QUATERNARY AMMONIUM COMPOUND on POLYVINYL CHLORIDE used in medical practice

a preliminary report

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► FOR THE PAST SEVERAL YEARS OUR LABORATORY HAS been investigating problems associated with the use of plastics in pharmaceutical and medical practice. Results from our studies, as well as reports from other sources, have indicated that drug-plastic interactions may and do occur which may not be evident to those using the particular plastic device.[1-14]

Nicolaides and Autian[15] have summarized two potential consequences in the use of plastics in medical practice. These may be stated as follows:

Direct Consequence. Many plastic substances may ha direct contact with the patient for a very short time or extremely long time. For example, a surgical implant mig well last for the lifetime of the patient while a draina catheter may remain for a very short period. In bo instances, the polymer or other ingredient in the plastic mig cause a tissue sensitivity or toxic response.

Indirect Consequence. Plastic administration devices, su as syringes and tubings, may react with the drug or nut tional product and either (1) release a constituent from t plastic to the solution which will then be injected into t patient, or (2) the plastic device may bind or adsorb significant quantity of the active ingredient, thus reduci the potency of the drug product to be administered to t patient.

Since at the present time there are no standar for safety of plastics to be used in medical practic a great responsibility rests upon those who purchas distribute, and use these devices. The hospital pha macist, of course, is very much involved with the devices and should be continually alert to practice h professional judgment in the selection of plastic d vices to be used in his own hospital. A guide to th hospital pharmacist in the evaluation of plastic devic has already been published.[10]

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name "vinyl" or "polyvinyl chloride" is assigned to this material, other ingredients are added to the polymer which gives to the final material flexibility as well as other desired properties. Often the other additives in the formula amount to as much as 40 percent by weight of the total weight of the plastic.

The very high proportion of other ingredients added to the basic polymer, polyvinyl chloride, increases the opportunity of one or more of the additives to migrate into a solution having contact with the plastic. For example, previous studies have shown that polyvinyl chloride tubings used for medical purposes would leach a constituent to various alcohols and that certain of these tubings would react with a parenteral drug product.[3,8,9,10]

A year or so ago, our laboratory received reports that certain hospitals were resterilizing disposable tubings by a "cold" method using benzalkonium chloride. This directed our attention to other polyvinyl chloride materials which might also conceivably be sterilized by the use of a specific agent. In particular, we became interested in polyvinyl chloride sheets which are used for various and sundry purposes in a hospital.

This particular paper deals with a preliminary report on the observations made after benzalkonium chloride solution was kept in contact with a particular brand of PVC sheets which are now being used in certain hospitals. The results reported in this paper have also been been noted for commercially obtained PVC tubings used in medical practice. The information in this preliminary report should once again emphasize the seriousness of the "misuse" of plastics and alert the hospital pharmacists and others to test or have tested the plastic device for safety until proper standards are formulated and followed in the manufacture, distribution, and use of a plastic item to be used by the medical profession.

EXPERIMENTAL

Materials
- Polyvinyl Chloride Sheet (4 mils)
- Benzalkonium Chloride (as Zephiran® Chloride Solution)
- Sodium Lauryl Sulfate Solution 0.012%
- Alcohol, Absolute
- Propylene Glycol, U.S.P.
- Glycerin, A. R.
- Polyethylene Glycol 400, U. S. P.

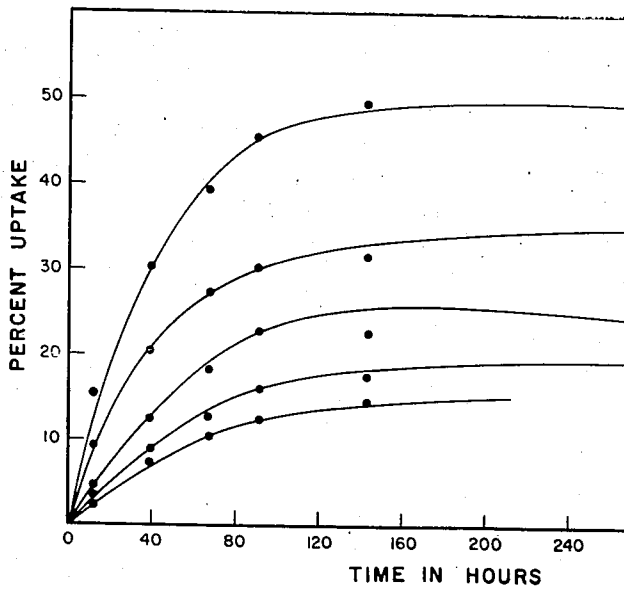
Apparatus
- Leeds & Northrup *p*H meter
- Semi-micro Burette
- 200 ml. Glass Stoppered Pyrex Tubes

0.01 percent W/V solution of methyl yello
ml. of chloroform. After thorough agitation, t
konium chloride was titrated with a 0.01
solution of standardized sodium lauryl sul
a semi-micro burette. This assay follows t
dure as outlined by Carkhuff and Boyd.[16] Pro
controls were used during each series of ana

Effect of Concentration on Uptake

Previously washed and dried strips of
chloride (PVC) sheets (approximately 20 g
ples) were accurately weighed and transfe
specially constructed glass stoppered tubes
exactly 150 ml. of benzalkonium chloride
at four different concentrations. Each tube
sealed with a silicone-grease coated, ground
per and further secured by the use of rubb
These prepared tubes were placed in a cons
perature water bath adjusted to 49° ± 0.
certain time intervals 1 ml. aliquots of solu
withdrawn and assayed according to the
previously outlined. The data obtained were

Fig. 1.—EFFECT OF CONCENTRATION ON UP
BENZALKONIUM CHLORIDE BY P.V.



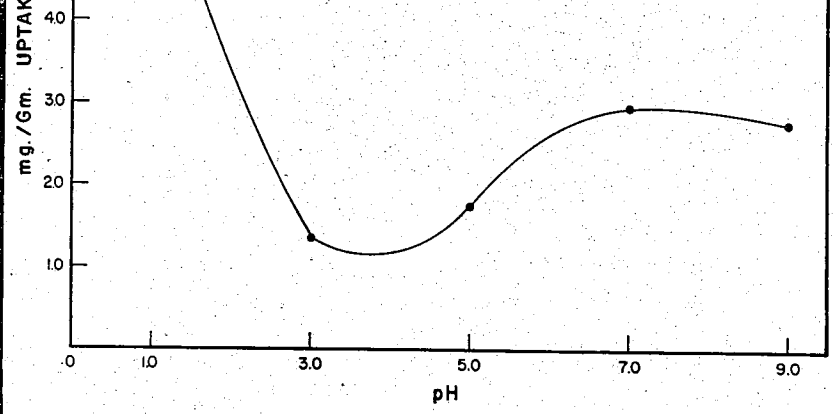


Fig. 3.—EFFECT OF pH ON UPTAKE OF BENZALKONIUM CHLORIDE BY P.V.C.

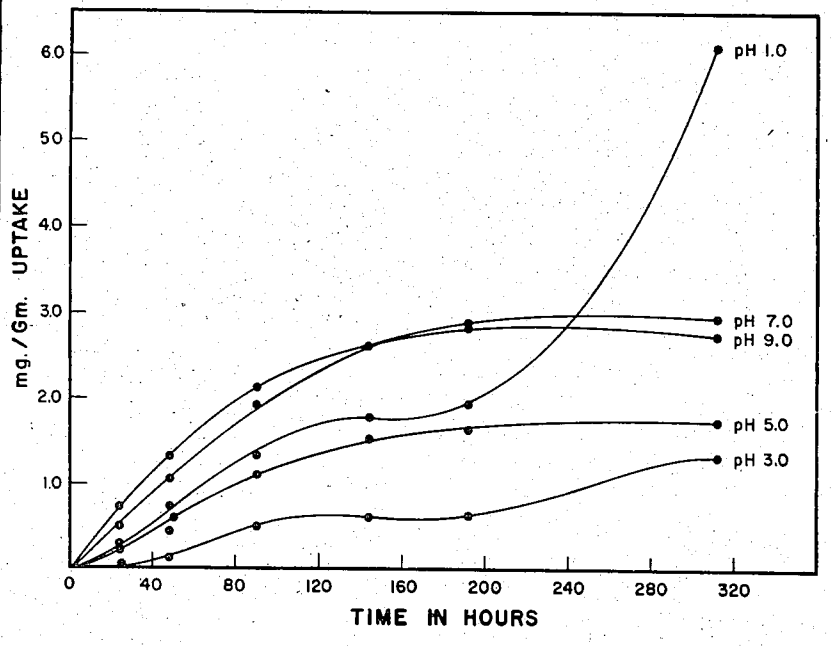
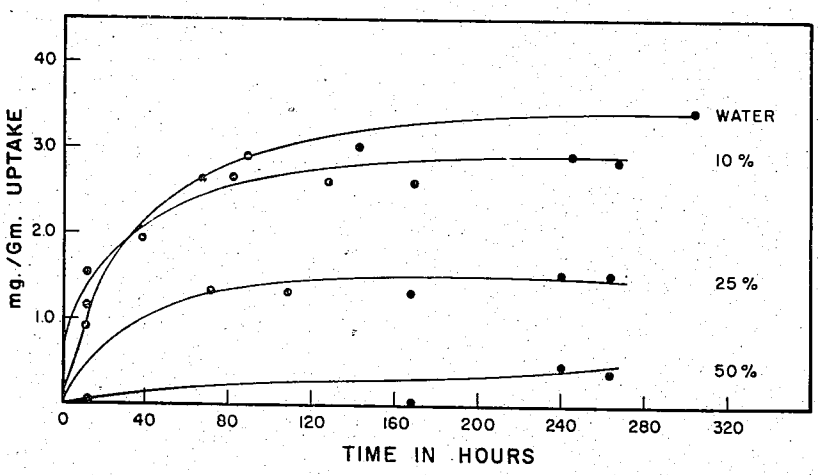


Fig. 4.—EFFECT OF ETHYL ALCOHOL ON UPTAKE OF BENZALKONIUM CHLORIDE BY P.V.C.



Effect of pH on Uptake

In order to determine the influence of *p*H on th uptake of benzalkonium chloride by PVC, weighed strij of PVC film were placed in 150 ml. of solution co taining 1.28 mg. of benzalkonium chloride per ml. an adjusted to various *p*H's by the addition of sulfur acid-ammonium sulfate solutions for acidic *p*H's an sodium hydroxide-ammonium sulfate solutions for th basic *p*H's. These buffer systems were chosen because has been reported[16] that acids, other than sulfuric aci interfere with the assay. The procedure for the ex periment was exactly as previously described excep initial *p*H and final *p*H values were determined. Thes experiments were run for a period of 312 hours. At th end of the experiment, the *p*H of the original solutio having a *p*H of 7.0 had dropped to 5.7 and the *p*l of the solution at 9.0 had dropped to 6.2. The resul of this study are shown in graphic form (uptake i mg./Gm. *vs* *p*H) in Figure 2 and (uptake *vs* time) i Figure 3.

Effect of Solvents on Uptake

In order to determine the effect various solven may have on the uptake of benzalkonium chloride b PVC, a study was conducted using various concen trations of glycerin, propylene glycol, alcohol and poly ethylene glycol 400. Weighed strips of PVC film wer placed in the glass tubes and exactly 150 ml. of solution containing 1.28 mg. of benzalkonium clorid per ml. with the required amount of test solvent wa added. The tubes were sealed as before and placed i the water bath set at 49° + 0.5° C. At certain tim intervals, aliquots were withdrawn and assayed a outlined. The results are presented graphically in Fig ures 4 to 7.

Desorption of Benzalkonium Chloride

Previous experiments had shown that some of th benzalkonium chloride which had been absorbed by th PVC would be leached back out of the plastic if th plastic were exposed to distilled water. Therefore

* In all experiments which contained benzalkonium chlor ide, the PVC released a constituent to the solution as evi denced by the original, clear solution becoming progressivel cloudy. Attempts were made to isolate and identify th leached constituent but this was soon relegated for futur studies. The leached constituents did not materially alter th assay results.

Partition coefficient experiments were also conducted bu the results could not properly be interpreted because of th leaching.

exposure to the distilled water, the PVC samples were rinsed three times in distilled water to remove any surface solution of benzalkonium chloride adhering to the plastic. The surface moisture was then air-dried so that the exact volume of added distilled water would be known. At the end of 222 hours from 24 to 30 percent of the absorbed benzalkonium chloride was released back to water.

DISCUSSION

The results found in the various experiments clearly indicate that a reaction will take place between a solution of benzalkonium chloride and flexible PVC. Even though cold sterilization is usually carried out at a much lower temperature and for much shorter periods of time, than employed in the experiments reported here, the more severe conditions were used to accentuate the reaction and to permit the collection of useful information in a much shorter period of time.

Effect of Concentration

It may be surprising to note that large quantities of benzalkonium chloride were removed from the various aqueous solutions in contact with the PVC, as may be noted in Figure 1. The uptake of the agent can occur at either the surface of the plastic (*ad*sorption) or the benzalkonium chloride can penetrate the plastic (*ab*sorption). Even though *ad*sorption is probably taking place, this could not account for the large amounts of uptake. Surface adsorption on plastics is usually instantaneous and thus a state of equilibrium would be reached within a very short time, but as the data indicates, many hours were needed before an apparent equilibrium was approached. This would suggest that the main route of uptake was by absorption.

The question still to be answered, however, is the mechanism of interaction. There is no theoretical reason to indicate that a quaternary ammonium compound is interacting with the polyvinyl chloride since this polymer is relatively a non-polar molecule with no real sites to attract large amounts of an ionic compound such as benzalkonium chloride. The compound must be interacting with one or more of the additives, or partitioning itself between the solvent and the plastic. Delineation of one from another was not possible since the ingredients in the final PVC sheet were not made known to us and since the partition coefficient experiments were continually being marred by the leaching of an ingredient into the aqueous phase. The large amount of desorption into pure water, however,

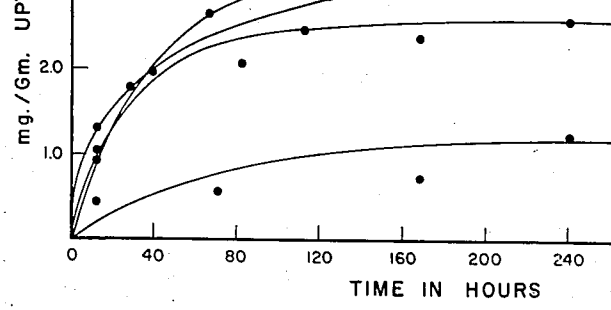


Fig. 6.—EFFECT OF GLYCERIN ON UPT
BENZALKONIUM CHLORIDE BY P.V

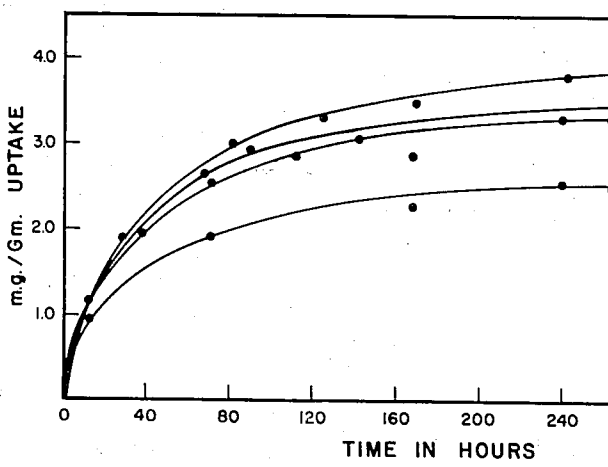
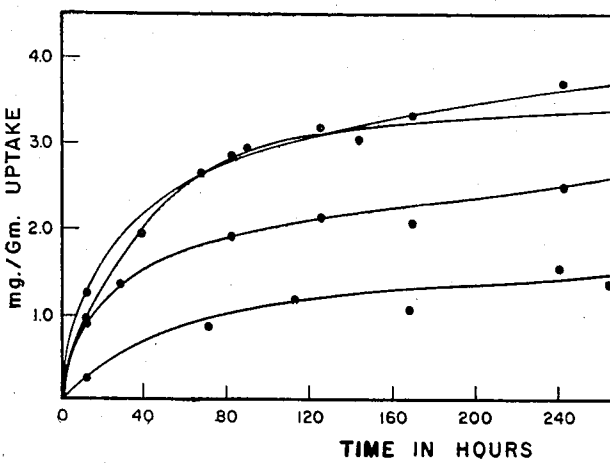


Fig. 7.—EFFECT OF POLYETHYLENE GLYCOL 400
BENZALKONIUM CHLORIDE BY P.V.



uptake as depicted in Figure 1 the relationship reverses and must be interpreted as meaning that dilute solutions will loose more of the solute to the plastic *as percent* than a more concentrated solution. Since benzalkonium chloride is often used in dilute solutions (1:1000 to 1:10,000) much of the original solute may be removed from a solution, thereby reducing the effective bacteriostatic or bacteriocidal activity of the agent. Kundsin and Walter[17] and Myers and Lefebvre[18] have emphasized the importance of this point.

In the experiments conducted, apparent equilibrium was approached but true equilibrium was probably never attained since leaching from the plastic would keep altering the equilibrium. For this reason the quantitizing of the concentration data by the usual Freundlich or Langmuir adsorption isotherms was not possible.

Effect of pH

The effect of *p*H on the uptake of benzalkonium chloride presents an interesting result in that the uptake at *p*H 1.0 is very high, decreasing at *p*H 3.0 and then rising at *p*H 5.0 and beyond. The very low *p*H (1.0) apparently alters the PVC to a greater extent than the other *p*H's, permitting greater uptake of the benzalkonium chloride. Figure 3 illustrates the leaching tendency of one or more of the additives which are of an acidic nature since the buffer capacity is broken at the higher *p*H values (7.0 and 9.0) and the *p*H reduced to within an acid range.

Effect of Solvents

Reducing the dipolar characteristic of the solvent system by replacing the water with less polar solvents tends to decrease the uptake by the PVC. In two cases, (alcohol and propylene glycol) the decrease in uptake of benzalkonium chloride by the plastic was observed for all three percentages of solvent added while in the case of polyethylene glycol 400 and glycerin, the decrease in uptake was not noted except at a solvent concentration of 2 percent or more. The explanation for these observed effects is difficult to elucidate within the experimental framework employed in the study.

Summary and Conclusion

Since flexible polyvinyl chloride and tubings and sheets are being used in medical practice for one reason or another, it was thought judicious to investigate ium chloride will be bound by certain substrates,[1] no such information appears to have been report for PVC. The implications of uptake and leachi should caution those in the medical field employi PVC sheets and tubings to test their own particu PVC item prior to actual use to ensure safety. T results of this study once again emphasize the ne for standards for plastics to be used in medical pract if better and safer patient care is to be achiev Further work on this problem is continuing and v be reported at a later date.

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