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Review article

Biocompatible poly(methylidene malonate)-made materials for pharmaceutical and biomedical applications

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Abstract

In the past 20 years, mainly with the sponsorship of Laboratoires UPSA (France) and, afterwards, its spin-off company Virsol (France), several authors have studied methylidene malonate-based polymers used in drug delivery approaches and in the development of novel biomaterials. The present paper aims at summing up the preparation of methylidene malonate monomers, and essentially a novel asymmetric diester structure: 1-ethoxycarbonyl-1-ethoxycarbonylmethylenoxycarbonyl ethene named methylidene malonate 2.1.2. Their polymeric and copolymeric derivatives and a few of their applications which were reported in the literature are also presented. It encompasses the manufacturing of particulate systems such as nano- and macroparticles designed for the delivery of hydrophilic or hydrophobic drugs and biomolecules. This review article also describes their use as biomaterials of interest in the fields of tissue repair, as drug reservoirs or ophthalmology, as implants. Copolymers based on these monomers offer a large range of properties and could be used as new surfactants, micellar vectors, or particulate systems for gene delivery. Therefore, this review, certainly the first dedicated exclusively to methylidene malonate-based materials, highlights the great biomedical and pharmaceutical technology potential of these new materials.

Keywords: Methylidene malonate; Polymers; Polymeric materials; Cationic polymers; Drug delivery; Biomaterials; Implants; Particles; Encapsulation

1. Introduction

In 2000, the biomaterial engineering served a huge global market evaluated approximately at US$ 39 billion. Expectedly, at an average annual growth rate of 12%, estimations forecasted a worldwide turnover of US$ 55 billion for 2003. Presently, orthopaedic, cardiovascular, drug delivery, dental, surgical and wound care sectors represent the largest sources of applications and revenues for biomaterial-based products while, according to available data, drug delivery, urology and ophthalmic fields showed the highest annual growth rate, at over 16%. Many significant companies, like Baxter Healthcare, Bausch & Lomb, Convatec, Smith & Nephew, Alkermes, ALZA, Biocompatibles, Boston Scientific, Cordis (J&J), Genzyme Biosurgery, IsoTis, etc. are involved in this very competitive market segment [1].

Besides ceramics and metals, synthetic polymers and polymer-based biomaterials were first extensively considered for biomedical applications in the fifties, sixties and seventies and are still the topic of many investigations throughout the world [2–6]. Especially, Merrill's group spent considerable efforts understanding what could cause biocompatibility of a material when it was in contact with blood or other physiological fluids [7,8]. For the past 40

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years both hydrophobic (*e.g.* poly(methyl methacrylate), polysiloxanes, polyethylene, polyurethanes, etc.) [9] and hydrophilic (*e.g.* poly(ethylene oxide)) [10] polymers were studied and tested in various biomedical or pharmaceutical applications. Synthetic polymeric materials have been used in a wide range of formulations such as gels, hydrogels, films, coatings or particle suspensions and became key elements of tissue engineering, constituants of implantable devices, drug reservoirs or drug vehicles. The design, preparation and characterization of such materials now represent a still growing part of worldwide biomaterials R&D efforts and investments [11]. Either bioresorbable or fully stable over time, these polymeric systems incorporate various types of homopolymers or copolymers made of poly(esters), poly(anhydrides), poly(acrylates) or many others. In the context of chemical engineering science and biopharmaceutical engineering, these polymeric materials have played a crucial role in the development of controlled drug delivery and targeting systems and were the topic of many reviews in this field [12–15].

As a matter of fact, during the mid-late seventies, synthetic polymers and especially acrylic polymers started to be carefully considered for the advanced formulation of drugs [16]. Poly(methylmethacrylate) [17], poly(acrylamide) [18], poly(*N*-(2-hydroxypropyl)methacrylamide) [19], poly(styrene) [20] and poly(alkylcyanoacrylate) [21] were first retained for such an application and drug-loaded particulate systems (*i.e.* nanospheres or microspheres) were produced and carefully studied.

In the mid-1980s, Laboratoires UPSA, a French analgesia world leader company of high repute for its unique know-how in production of effervescent drug formulations, wished to perpetuate and reinforce its leadership in pharmaceutical technology and decided to invest in the development of proprietary pharmaceutical technologies based on the use of poly(methylidene malonate)-made materials [22,23]. Initially involved in the preparation of novel nanoparticulate systems that can be drug loaded [24], poly(methylidene malonate) and, more specifically, poly(methylidene malonate 2.1.2) (PMM 2.1.2), were extensively studied by Laboratoires UPSA and then by VIRSOL, after Bristol-Myers and Squibb took over Laboratoires UPSA in 1994. In the past years, VIRSOL has explored different pharmaceutical and biomedical applications where methylidene malonate 2.1.2- (MM 2.1.2) and PMM 2.1.2-based materials could be of interest.

This paper aims at reviewing the main R&D advancements having been accomplished for the past 15 years on MM 2.1.2, PMM 2.1.2 and all of their derivatives.

2. Methylidene malonate monomers

2.1. General structure

The general formula of methylidene malonate species is depicted on Fig. 1a. The structural backbone is a malonic acid, for which the two carboxyl functions are esterified

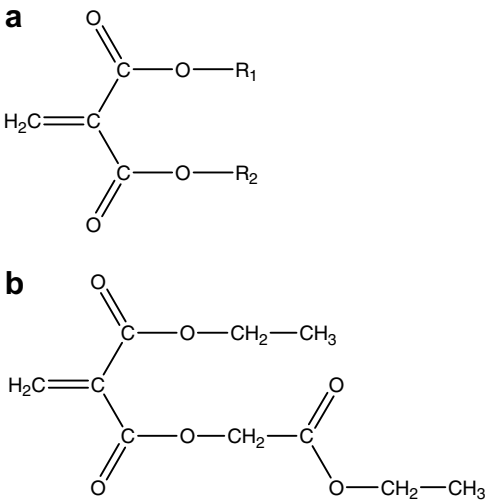

Fig. 1. General molecular structure of methylidene malonate (a) in which R_1 and R_2 are identical or different and can represent H, an alkali metal or alkaline earth metal atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms, an alicyclic group having from 3 to 6 carbon atoms, an alkenyl radical having from 2 to 6 carbon atoms, defined in their *cis* or *trans* configuration, or an alkynyl radical having from 2 to 6 carbon atoms, the said groups optionally being substituted by one or more functional groups such as ether, epoxide, halogeno, cyano, ester, aldehyde, ketone, aryl or hydroxide. Molecular structure of methylidene malonate 2.1.2 (MM 2.1.2) or 1-ethoxycarbonyl-1-ethoxycarbonylmethylenoxycarbonyl ethene (b).

by various residues R_1 and R_2, identical or different, that can represent linear or branched alkyl, alicyclic, alkenyl or alkynyl groups optionally being substituted by one or more functional groups such as ether, epoxide, halogeno, cyano, ester, aldehyde, ketone, aryl, etc. Carbon 2 of malonate is substituted by a methylene group through a polarized double bond that is quite easily reduced in the course of a Michael's addition or a polymerization reaction [25,26].

2.2. Synthesis

Synthesis of simple methylidene malonate esters had been the topic of several reports in the literature since the late thirties up to the 1980s [27–34]. Among the chemical processes implemented, the most frequently described was the Knoevenagel condensation of paraformaldehyde with symmetric malonic acid esters in presence of various catalysts. However, except for the methylidene malonate di-*tert*-butyl ester [34], under the usual experimental conditions, yielded methylidene malonate esters were very unstable and polymerized very easily.

Noteworthy were the work and data patented by researcher groups at Eastman Kodak Co. [32] and also published by Ponticello [33]. To stabilize dialkyl methylidene malonates, these authors described similar chemical procedures in which acrylic derivatives were trapped by various dienes using a Diels–Alder mechanism to avoid polymerization in the reaction mixture. Such adducts were