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PHOTOPOLYMERIZATION IN DRUG DELIVERY, TISSUE ENGINEERING AND CELL ENCAPSULATION: ISSUES AND POTENTIALITIES

Recently, photopolymerizable monomers and macromers have received great attention as starting materials for the production of three–dimensional matrices upon exposure to a light source, mainly UV and visible light. These matrices have also the great advantage to be potentially fabricated in vivo, at the site of interest, via minimally invasive surgery, thus suggesting their utilization for drug delivery (An Y 2000; Lu S 1999; Elisseeff J 2001; Mellott MB 2001; Burdick JA 2002, a) and/or tissue engineering (Fisher JP 2002; Schmedlen RH 2002; Burkoth AK 2000; Anseth KS 2002), cell encapsulation (Burdick JA 2002, b; Elisseeff J 2000; Cruise GM 2000; Desmangles AI 2001), tissue barriers (Hill–West JL 1994, Hubbell JA 1996) and fillers (Maffezoli A 1994; Bland MH 1996).

The rational beyond the received interest, confirmed by the increasing number of articles found in literature, is maybe due to a combination of properties held by the photopolymerized matrices. Some of the most important attributes are: easiness of production and implantation; in several cases, spatial and temporal control of the polymerization process; versatility of formulation and application; possibility to entrap a wide range of drugs since the formulation of photopolymerizable mixtures does not involve the use of organic solvents and vigorous mixing, which are known to negatively affect proteins and related molecules; the extemporaneity of matrix production, which allows to store ingredients of each specific formulation in the most appropriated conditions until use.

Nevertheless and although great advancements in the biomedical field have been accomplished, to completely develop this technology there is a need to further investigate some of its inherent and annexed features. These aspects could be grouped in four broad interrelated categories: technology issues; formulative issues; material issues; toxicological issues.

Therefore, this presentation aims to describe the photopolymerization technology, review some biomedical applications, highlight potentialities and issues, and brainstorm on possible solutions or indicate investigative directions that should be pursued.

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MATERIAL AND METHODS

In the simplest case, a photopolymerizable system is composed by (1) a monomer, (2) a photoinitiator, and (3) a source of light. This simplest formulation can be then supplemented with other molecules or cells to fulfill requirements of the desired application.

Photoinitiators and polymerization

Photoinitiators should be chosen accurately to satisfy the following criteria. They should be (i) highly adsorbing the light used to polymerize, (ii) soluble in aqueous media, (iii) biocompatible and non–toxic both locally and systemically. In addition, in some cases it is preferable to use a combination of an initiator and an accelerator.

Upon UV or visible light irradiation, photoinitiators adsorb energy and dissociate in free radicals, which will initiate the polymerization by (i) photo–cleavage, (ii) hydrogen abstraction, or (iii) generation of cationic species. The first two mechanisms of initiation will generate a free radical photo–induced polymerization, and are the most commonly used for the applications inhere discussed.

Monomers and macromers

Molecules and macromolecules used as monomers and macromers have been di–methacrylic or di–acrylic derivatives with internal degradable or non–degradable bonds. Therefore, it is possible to produce non–degradable or semi–degradable matrices, where dimensions of cross–linked network meshes might be modulated by varying the molecular weight of the monomers. Fully degradable matrices cannot be produced since the polymerization of methacrylic or acrylic derivatives creates a non–degradable hydrocarbon polymeric backbone chain to which potentially degradable lateral chains are found attached. The introduction of other specific properties (e.g.; cell and protein adhesiveness or non–adhesiveness, mechanical strength, absence or limited mass transport constrains) in the polymerized matrix can be achieved by selecting

appropriately monomer(s) and/or macromer(s), and supplemental molecules during the formulative step.

Polymerization and Fabrication

Photopolymerization can be carried out previous to implantation or in situ, and can be further classified as bulk or interfacial photopolymerization. In the case of bulk polymerization, formulation ingredients are mixed together and the resultant liquid or putty mass is cross–linked by irradiation with the appropriated light. Whereas, in the case of interfacial photopolymerization, photoinitiators are previously adsorbed onto the surface of interest (e.g.; cells, tissue, metallic or polymeric surfaces), which is then exposed to the photopolymerizable mixture and successively irradiated. Following this polymerization technique, which is greatly preferred for cell encapsulation and intravascular biomedical applications, it is possible to isolate a group of cells from the external environment by thin layers/barriers of photopolymerized materials.

Liquid and putty photopolymerizable masses will tend to occupy the space where they will be localized; shapes will be then retained upon polymerization. In contrast, particularly structured shapes (e.g.; a matrix holding a complex system of channels or holes) can be only fabricated in vitro prior to implantation. Non–polymerized materials can be placed in situ with the aims of catheters, laparoscopic devices, or when possible needles through which light can be irradiated. In some cases, light can reach the photopolymerizable formulations transdermally (Elisseeff J, 1999) or with optical fibers.

RESULTS AND DISCUSSION

Besides the wide range of biomedical applications derivable from this technology, some aspects have not been fully explored yet.

First, and with regards to the *technology* itself, there might be some concerns related with the energy of the polymerizing light, the heat and the radical species produced during the polymerization, which could be source of damage for the surrounding tissues and/or for the entrapped molecules. Since it is possible that each formulation, designed for a specific application, might be more or less sensitive to one of these three aspects, it should be desirable that the major source of damage (if any) could be identified and the formulation modified accordingly.

Second, among the *formulative* aspects that can potentially and dramatically affect the body response to the implanted material there are: (1) sterilization and sterilizability. All implantable materials/formulations have to satisfy sterility test, absence of pirogens and immunogenic molecules. The sterilization of either every single formulation component, or the pre–polymerized formulation or the polymerized matrix, and the sterilization method used can greatly affect both/either the sterility of the product and/or the degradation pattern of the polymers, and/or the integrity of the molecules entrapped within the matrix. (2) Immunogenicity can play a major role in the adverse responses of implanted material especially when matrices are used to deliver some potent molecules that are normally present in the body at extremely low concentrations (e.g.; cytokines, growth factors). It should be noted that a protein might become immunogenic while maintaining intact its activity. This situation stresses the importance of accurately investigate the compatibility of matrix ingredients and identify possible sources of damage. (3) Transparency of the non–polymerized mixture to the polymerizing light does not seem a significant issue until one have to prepare a thick matrix (e.g., bone filling after a tumor ablation). Light ability to penetrate completely the non–polymerized formulation will assure the maximum conversion of reactive groups during polymerization. (4) Viscosity of the non–polymerized mixture will affect its delivery through needles and catheters, and the easiness of filling rough body cavities. (5) Pre–formulative studies are instead crucial when mechanical, superficial and adhesion properties of polymerized matrices need to satisfy particular requirements.

Third, the synthesis of new photopolymerizable *materials* should regard both photopolymerizable groups and molecule backbones, and photoinitiators. Under this perspective, it would be possible to generate molecules that could be polymerized or initiate the polymerization under different light conditions. In addition, a wide range of photopolymerizable molecules will certainly enlarge the biomedical applications of this technology by enlarging the possibility to better tailor specific needs. It should not be underestimated the possibility of generating molecules that may be less toxic and better controllable in terms of polymerization and degradation. As a consequence, even formulative studies will accordingly increase their potentialities to better suit needs.

Forth and related with previous paragraphs, it should not be underestimated the possibility of *toxicological risks* associated with implanted materials that can be exerted by citotoxicity, tissue and fluid incompatibility, acute and chronic inflammatory responses, local and/or systemic toxicity, fibrotic processes, difficult elimination of degraded materials, non–inertness of non–degradable matrices. This general recommendation applies to any implanted material and should be carefully considered during the formulative step and preliminary experimentations.

CONCLUSIONS

As many other technologies applied to the biomedical field, photopolymerization may be considered a promising multidisciplinary technology, which is moving its first steps in this direction. Therefore, the great potentialities of photopolymerization are still mellowed by several aspects that have not being fully investigated yet. This contribution aimed to elucidate both potentialities and issues, indicating that a multidisciplinary approach might be necessary to overcome those aspects that could limit the marketability of products obtained with this technology.

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