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**BIOCOMPATIBILITY AND REACTION OF DENTAL POLYMERS IN ORAL ENVIRONMENT**

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**Abstract:** Dental polymers, commonly known as “Dental Resins” were first used in dentistry in 1839, and since then they have emerged as a favorable candidate for restorative dentistry and cosmetic and functional purposes. Many prosthesis and implants made from polymers have been in use for the last three decades and there is a continuous search for more biocompatible and stronger polymer prosthetic materials. Typical applications of polymers in dentistry are impression materials, relining materials, temporary crown materials, denture base materials, obturation materials (endodontic treatment), and filling materials (composite, cements, adhesives). The dental polymers that are to be used in the oral cavity should be harmless to all oral tissues – gingiva, mucosa, pulp, and bone. Furthermore, it should contain no toxic, leachable, or diffusible substance that can be absorbed into the circulatory system, causing systemic toxic responses, including teratogenic or carcinogenic effects. The materials should also be free of agents that could elicit sensitization or an allergic response in a sensitized patient. Rarely, unintended side effects of dental polymers may occur as a result of toxic, irritative, or allergic reactions. The most widely used polymer in prosthodontics is polymethyl-methacrylate resin (PMMA), which is used for fabrication of various dental prostheses and denture liners, temporary crowns and orthodontic appliances. The aim of the current paper is to provide an overview of the current literature on toxicology of dental polymers and to give implications for possible improvements concerning their biocompatibility.

**Keywords:** dental polymers, biocompatibility, reaction, prosthodontics

**INTRODUCTION**

Dental polymers, commonly known as “Dental Resins” were first used in dentistry in 1839, and since then they have emerged as a favorable candidate for dental restoration of dead, degraded, or missing tooth structures. They are extensively used today for a wide variety of cosmetic and functional applications such as sealants, dentin bonding agents, restorative composites, fiber-reinforced resin materials, cementing and relining materials, denture base materials, denture teeth, denture liners, obturation materials (endodontic treatment), filling materials (composites, cements, adhesives), maxillofacial prosthetic products, core buildup materials, orthodontic appliances, splinting materials, temporary restorative materials, and veneers. These numerous applications make resin-based composites one of the most important group of materials in dental practice. [1,2]

Dental polymers are commonly used in every day dental exercise, as they are able to provide the necessary properties and have necessary characteristics for their use in diverse functions. Polymethyl methacrylate (PMMA)-based acrylic resins are used for fabrication of various dental prostheses and denture liners, temporary crowns and orthodontic appliances.

Although the exact composition of these materials is a trade secret, most of them are known to contain monomers of acrylate derivatives, initiators and accelerators of polymerizations, and stabilizers, among others. Most resin systems used in dentistry are based on methacrylates, particularly methylmethacrylates (MMA). One of the most intensively studied and used group of polymers in dentistry is polymethyl methacrylates (PMMA).

Today, PMMAs are used primarily for dentures and temporary crowns, individual impression trays and orthodontic devices. [3,4]

PMMAs are classified as heat curing, chemical (auto) curing, light curing or microwave curing according to their mode of chemical reaction. [2]

Several difficulties exist in producing a satisfactory denture material or designing a technique that is useful for its application. Conditions in oral cavity seem almost suited to annihilation. Biting stresses on dentures can be extremely high, temperatures may fluctuate between 25°C to 45°C [1] and pH may change instantaneously from acidic to alkaline. The warm and moist oral environment, which is also enzyme and bacteria rich, is conducive to further decay. The soft tissues and structures in contact with the denture polymers may be injured from the toxic leaching or breakdown of the material.

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Towards developing a successful denture material, it is of prime importance to possess information on the chemical, physical and mechanical properties of the material together with the bacteriological, physiological and pathological responses of the material, which cannot be divorced from the former.

The most important requirement for a material to be used in dental applications is its biocompatibility which means not only the material's physical and chemical properties but also their behavior at the time they come into contact with the oral tissues. In the oral cavity, the dental polymer that is to be used should be harmless to all oral tissues, namely gingiva, mucosa, pulp, and bone. Nevertheless, these materials are biologically inert and shrink. In addition, they are subject to degradation via abrasion, and therefore evenly accommodate pathogenic settlements of bacteria. Therefore, their clinical use may lead several problems. The methacrylate monomers are polymerized through radical chain polymerization, and they are responsible for major clinical disadvantages, such as polymerization shrinkage of the composites which, in turn, leads to microleakage phenomena in the tooth-material interface. [5-7] Likewise, substances released from the resinous matrix due to incomplete polymerization or resin degradation may cause adverse effects. [8,9] The release of methacrylic monomers together with compounds of the polymerization system from dental composites has been considered as a source of a wide variety of adverse biological reactions, which include local and systemic toxicity, pulp reactions, allergic and estrogenic effects. [5] To date, significant concern still remains regarding biocompatibility of dental polymers.

### **BIOCOMPATIBILITY**

Biocompatibility can be defined as the properties of materials being biologically compatible without causing local or systemic responses of a living system or tissue. According to regulatory rules, biocompatibility is a number of tests for determining the possible toxic effects resulting from contact of the components of medical devices with the body. Another definition refers biocompatibility as the ability of a polymer material or a device to remain biologically inert during its functional period. Like the other medical materials, there are number of obligatory tests for the dental polymers before they can be used in applications, including biocompatibility. [10]

Recently the biocompatibility has been point of interest in too many works which evaluate biomaterials especially the dental polymers.

Biomaterials such as dental polymers should not cause any adverse inflammatory event or immune reaction after administration. The regulatory guidelines suggest that a biomaterial should not produce any adverse local, systemic, tumorigenic, reproductive, or developmental effects. Assessment of biocompatibility, which are defined in ISO 10993 [11], are consist of overall safety and efficacy evaluation of medical devices, including dental polymers. These safety and efficacy studies include analytical chemistry, cytotoxicity, sensitization, irritation/intracutaneous reactivity, acute systemic toxicity, pyrogenicity, subacute/subchronic toxicity, genetic toxicology, implantation, and hemocompatibility. Moreover, in these studies, chronic toxicology, carcinogenicity, reproductive/development toxicology and biodegradation are evaluated additively.

#### **Biocompatibility testing methods**

There are several tests for determining the biocompatibility of dental polymers because this process is complex and extensive. These tests can be either in vitro or in vivo which vary from analysis of cytotoxicity to potential systemic toxicity in animals. In vitro tests evaluate the properties of the material in the cultured cells directly. In vivo tests are basically carried out by implanting the material subcutaneously or intramuscularly in rodents to assess tissue response to the implanted material after an observation time. [12]

The Direct Contact Test is recommended for low density materials, in which a piece of test material is placed directly onto cells growing on cell culture medium. The cells are then incubated. During incubation, leachable chemicals in the test material can diffuse into the culture medium and contact the cell layer. Reactivity of the test sample is indicated by malformation, degeneration and lysis of cells around the test material.

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) assay is another important method for evaluating the cytotoxicity of biomaterials in vitro. MTT test, which evaluates the mitochondrial succinate dehydrogenase enzyme activity and measures the conversion of water-soluble tetrazolium salt in insoluble blue formazan by spectrophotometry. This test is an excellent marker of cell survival because it evaluates cellular respiratory activity. Polymers and its components may change the enzyme activity of primary cell lines. [13] The Agar Diffusion Assay also known as agar overlay test, is appropriate for high density materials. In this method, a thin layer of nutrient-supplemented agar is placed over the cultured cells. The test material (or an extract of the test material dried on filter paper) is placed on top of the agar layer, and the cells are incubated. Usually red vital stain is used as dye in this study. A zone of malformed, degenerative or lysed cells under and around the test material indicates cytotoxicity. Barrier Screening Test is based on that a layer of dentin would be normally present between the pulp tissue and the material to be used. In this test a barrier of dentin disc is located between the tested material and the cell culture. If

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the materials (or its by-products) penetrate the disc, it's evaluated as a positive cytotoxic response. Filter Diffusion Testing method is similar to the agar diffusion tests. A cellulose acetate millipore filter is interspersed between tested material and the primary cell line. Presence of any leachable component passes through a pore size of 0.45  $\mu\text{m}$  filter pore. Tested material side the filter paper is examined and graded based on a criterion by ISO. Dentin Barrier Test mimics the oral environment although this is an in vitro test and also known as cavity model method which was first described by Outhwaite et al. [14]. These tests evaluate the cytotoxic materials which pass through the dentinal tubules. Tooth Slice Culture Assay provides to sustain the vitality of the tooth and hence a possible projection of a legitimate clinical scenario. The method is suitable for both animal and human testing and allows evaluating the cytotoxic effects on the pulpal tissue, growth factors, stem cell and gene therapy accurately. [15] For testing carcinogenicity, the Ames Test is one of the popular in vitro tests which was first described in the 1970 by Prof. Bruce Ames. This test uses several strains of the bacterium *Salmonella typhimurium* that carry mutations in genes involved in histidine synthesis which require histidine for growth, but cannot produce it. Bacteria cannot grow and form colonies on a histidine-deficient culture agar, if any mutagenic substance is present; the growth of the bacteria is evident suggesting mutagenicity. [16] A modified test that uses normal fibroblasts, cultured from baby hamster kidney is called Style's Test is also used to test carcinogenicity. [17] Cytotoxicity tests are rapid, sensitive and standardized methods to evaluate the toxicity of a material. They are simple to perform and findings are reproducible. However, it is always necessary to test and assess a material in comparison with similar materials tested before. It is usually possible to extrapolation of these results to patients but differences between cell culture data and patient reactions have been reported. These problems could be solved by using tests which simulates best possible clinical situations like dentin-barrier test.

Testing on animals simulates a near clinical scenario especially on the systemic and cytotoxic properties. These tests are based on tissue assessment of animals that received implants subcutaneously and intramuscular injection of a material with potential to cause systemic toxicity by inhalation, skin irritation, among other responses. The release of the chemical constituents of a polymer, either by leaching or breakdown of the device, into the body has the potential for systemic toxicity. Systemic toxicity tests are generally conducted by administering the extracts as a single dose to test animals, and the health status of the animals is verified periodically—typically 24, 48 and 72 hours after dosing. Control animals are administered the extraction vehicle. The clinical observation includes evaluation for severity ranging from respiratory, motor activities, convulsion, reflexes, ocular signs, cardiovascular signs, salivation, piloerection, and analgesia, muscle tone, gastrointestinal and skin. Tests for sub-chronic toxicity are used to determine potentially harmful effects from longer-term during a period of up to 10% of the total lifespan of the test animal (e.g. in rats up to 90 days). Actual use conditions of the material need to be taken into account when selecting an animal model for subchronic toxicity.

Once the tested material is clear in the initial and the usage tests, clinical performance and diagnostic tests on patients are evaluated. Some ethics and legal issues may exist while performing these tests. There are especially two criteria present for clinical testing for dental polymers which are United States Public Health Service or Ryge criteria. [18]. According to the regulations the materials should be monitored for a prolonged period, i.e. 1 year and have to obtain 90% success rate. If there is a failure for either criteria, the material should be withdrawn from market.

The commonly used allergy tests are patch test, prick test and radioallergosorbent test (RAST). In the patch test which was first described by Jadassohn [18], the adhesive tapes loaded with at quietly high concentrations of allergens are attached at the patients back. These reactions can be categorized as mild, non-irritating and essentially harmless. Patients must be warned to avoid from direct sun exposure, increased sweating and scratching the patch attached area. Redness, itching, blisters are the most common signs. Skin and oral mucosa are comparable. When the same test is performed at the oral cavity, it is called as epidermal test. But the factors such as saliva and difference in the immunological reaction, the allergic reaction cannot be properly assessed. For overwhelming this problem the concentrations can be increased but the ideal place for this test is always the patient's back. [19]

Radioallergosorbent test (RAST) is an in vitro test which uses the patient's serum. The allergen is linked to a material that is insoluble is added to the serum. The allergen causes a response by binding to the antibody if the added serum has antibodies to it. It is a quantitative test in the sense, the linked radioactivity determines the amount of serum IgE released for a given allergen. [20]

#### **Biocompatibility of dental polymers: Vascular actions**

Because the oral cavity is highly vascularized, our knowledge about the effects of the dental polymers, which contain various diluent monomers that can interfere with vascular function, can be relevant to dental clinical practice. Therefore, dentists have studied vasoactive properties of dental polymers by examining their effects on vascular diameter of pulpal vessels by means of vital microscopy and Laser Doppler Flowmetry. Pharmacologists

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have joined the study by evaluating the effect of dental polymers on endothelium and smooth muscle of isolated rat aorta, which provided a practical, accurate, and reproducible study model. Using these methods, recent studies have shown that the newly developed dentin bonding agents and pulp capping materials contain various diluent monomers that can interfere with vascular function by causing vasodilation. [21,22]

Accumulating evidence suggests that the key mechanism behind the vasodilatory action of dental polymers is through calcium antagonistic action. [23] Furthermore, it should be noted that several studies have shown that clinically relevant concentrations of these materials induce vasodilation in endothelium-denuded vessels, suggesting that the vasodilatory action is independent of the endothelium.

A lot of experimental studies provided evidence for the marked vasodilating effect of resin components. However, results from these *in vitro* studies need to be carefully extrapolated to the clinical situations, where the condition of the pulpal and apical vasculature is more complicated. Provided that these initial results are confirmed by clinical experimentation, more data will be available on future therapeutic opportunities for the dental pulp against the biological risks induced by such adhesive resins. In this regard, further studies especially with each of the various components available, are essential to understand the exact mechanism of the vasodilatory effect of dental polymers and to fully realize their implications in clinical dental practice.

### CONCLUSION

Dental polymers are extensively used today in dentistry. As stated above, the results from published studies have indicated that dental polymers possess not only beneficial but also undesirable properties. Therefore, developing more biocompatible materials while maintaining or improving their mechanical, aesthetical, and functional properties remains a challenge. Whether or not a polymer is biocompatible depends on physical function in a specific application that we inquire about the material and the biological host response we demand from it. Accordingly, the biocompatibility evaluation of dental polymers involves not only the biological and physical aspects of the polymers, but also those of the natural tissues in the oral cavity. All dental restorative materials have the potential to elicit allergic reactions in hypersensitive individuals. Even though the prevalence of allergic reactions caused by resin-based dental restorative materials has increased over the past years, overall risk seems to be quite low since the percentage of patients experiencing adverse reactions is relatively low in total population. However, in severe allergic cases, the individual health risk due to chronic exposure of dental resins cannot be underrated. Scientific evidence concerning the toxicological effects of dental polymers is growing substantially. Besides, improving the quality of dental restorative materials is the responsibility of the dental industry. However, the companies show little performance to develop more biocompatible dental polymers while maintaining or improving their mechanical, aesthetical, and functional properties. On the other hand, some promising new technologies using different chemistry and polymerization mechanisms are still being investigated from the viewpoint of biocompatibility. Since dental polymers are essentially used in dental clinical practice, setting a future goal for development of new “biomimetic” materials which maintain the vitality of the compromised oral tissues and stimulate natural tissue repair is substantial. Reports on the biological safety profile of different resin-based dental materials show that there are contradictory data obtained from *in vitro* and *in vivo* studies. In general, *in vitro* systems are more sensitive to test materials than *in vivo* systems. The most relevant, efficient and cost-effective way is to use a combination of *in vitro*, animal and usage tests to ensure the biocompatibility of these materials. In addition, new experimental designs should be improved in order to simulate the intraoral conditions. Recently, some antioxidant molecules are incorporated into these materials to enhance their biocompatibility. More *in vivo* studies are required to increase our knowledge regarding biocompatibility of dental polymers and hence, to spread out their usage not only in dentistry but also in other applications.

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