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# Toxicology of Biomedical Polymers

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**ABSTRACT**

This paper deals with the various types of polymers, used in the fabrication of medical devices, their diversity of applications and toxic hazards which may arise out of their application. The potential toxicity of monomers and the various additives used in the manufacture of biomedical polymers have been discussed along with hazards which may arise out of processing of devices such as sterilization. The importance of quality control and stringent toxicity evaluation methods have been emphasised since in our country, at present, there are no regulations covering the manufacturing and marketing of medical devices. Finally the question of the general and subtle long term systemic toxicity of biomedical polymers have been brought to attention with the suggestion that this question needs to be resolved permanently by appropriate studies.

## 1. INTRODUCTION

Man made replacements for broken or sick units of the human body was in the imagination of man in the past. This has given birth to a new branch of science, called 'BIOMATERIAL SCIENCE'. This branch of science is interdisciplinary in nature and encompasses a variety of disciplines such as, Engineering, Physics, Chemistry, Biology, Toxicology, Biochemistry, Surgery, Dentistry. Metals, Ceramics, Polymers and Composite materials are used in the fabrication of medical devices. Their acceptance for use was partly through the time proven process of trial and error than prior certification. This paper mainly deals with the use of polymers as medical devices and their potential health hazards.

Polymers in the form of elastomers and plastics have improved the quality of life over the last three decades. In 1855 Charles Goodyear detailed the use of gum-elastic for manufacturing irrigation syringes, hospital water beds, gloves etc. for medical use.[1] In this paper the discovery of vulcanization has been given. If we take 1855 as

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the year of initiation of polymers into medicine, they have achieved tremendous diversity today in use and application. From simple disposable syringes and baby nursing nipples to artificial heart valves and total hip joint prosthesis are presently available in the market for medical use. Present day medical device industries are multimillion dollar projects with automated fabrication, quality control and packing facilities. Further, some of these factories have inhouse facilities for research and development to evolve better and newer formulations and designs.

## 2. POLYMERIC MEDICAL DEVICES

Polymeric devices that are being used in medical application can be broadly classified into five basic groups (Table 1). These devices have either direct or indirect contact with the body.

**Table 1. Classes of medical devices and their possible potential hazards**

| Class | Device | Examples | Possible potential hazards |
|---|---|---|---|
| 1. | oPermanent implants | Heart valves, various vascular grafts, orthopaedic implants, other artificial internal organs | Haemolysis, thrombosis, systemic toxicity, allergy, carcinogenicity |
| 2. | oImplants having contact with mucosal tissue | Artificial eye, contact lens, dentures, intrauterine devices, certain type of catheters | Eye/tissue irritation, allergy, systemic toxicity |
| 3. | •Corrective, protective and supportive devices | Splints, braces, films, protective cloths etc | Tissue irritation, systemic toxicity, haemolysis, allergy pyrogenicity |
| 4. | •Collection administration devices | Blood transfusion sets, various types of catheters, dialysing units, hypodermic devices etc | Tissue irritation, systemic toxicity, haemolysis, pyrogenicity, allergy |
| 5. | •Storage devices | Containers, bags for blood, blood products, drug products, nutritional products, diagnostic agents etc | Haemolysis, systemic toxicity, pyrogenicity, allergy |

Autian, J. Toxicology. IInd Ed. (Casaret and Poull's) Plastics. Page 534 (modified)

o Direct contact with the body

• Indirect contact with the body

All the polymers used in the fabrication of medical devices are not specifically compounded for clinical use. Two of the most prominent ones that are specifically manufactured for medical use are polyurethanes and silicone elastomers. These two groups of polymers appear to make use of the advances in plastic technology to produce purer polymers. In reality these two biomedical polymers are used in only a small fraction of the medical devices produced. A much larger volume of medical devices are manufactured from polymers that are made principally for other commercial applications in automobile industry, aerospace industry etc. Commonly used medical devices in which polymers are used and their approximate consumption is given in Table 2.

**Table 2. Commonly used biomaterials and their approximate consumption in an year**

| | |
|---|---|
| Heart valves | 60,000 |
| Pace makers | 100,000 |
| Vascular grafts | 160,000 |
| Dentures/dental devices | 200,000 |
| Mammary glands/cosmetic replacements | 110,000 |
| Nose | 5,000 |
| Chin | 3,000 |
| Facial/different places | 6,000 |
| Testicles, penis | 5,000 |
| Lenses | 250,000 |
| Retinal surgical aids | 500,000 |
| Other prosthesis | 10,000 |
| Hip joint | 110,000 |
| Knee point | 70,000 |
| Other joints, splints, rods | 150,000 |
| Oxygenators | 200,000 |
| Accessories for open heart/bypass surgery | 210,000 |
| Renal dializers | 620,000 |

Prepared in 1982. Collected from various sources.

Pure polymers themselves are of higher molecular weight and do not usually present a health hazard unless harmful chemical groups are attached to it. In the fabrication of plastic medical devices monomers are not the only raw materials but also substances like plasticizers, stabilizers, antioxidants, fillers, etc. are used to achieve the necessary physical and mechanical properties to the end product and for ease of fabrication. These intentionally added substances are collectively termed as additives.

Polymeric materials that go into the fabrication of medical devices are foreign to the human body environment. These devices when come into contact with tissue may release one or more of their constituents causing local response at the site of contact. It is also possible that the leachants may get absorbed into circulation and may produce harmful effects on organs that are remotely placed. They may also initiate allergic responses, besides producing teratogenic, mutagenic and carcinogenic effects. Residual monomer if present in the finished medical device can pose a toxic hazard to the patient. Potential toxic contaminants may also get introduced into the product during processing, sterilization, packing, storage, transport etc. Though the majority of the polymeric medical devices are available in a fabricated final form, in certain cases the end product is formulated and polymerised just prior to being used. Surgical cements for orthopaedic use, adhesives and fillers for various dental applications etc. are some examples. Therefore, the toxicology of a polymeric medical device depends on the presence of residual monomer, effect of additive loss, degradation of plastics and the

effect of the degradation products, toxicity of leached additives and effect of sterilization methods on the nature of plastics or its constituents.

## 3. RESIDUAL MONOMERS

At the present time there is no evidence to indicate that a monomer such as vinyl chloride has caused cancer in clinical situation where PVC made devices have been in use. Nevertheless, from the occupational health hazard point of view, there is a serious implication here. Epidemiological surveys and monitoring of concentrations of vinyl monomer in the proximity of industries producing VC or PVC manufacturing plants in U.S.A. have shown that there is the hazard of liver cancer for people living around the plants handling large quantities of VC monomer. There is sufficient evidence that VC is a human carcinogen.[2] Its target organs are the liver (angiosarcoma), brain, lung and haemo- and lymphopoietic systems. Since there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans, various regulatory agencies in U.S.A. like the Food and Drug Administration, Bureau of Foods Occupational Safety and Health Agency (OSHA) etc. are constantly reviewing the standards for maximum permissible limits of the monomer and are aiming to obtain zero levels of the monomer content even in food packaging material.[3] Methyl methacrylate is the principal monomer used in the manufacture of acrylic polymers. In orthopaedic surgery, when an acrylic cement is prepared and used by the surgeon for anchoring hip prosthesis systemic toxicity has been observed in humans. Depending upon the nature of mixture, the quantity of monomer used and the insertion technique employed, sufficient free monomer may be released, which is absorbed by the blood stream leading to a dramatic drop in blood pressure and in some instances to death.[3-6] Dentists may detect pulp toxicity, general irritation effects as well as hypersensitivity when various types of extemperaneously prepared acrylic adhesives, cements and filling materials were used in their patients.[7]

## 4. EFFECT OF ADDITIVE LOSS

Cannulae, in particular, those made up of polyvinyl chloride could become hard because of the release of the additive plasticizer, leading to mechanical rigidity and irritation of the blood vessels or tissue in contact with the cannulae.[7] The tissue irritation was elicited by the leached out plasticizer. Tin stabilizers used in earlier PVC compositions also turned out to cause very strong tissue irritation leading to tissue necrosis.[7]

## 5. POLYMER DEGRADATION

When an implant polymer device is placed into a biological environment containing various cellular components and enzymes, it becomes very difficult to predict the fate of the implant. Polystyrene, polyethylene and polymethyl methacrylate polymers were radiolabelled and implanted in animals to study their *in vivo* degradation. With the above three plastics the degradation was found to be very

slow.[8] Polyamide and polyurethane plastics which are more hydrophilic than the above three plastics showed a more rapid rate of degradation. But, teflon, highly rated as an inert plastic when used in leaf type heart valves has broken and fragmented and caused embolism in coronary arteries.[3] It is also well known that, when nylon sutures and nylon vascular grafts were implanted *in vivo,* they became hard and later fragmented in some instances. The degradation processes of polymers and the fate of such degradation products have been only poorly understood.

## 6. TOXICITY OF ADDITIVES

### 6.1 Plasticizers

Plasticizers are added to a polymer to impart required flexibility. Polyvinyl chloride is the most widely used material in the manufacture of medical devices and about 70 per cent of the total annual production of plasticizers are used in PVC items. Di-2-ethyl hexyl phthalate (DEHP) is the most widely used plasticizer in medical PVC production and may comprise 30 or more per cent of a device by weight. Numerous studies have demonstrated that DEHP is extracted from PVC containers by saline, ACD solution, plasma-blood etc. stored in them.

Jaeger and Rubin have shown that rate of DEHP accumulation in blood is 0.25 mg/100 ml kg day over a period of 21 days storage in PVC bags.[9-12] Studies carried out in patients who underwent multiple transfusions and involving cardiopulmonary bypass showed no DEHP in systemic circulation[13,14]. But the same study showed significant levels of DEHP in lung (91.5 $\mu$g/g dry weight), liver (69.5$\mu$g/g) and spleen (25.3 $\mu$g/g). DEHP is also known to either depress or stimulate reticulo endothelial function, to increase the microaggregation of platelets in stored blood and to be lethal to 97 per cent of cultured chick heart cells at a concentration of only 4 $\mu$g/ml. In spite of large amount of experimental data, the subtle effects that may arise from the accumulation of minute quantities of DEHP in human tissue is still not understood. In recent studies significant evidence has been advanced for the carcinogenicity of DEHP in experimental animals[2,15-17].

### 6.2 Stabilizers

Polymers are susceptible to environmental degradation and effects of heat, light (ultraviolet) and oxygen are of particular importance. The manufacturing and preparatory process of most of the medical plastics involve heating in the presence of oxygen, then sterilization and exposure to light during transportation and storage. The degradation of a PVC device due to heat may yield HCl from the polymer chain and if not prevented will continue the depolymerisation process. Stabilizers used to prevent this either accept or scavenge the HCl thereby blocking the propagation of the reaction. Organotins were used very effectively in early 1960 but when they were found out to be toxic to tissues their use in medical PVC was restricted. A large number of stabilizers have become available to replace organotin compounds. Calcium, magnesium and barium salts are being used singly or in combination. Various types of epoxies also are included in the stabilizing system. Toxicology data on most of the

stabilizers are either not available or incomplete. For those available, data on oral studies are only at hand. It is recommended that when more than one stabilizer is used, toxicity must be measured by considering the combination rather than each agent alone, since a different synergistic effect could be the outcome very often[7].

### 6.3 Antioxidants

These are included in the polymer formulation to inhibit the attack of oxygen during the processing and sterilization of the device. Oxidation normally proceeds by a free radical chain reaction. Free redicals present or generated within a polymer react with oxygen to form peroxy radicals which in turn may extract hydrogen atoms to form a hydroperoxide. Phenols, amines, sulfur or phosphate compounds are used as antioxidants depending on the free radicals expected to form. For many antioxidants toxicology data is available from feeding studies only. Chronic toxicity studies, using parenteral routes in animals have not been reported.[7]

### 6.4 Fillers

As in commercially used polymers medical polymers also contain fillers for economic reasons and for improving mechanical properties. Quartz, glass, silicates etc. are the common fillers used in medical polymers. These fillers are known to produce irritation to tissue and may act as allergens. A very good example of the irritant behaviour of filler is that of silica in medical grade silicone rubber. Asbestos fibres added as filler in peridental dressings have been noted to elicit marked epithelial damage.[18] Toxicology data on commonly used fillers are incomplete and warrants further elucidation.[7]

### 6.5 Catalysts

Polymerization of a polymer is a chemical reaction and requires the presence of an initiator and naturally another agent to control the kinetics of polymerization and cross-linking if any. This is true for any device which is going to be a finished polymer device or on the spot mixed, cured and used polymer composite. Peroxides are very widely used for this purpose, especially benzoyl peroxides. Aliphatic azo compounds, titanium tetrachloride, boron trifluoride etc. are few examples of catalysts generally used. These are very reactive chemicals and are likely to be toxic. Catalysts are needed only in small quantities and for this reason the possibility of toxicity arising from them is low and therefore, not given much attention so far.

### 6.6 Lubricants

Lubricants are used in the manufacturing process to decrease the viscosity of the resin metal friction during plastic processing. Lubricants also lower the die-swell of extruders and promotes surface gloss. Metallic stearates, waxes, fatty acids amides, fatty acids esters etc. are used as lubricants. Polyvinyl chloride is the major consumer of lubricants among polymer production. Recently, silicones,molybdenum salts and

polyflurocarbons are being used as lubricants during polymer production. When these agents are used for production, it becomes necessary to add additional chemical agents to prevent sticking of finished goods. These additional agents are known as anti-blocking agents. Data on the toxicity of agents used as lubricating and antiblocking agents are not available[7].

### 6.7 Blowing Agents

Volatile fluorocarbons, methyl chloride, sodium bicarbonate, nitrogen, carbon-dioxide etc. are used as blowing agents in the manufacture of certain types polymer materials – when blow moulding techniques are employed. Studies on the presence of blowing agent residues in finished polymer devices are not available.[7]

### 6.8 Flame Retardants

Addition of flame retardant chemicals yield polymers that will not ignite or propagate flame readily and rapidly. Aluminium, antimony, boron, bromine, chlorine, molybdenum, nitrogen etc. are routinely used as flame retardants. Toxicity data on a number of these items are available though not with reference to medical device. Among the different polymers rigid PVC need not require addition of flame retardants because of its inherent chlorine content. But flexible PVC items however consume a good amount of flame retardant agents[7].

### 6.9 Colourants

In the fabrication of medical device, colourants find only limited application. In the case of disposable plastics, especially containers, colour is used in connection with printing or labelling. Dyes and pigments are available in plastic industry as it is for textiles. Colour migration and bleeding are to be positively avoided in their application in medical polymers. Manufactures are required to use only approved colours. Toxicology of various dyes and colours worked out for use in food containers are available for reference.[7]

There are however other hazards that can arise due to treatment of a finished medical device, such as, sterilization. If ethylene oxide used for sterilization of polymeric devices is not desorbed properly it can produce irritation of tissues with which it may come into contact. It can also react with chlorides if present in the plastic surface, to produce ethylene chlorhydrin, a very toxic substance. A number of biomedical devices such as dialysis units are sterilized by the use of formaldehyde solution. This formaldehyde becomes sorbed to the plastic portions of the device and in turn can be released into blood or fluids which may come in contact with the device.[19] Presence of residual glutaraldehyde used as a preservative and cross-linking agent for the small diameter synthetic vascular grafts was found in our own laboratories to give rise to Central Nervous System toxicity in experimental animals.[20] Later it was found that adequate rinsing in sterile saline could solve this problem.

## 7. QUALITY CONTROL OF BIOMEDICAL DEVICES

In the foregoing discussion, we have enumerated the various toxic health hazards that can be caused by polymers. This problem of toxicology of biomedical polymers assumes a special significance since in our country medical devices are not subject to any kind of survelliance by regulatory agencies of the state or central government. The ingredient which go to make up the device are not also certified as fit for medical use. Under these circumstances, the onus of responsibility to make and market a safe medical device solely and unilaterally rests on the manufacturer. As pointed out earlier one has to choose the ingredients for a Biomedical polymer formulation from those that are generally marketed for non medical applications. It, therefore, becomes imperative to enforce thorough quality control checks on the raw materials (candidate materials) to ensure safety of the end product. It will be ideal to subject pre-shipment samples to appropriate chemical, physical, mechanical and toxicological tests (Table 3 & 4) to see whether they meet the established standards. Precautions must be taken to protect the inventoried co-polymer and other additives from moisture, heat and contamination from other sources. It will be highly desirable to analyse the end product and gather data on the levels of residual monomers, oligomers, catalysts and other by-products, antioxidants, lubricants, slip agents etc. At present nothing is known about the presence of these low molecular weight species when in contact with body tissues. The user does not know the risks involved and has to passively ignore the consequences. The above mentioned data analysis will help the manufacturer to see that potential hazards, arising out of excessive levels of monomer residues, contaminants, low molecular weight additives etc. are avoided besides assuring that the physico-chemical and mechanical properties of the end product are in their limits of the safe functioning of the device.

A note of caution may be made here regarding the reuse of disposable polymeric medical devices. For considerations of cost and lack of availability, there is a tendency in developing countries like ours to subject various polymeric disposable devices to repeated use. Even in economically advanced countries this practice is not uncommon. It is not possible to dwell at length the physiological, ethical and legal implications of reuse of disposable medical items in an article of this nature. There have been on record various adverse effects on patients resulting from this practice. To cite an example, a cardiac catheter broke and became lodged within the blood vessel of the patient's through. The catheter had been labelled by the manufacturer as being usable for a maximum of three times, whereas, in fact it had been used at least 19 times. An investigation which followed the incident revealed that 53 other catheters stocked in the hospital were being regularly reused eventhough some of them have never been resterilized.[21] It will be, therefore, to the advantage of all concerned to adhere to the stipulations of the manufacturer in making effective use of disposable devices.

## 8. CONCLUSION

The more subtle and general issue of systemic effects of biomedical polymers need attentions. Polymeric implants can release compounds by structural degradation

**Table 3. Summary of test procedures for biomedical materials**

| | Test | Significance | Standard test |
|---|---|---|---|
| Physical | Infra-red spectroscopy | Molecular structure and changes in chemical groups present. | ASTM D1638-61T |
| | X-ray diffraction | Crystalline structure | |
| | Molecular weight | Presence of low molecular weight fragments following degradation | |
| | Melt index | An indication of processability; empirical; not necessarily related to biomedical application | ASTM D1208-65T; ISO/R292 : 1967 |
| | Swelling index | Related to structure and to *in vivo* swelling and ion permeability | BS 903 Part A16 |
| | Refractive index | Optical plastics. Purity control | ASTM D542-50; ISO/R489 : 1966 |
| Mechanical | Tensile properties | Mechanical strength and stiffness. Particularly valuable for weight bearing materials. Indicator of degradation. Use to find design accommodation of stresses within safe limits | ASTM D638-61T; ASTM D882-56T; BS2782-1965 and PD5850m 6008, 6269 cover all tests; BS4077-1966 (AMD65-1968); ISO/R527 : 1966 |
| | Flexural properties and flexural fatigue test | For cracking resistance and general deterioration after continuous flexion | ASTM D790-63 ASTM D671-51T. |
| | Impact strength | Toughness and impact resistance. Useful for design. Indicates if sharp corners to be avoided. | ASTM D256-56; D1822-61T; ISO/R180 : 1961 |
| | Compressive strength | Minimal value but useful for comparisons of different grades | ASTM D695-63T; ISO/R604 : 1967 |
| | Stress relaxation | Long-term dimensional changes in weight bearing application "Creep" | ASTM D674-56 ASTM D621-64 |
| | Abrasion resistance frictional and wear characteristics | Where use in a moving surface is intended. | ASTM D1242-56 |
| Chemical | Hydrolytic resistance | To determine possible biodegradation resistance and products resulting from this. | |
| | Extractability | Shows up presence of soluble toxic ingredients | ASTM D1239-55, part 27, 1965 |
| | Effects of sterilisation | Suitability of various methods in correlation with tensile tests, crystallinity by X-ray diffraction, and surface examination. | BS11333 sect 22 & 23 refer to packaging |
| | Resistance to chemicals | Determines effect of immersion in chemical substances | ISO/R426 : 1965; ISO/R175 : 1961 |

From : Plastic materials in surgery (Charles & Thomas), 1972.

**Table 4. Toxicity screening protocol (general)**

| |
|---|
| 1. Acute toxicity studies |
| (a) *In-situ* implantation |
| (b) Tissue culture |
| (c) Haemolysis |
| (d) Thrombogenicity |
| (e) Systemic toxicity |
| (f) Irritation test |
| 2. Chronic toxicity studies |
| (a) *In-situ* implantation |
| (b) Systemic toxicity |
| (c) Irritation test |
| 3. Sensitization |
| 4. Carcinogenicity |
| 5. Mutagenicity |
| 6. Special tests |
| (a) Pyrogen test |
| (b) Sterility test |
| (c) Safety test |
| (d) In-use test |

(depolymerisation and hydrolysis), elution or enzymatic attacks. These general systemic effects could be broadly classified as (i) carcinogenic effects, (ii) Metabolic effects, (iii) Bacteriologic effects and (iv) Immunologic effects. Very convincing arguments and evidence have been advanced to validate this concern over long term toxicity.[22] The task, though colossal and daunting, must be taken up to resolve the issue in a satisfactory manner.

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