PLASTICS IN PHARMACY AND MEDICINE*

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Modern packaging and manufacturing trends are such that the medical and paramedical sciences are almost daily using plastic materials in the form of tubing, syringes, containers, transfusion kits, etc. The field of plastic materials is an enormous one, and the purpose of this article is to point out some of the disadvantages or hazards of plastic materials as related to para-medicine, while acknowledging in general the undoubted usefulness of these polymers, and accepting their continued introduction into medicine as inevitable.

Autian[1] has given an excellent review of plastics in pharmaceutical practice and in related fields, and although this review appeared less than a decade ago, his work has given impetus to much research on plastic-drug interactions. The use of plastics as packaging materials has been reviewed more recently by Sacharow,[2,3] Hughes,[4] and Polack.[5] It has been shown that plasticizers in plastic films may actively support the growth of fungi, while polyethylene and cellulose acetate are reported to be permeable to bacteria.[3]

TYPES OF PLASTIC

The types of plastics most likely to be encountered in para-medicine are polyethylene (polythene), polypropylene, polycarbonate, polyvinylchloride (PVC) and nylon. Polystyrene is used for the packaging of tablets, but is easily cracked because of its low impact strength. Killingback[6] has outlined many of the advantages of polystyrene, but its high water vapour transmission rate, as also its high oxygen permeability, makes it unsuitable for liquids, or for solids requiring protection from moisture. Killingback[6] points out that, in the USA alone, some 4 500 million plastic containers are used annually, and with the introduction of PVC medicine bottles into use in Great Britain this year, glass containers may become redundant, which in my opinion would be a pity, since glass can be closely standardized in its properties, whereas a plastic (e.g. polythene) may vary from batch to batch even from the same manufacturer. This is largely due to the various additives added to the polymer during manufacture.

PROPERTIES OF PLASTICS

Plastic containers are lighter, cheaper and less fragile than glass containers. Certain plastics are deformable, and thus are useful for 'squeeze-packs' (nasal sprays, wash bottles, etc.) but it must be remembered that air is sucked back into such containers on release, and this forms a potential source of contamination by aerial flora. Rigidity of plastic usually increases with increase in density, and thus one speaks, for example, of low-density or high-density polythene. The latter is stiffer, less permeable to gases and vapours, and more opaque than the former. Opacity is a disadvantage not shared by glass, where the container contents may quickly be scanned for precipitation or microbial growth. PVC is transparent, as also are film packagings, but denser (container) plastics are usually opaque, although some are translucent. It should be remembered that plastics, like clear glass, do not afford protection from actinic light, which causes photochemical decomposition. Many drugs these days (steroids, tranquillizers, vitamins) require protection from light, and coloured glass or specially formulated plastics filter out the ultraviolet rays which cause decomposition. However, it must be stressed to dispensing doctors who keep winchester (stock) bottles of ethicals supplied in coloured glass containers that dispensing of smaller volumes of such solutions (or tablets) into containers of clear glass, or of plastic, will result in rapid decomposition of the active ingredient(s).

Glass is chemically very unreactive, and can thus be used to store a wide range of substances or solutions. Alkaline solutions require to be stored in lead-free glass, while soda glass can impart sufficient alkalinity to stored solutions so as to precipitate salts of weak bases, such as alkaloidal salts. Good quality glass (ampoules) is virtually unreactive. Plastics, on the other hand, are soluble in certain organic solvents (e.g. benzene, furan), but this is not of any great significance in medical practice. However, the effect of certain medicaments will be mentioned later. What is of greater significance is the fact that plastics frequently contain additives such as plasticizers, thermal stabilizers, fillers, anti-oxidants and mould lubricants. Leaching out of such constituents will later be shown to cause toxic reactions in patients (tubing), or untoward reactions in medicines.

Further unwanted properties of plastic not possessed by glass are transmission and sorption. Transmission refers to vapours, flavours, gases (especially oxygen) and moisture vapour. This transmission may be inward or outward, and such permeability is obviously undesirable. Polystyrene and PVC have the highest water vapour transmission rates, while the former, and the lower density polymers, allow the highest vapour transmission. However, there have been good reports of pharmaceuticals packed both in PVC and in high-density polythene. The latter, nylon, and high-density polypropylene are all autoclavable, but volatile substances, especially phenolic preservatives, are lost under such conditions, and this leads us to sorption.

Sorption applies to both surface adsorption, and penetration by absorption. When the absorbed substance reaches the outer wall it is lost to the atmosphere. If adsorbed onto the container wall its concentration obviously decreases in the bulk solution, and atropine-borate eyedrops stored in polyethylene bottles have been shown to have lost most of the active ingredient in this manner.

PARAMEDICAL DISADVANTAGES OF PLASTIC

Although certain pharmaceuticals have been satisfactorily stored in plastic containers, there have also been several adverse reports. The preservative benzyl alcohol (2%) is capable of dissolving polystyrene syringes,[7] and the

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latter type has also been dissolved by paraldehyde injection within 5 hours. Dimercaprol injection causes etching and clouding on polystyrene barrels, but does not affect polythene or nylon barrels. However, nylon barrels, being polyamide, have been found to be very reactive,[5] and nylon syringes stored for one week at 50°C in various preservative solutions sorbed from 40% to 80% of the 10 phenolic or acidic (organic) preservatives used.

My interest lies in preservative inactivation,[9-13] since most modern pharmaceuticals are factory-produced, and to many such products, particularly liquid preparations, a preservative is added, because, unlike extemporaneously dispensed medicines, these products may stand on the shelf for months before use. Any material causing destruction of the preservative, or diminution below its inhibitory concentration, must obviously be rejected. Adjuvants in the formulation of a medicine may themselves cause preservative inactivation, but this is a pharmaceutical rather than a medical problem. However, inactivation by the container may well affect the dispensing doctor, and sorption of preservatives into plastic containers has been studied by several workers.[7,8,14-16] I have studied South African-made PVC and polythene (medium density) bottles,[37,38] and found the former resistant to most commonly used preservatives at normally used concentration (*ca.* 0·1%). The polythene bottles were satisfactory for long-chain molecules such as benzalkonium (Zephiran) or chlorhexidine (Hibitane), as also for organic acids (benzoic), but substituted phenolics, such as chlorocresol, O-phenylphenol and dichlorophenol decreased (respectively) by about 25%, 80% and 90% of the initial concentration (0·05% w/v) after only 4 weeks' storage at 25°C. At present a study is being undertaken on a series of substituted phenols, cresols and xylenols solubilized in Tween 80 and stored in polythene.

Autian[5] has listed 16 parenteral products which discoloured polythene hypodermics (after accelerated storage at 50°C for one week) and these include such well-known medicinals as adrenaline hydrochloride, Phenergan, Seconal sodium, Serpasil and terramycin. Steroids are adsorbed to polythene tubes, and such adsorption is normal from dilute solutions, whereas from more concentrated solutions dimerization of certain molecules may occur, and the plastic may actually be attacked and dissolved at certain points. Two interesting articles[19,20] on ophthalmic preservative loss from polythene on autoclaving have appeared, and although the use of gamma-irradiation presterilization of containers will largely obviate the accelerated loss on heating, as will the excellent innovation of unit-dosage (where no preservative will be required), the interaction at room temperature between plastic ophthalmic containers and their preservative could still be a pitfall for the unwary.

In contrast to sorption problems, where loss of constituent is observed, leaching from plastic into the solution introduces unwanted and potentially toxic products. PVC has been shown to release both stabilizers and plasticizers to solutions of dextrose and of saline, and one such stabilizer, although showing no haemolytic effects (as had been reported previously for PVC tubing extracts), caused a cardiotoxic response to an animal heart when released from the (PVC) tubing to the perfusion fluid. A colourant used in plastic-hubbed hypodermic needles released into saline a constituent lethal to mice. Sterilization may cause further problems. Ethylene oxide should not be used to sterilize PVC because of the danger of formation of ethylene chlorhydrin. However, polypropylene transfusion kits have passed rigid Swedish tests, and have the decided advantage over glass of not shedding anywhere near the amount of particulate matter to solutions.

Legislation

Finally, what protective legislation regarding the safe use of plastics has been formulated? Simpson[21] has reviewed this well, and it is encouraging to note that the British Plastics Federation has already applied a toxicity rating to some 500 plastic ingredients. Pyrogenic and toxicity tests are performed, as well as carcinogenicity testing for implants. In this connection a most interesting article by Grasso[22] on carcinogenicity testing is worthy of mention. Several plastics were effective in inducing tumours when implanted subcutaneously as 2-cm² discs in rats. (Noble metals and glass were equally potent sarcoma inducers.) What was interesting was that perforation of the plastic implant with a sewing needle considerably reduced tumour formation, while the same material in powdered form (even though this produces a larger surface area) produced no tumours at all. Thus tumour formation seemed to be of physical rather than chemical origin.

Plastics are here to stay. Seeing that the polymers differ tremendously in chemical composition it will not be easy to predict untoward reactions, and consequently an awareness of potential problems will not be amiss.

SUMMARY

The use of plastic materials in the paramedical disciplines is increasing. Some of the properties of the more commonly used plastics have been described, as also the disadvantages with respect to certain intrinsic properties of plastics not normally encountered in glass, namely, leaching, sorption and transmission. Although transmission of oxygen, water vapour, flavours, etc., may rightly be regarded as a problem for pharmaceutical manufacturers, the effects of leaching and sorption apply equally to both pharmacy and medicine, and at a time when untoward effects from drug interaction are increasingly being reported, the potential hazards of plastic materials must be mentioned.

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