamil polyphosphate complex was prepared and was found to contain 91%w/w verapamil. However, because of the hygroscopicity of the complex it would be difficult to process and store. The complex produces a prolonged dissolution profile in an acidic medium compared to pure verapamil. Physical mixtures of verapamil and sodium polyphosphate reduce some of the processing difficulties, yet produce prolonged dissolution profiles similar to those of the preformed complex.

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