Review

Homo- and copolymers based on dialkyl fumarates: A review on radical polymerization, properties, current and future applications

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ABSTRACT

Fumaric polymers are macromolecules obtained from 1,2-disubstituted monomers, which provide special structural characteristics and therefore attractive physicochemical properties for their applications. Thus, in the present review, different radical polymerization mechanisms (conventional or living) are detailed and their characteristic kinetic parameters are shown. For example, the use of the initiator 2,2′-azobis(isobutyrate) (MAIB) allows to obtain polymers of higher molecular weight since it generates more stable primary radicals than those achieved with other azo initiators. The emergence of different controlled radical polymerization methodologies has resulted in the generation of new fumaric homo and copolymers with different properties. The structural characteristics of these materials analyzed by spectroscopic techniques and their relationship with properties in solutions, glass transition temperature, thermal stability and mechanical behavior are detailed in the present work. Finally, several biomedical and energy applications are described in which copolymers from fumaric and acrylic monomers were employed, combined or not with natural polymers to be used as scaffolds in the regeneration of bone and cartilage tissue, drug delivery systems, as flow or asphalt modifiers. From the complete reading of this review, it will be possible to achieve a global vision starting from the synthesis to the application of fumaric polymers in which the need of scaling this type of productions to reach specific industrial applications is visualized.

1. Introduction

Fumaric esters are monomers characterized by a 1,2-disubstitued ethylenic structure whose homopolymerization was first considered not possible, due to the great steric hindrance of substituents present on adjacent carbons of the main chain. In 1975, the radical polymerization of diethyl fumarate was reported for the first time, showing that it was possible to obtain polymers [1]. Nevertheless, the number average molecular weights (M_n = 3–16 Kg/mol) and the reaction rates were much lower than those of other vinyl and acrylic monomers. It was just in the 1980s, with the pioneering works of Otsu and his group, that the radical polymerization reactions of this type of monomers were deeply studied and clarified [2–5]. In their research they carried out a systematic study on various fumaric esters monomers, and analyzed the role of the structure on the kinetics of polymerization and chain growth. Surprisingly, the results showed that the rates of polymerization increase with the increase in the bulkiness of the alkyl substituents. Thus,

methyl and ethyl esters polymerize at rates much slower than those of the bulky isopropyl and *tert*-butyl fumarates [6]. This result was attributed to a competition between the propagation and termination stages that occur during radical chain polymerization. The increased rigidity of propagating radicals with bulky substituents decreases the frequency of bimolecular termination reactions, thus giving higher molecular weights and faster polymerization rates. Subsequently, the propagation and termination rate constants (k_p and k_t, respectively) were evaluated using electron spin resonance, from which the mechanism of polymerization was analyzed [7]. This work revealed that, although the values of both kinetic constants (k_p and k_t) are smaller than other monomers, such as dialkyl methacrylates, itaconates or crotonates, the ratios $k_p/k_t^{0.5}$ were enough to produce high rates of polymerization and polymers of high molecular weight.

These works constitute the fundamental basis of the current knowledge on radical polymerization reactions of fumaric esters, which together with the particular structural and conformational characteristics of this kind of polymers has prompted subsequent studies on various

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Nomenclature

Abbreviations

ACN	2,2′-azocyclohexanecarbonitrile
AFCT	addition-fragmentation chain transfer
AIBN	2,2′-azoisobutyronitrile
ATRP	atom transfer radical polymerization
BA	benzyl acrylate
BPO	benzoyl peroxide
Ch	chitosan
CTA	chain-transfer agent
DCHF	dicyclohexyl fumarate
DEF	diethyl fumarate
DEHF	di-2-ethylhexyl fumarate
DFN	dioctyl fumarate-N-isopropylacrylamide copolymer
DIPF	diisopropyl fumarate
DnDF	di-n-docosyl fumarate
DODF	n-dioctadecyl fumarate
DOF	dioctyl fumarate
DPEF	di-2-phenylethyl
DRF	dialkyl fumarate
DSC	differential scanning calorimetry
EHA	2-ethylhexyl acrylate
FAF	fluoroalkylfumarate
FTIR	Fourier-transform infrared spectroscopy
GC–MS	gas chromatography-mass spectrometry
HEMA	2-hydroxyethyl methacrylate
LCST	low critical solution temperature
M_η	viscosity average molecular weight
MA	maleic anhydride
MAIB	2,2′-azobis(isobutyrate)
MDB	2-(methoxycarbonyl)-2-propyl dithiobenzoate
M_n	number average molecular weights

MW	microwave
M_w	weight average molecular weight
M_w/M_n	dispersity
NBA	p-nitrobenzyl acrylate
NIPAM	N-isopropylacrylamide
NMP	Nitroxide-mediated radical polymerization
NMR	nuclear magnetic resonance
ODA	octadecyl acrylate
PDEF	polydiethyl fumarate
PDIPF	polydiisopropyl fumarate
PDIPF MM	PDIPF macromonomers
PDMF	polydimethyl fumarate
PDtBF	polyditer-butyl fumarate
PFVH	partially hydrolyzed diisopropyl fumarate-vinyl acetate copolymer
PMtBF	polymethyl-butyl fumarate
RAFT	reversible addition-fragmentation chain transfer
RDRP	reversible-deactivation radical polymerization
RTCP	reversible chain transfer catalyzed polymerization
SEC	size exclusion chromatography
SEM	scanning electron microscopy
sem	standard error measurement
TDDS	transdermal drug delivery systems
TEGA	tetraethylene glycolmonoacrylate
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TERP	organotellurium mediated-living radical polymerization
Tg	glass transition temperature
TGA	thermogravimetric analysis
THF	tetrahydrofuran
UV	ultraviolet
VAc	vinyl acetate
VBz	vinyl benzoate
VP	vinyl pyrrolidone

polymerization methods, as well as on their properties and potential applications. The interest and relevance of this type of polymers is based not only on their peculiar structural characteristics, as the rigid chain polymers, being different from those of flexible polymers, but on their unique solid state properties as well as its behavior in solution [8–10]. Thus, their thermal, mechanical and optical properties enable them for multiple and particular applications.

This review aims to provide an overview of the current knowledge of polymeric materials based on fumaric polymers obtained by radical chain polymerization as well as their properties and fields of application.

2. Synthesis of homo- and copolymers

Few fumaric esters are commercially available; however they can be easily synthesized by two simple consecutive steps. The first of these is

the acid hydrolysis of maleic anhydride, a by-product of the oil industry; and the second is a Fischer esterification by addition of the selected alcohol, Fig. 1.

Alternatively, fumaric acid can be produced by fermentation processes from renewable resources [11,12]. In this way the derived fumaric can be obtained by esterification with an economic and environmentally interesting precursor. This reaction path is according to current trends related to the use of renewable sources as a substitute of raw materials from the oil industry and thus adds value to the use of fumaric monomers.

Radical polymerization of dialkyl fumarates (DRF), was carried out in bulk or solution initiated by thermal decomposition of 2,2′-azoisobutyronitrile (AIBN) or 2,2′-azocyclohexanecarbonitrile (ACN) at 60 °C, as illustrated in Fig. 2 [2].

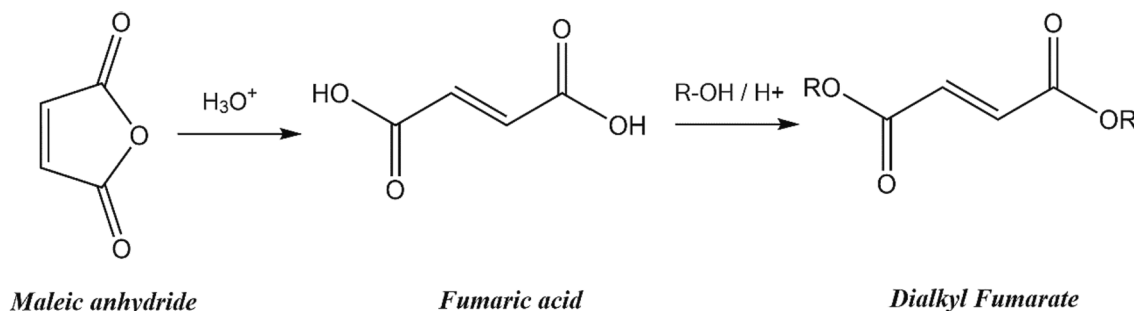In all cases, the product exhibited a less flexible alkyl substituted

Fig. 1. Schematic representation of two-stage synthesis of dialkyl fumarate (DRF).
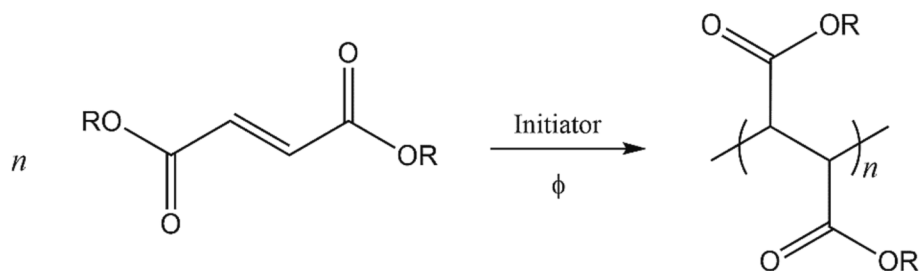
Fig. 2. Schematic representation of the radical polymerization reaction of dialkyl fumarate (DRF).

polymethylene structure than other vinyl or acrylic monomers which have structures derived from monosubstituted ethylenes. A particularity of some bulk polymerizations is that certain monomers lead to heterogeneous systems as the reaction proceeds, due to the insolubility of the polymer in its own monomer. This is the case of diisopropyl and disec-butyl fumarates, where it was preferable to carry out the polymerization in solution. Another singularity of these monomers was that the polymerization reactivities increase when dimethyl 2,2′-azobis(isobutyrate) (MAIB) is used as initiator instead of AIBN, contrary to what was observed for other monomers [13]. Otsu and Yoshioka showed that the rate of polymerization of methyl methacrylate and styrene was independent of the type of initiator used. The behavior of fumaric monomers was attributed to the primary radical generated from AIBN that has lower initiation efficiency than that from MAIB, which lead to the largest values of reaction rate using the latter initiator in the polymerization of DRF. These results were later confirmed by differential scanning calorimetry (DSC) measurement, analyzing the effect of several initiators on the polymerization reaction of different DRF [14].

The preparation of fumarates bearing different alkyl functional groups and the effects of the substituents on polymerization reactivities, structure and properties was subsequently examined [15]. This work showed that the introduction of functional groups in the monomer structure does not prevent *per se* their polymerization, but it renders polymerization complicated, requiring a proper selection of initiator and reaction conditions.

Other polymerization methodologies have been researched, with the aim of achieving reaction rates comparable to those of other vinyl or acrylic monomers. Thus, the emulsion polymerization of diisopropyl fumarate (DIPF) using a redox initiator was studied [16]. It was found that the reaction rate was very much higher than those obtained in bulk or solution polymerization; although at short times (20 min) a limit conversion was reached. This means that the increase in conversion as a function of time is linear up to a certain time, after which the slope decreases until it reaches a plateau beyond which no change in conversion is observed. The effect of different experimental variables on reaction kinetics was analyzed, finding a parallel behavior between conversion and particle number; i.e., a correlation between both variables was verified. In addition, very high apparent activation energies for the propagation and limiting conversion, compared to that observed for other monomers under similar conditions, suggested a complex behavior under the reaction conditions studied.

Alkasssir [17] polymerized diethyl fumarate by gamma irradiation in the range of 50–300 kGy, finding a linear increase in the polymerization yield during the reaction. Although it was possible to reach 90% yields after approximately 5 days, this result indicates that the reaction rate was very low. Data on the molecular weight of the products obtained were not reported.

The application of microwave energy in organic synthesis has been known for many years and its use has spread to polymer chemistry [18,19]. This methodology has been applied to the radical polymerization of some fumaric esters with the aim of improving the polymerization yield by reducing reaction times and analyzing the effect of the monomer structure on the characteristic parameters of polymerization [20,21]. The reaction of DIPF under microwave (MW) condition exhibited some significant differences in comparison with the thermal conventional polymerization previously reported. The results showed an important acceleration of the rate reaction under microwave conditions. Under the same initiator concentration, conversions of 38.6% after 10 min and 31% after 19.5 h for microwave or thermal conventional reactions, respectively, were observed. Differences were also detected regarding the type of initiator used, being benzoyl peroxide (BPO) more efficient than AIBN for polymerization initiation. The weight average molecular weight (M_w) was of the order of 10 Kg/mol with a dispersity (M_w/M_n) close to 2, which suggests that the same radical mechanism of polymerization is operating under microwave conditions. Subsequently, the effect of the structure of DRF on the kinetics of polymerization under microwave irradiation was researched. Dialkyl fumarate with different alkyl group (R: isopropyl, cyclohexyl, 2-ethylhexyl, 2-phenylethyl) exhibited the following reactivity order: DCHF > DIPF > DEHF > DPEF, which is consistent to those previously reported by Otsu et al. [6,7]. Fig. 3 shows the maximum conversion (%Conv) and weight average molecular weight (M_w) attained at 140 W and 20 min of reactions. These results demonstrate the greater efficiency of this methodology to polymerize monomers that are difficult to homopolymerize, such as the fumaric esters referenced here.

Contrary to the low reactivity of fumaric esters towards radical homopolymerization, their copolymerization behavior is known and has been previously studied. Systematic studies of radical copolymerization of DRF were carried out by Otsu et al. [22] in order to analyze the effect of the substituents on DRF reactivities with various vinyl monomers. From the values of the reactivity ratios obtained, it was deduced that DIPF exhibits a high tendency to alternating copolymerization against electron-donating comonomers (styrene, N-vinylcarbazole, isobutene or vinyl esters), while its reactivity decreases with electron-withdrawing monomers (methyl acrylate, methyl methacrylate and acrylonitrile). In addition, it was demonstrated that the relative reactivity of DRFs with different ester substituents toward a polystyryl radical depends on both steric and polar effects of the particular ester groups. Similar results were found by other researchers using bulky fumarates and fumaramides with electron-rich comonomers [23]. On the other hand, the copolymerization behavior between two different DRF has also been studied and in these cases the copolymers presented a random distribution of comonomers [24].

The radical polymerization under microwave conditions methodology was also applied to copolymerization reactions of this type of monomers. Copolymer of DIPF and benzyl acrylate (BA) or p-nitrobenzyl acrylate (NBA) with different composition, using benzoyl peroxide as initiator were prepared and the reaction conversion and reactivities ratio (r_i) were analyzed [25,26]. These studies showed an important reaction acceleration when the copolymerization was carried out under microwave conditions, as it can be seen by comparing the reaction rates (%Conversion/time) for both systems in Table 1.

Both systems exhibited a different copolymerization behavior, only dependent on comonomer pairs (independent of the heating conditions carried out during the reaction). The $r_1 \times r_2$ value found for the DIPF/BA system indicated a preference of both propagating macroradicals toward
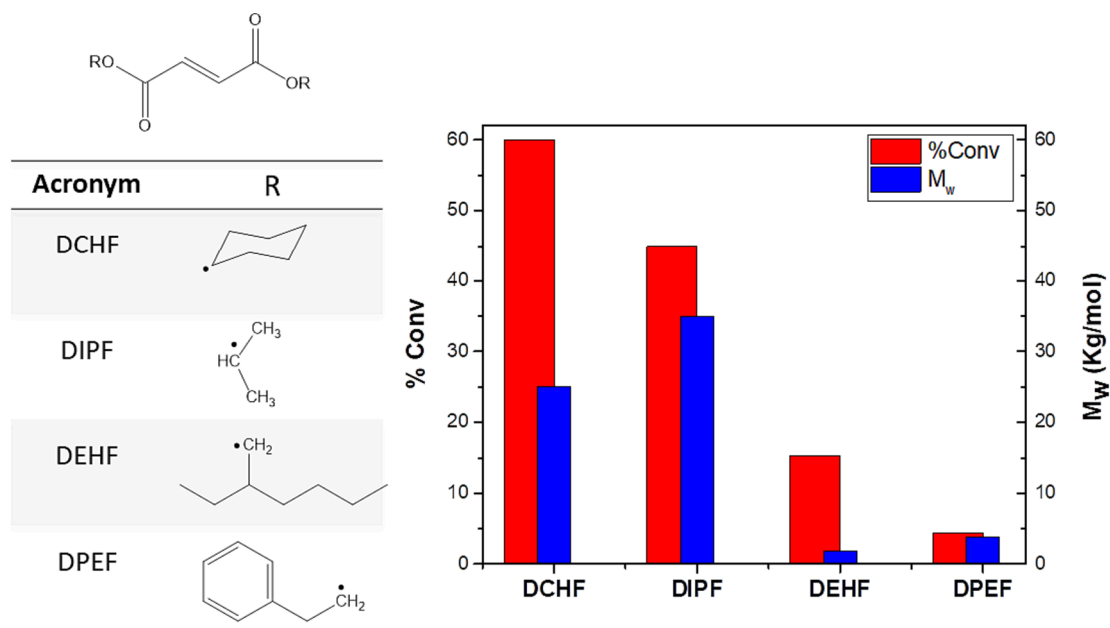
Fig. 3. Structure of DRF polymerized using benzoyl peroxide under microwave conditions (140 W, 20 min), percentage of reaction conversion (%Conv) and weight average molecular weight (M_w).

Table 1
Reaction rates (%Conversion/t) and the product of reactivities ratio ($r_1 \times r_2$) for copolymerization of diisopropyl fumarate/ benzyl acrylate (DIPF/BA) and diisopropyl fumarate/ p-nitrobenzyl acrylate (DIPF/NBA) under microwave (MW) or Thermal conditions.

Experimental parameter	Condition	DIPF/BA	DIPF/NBA
%Conversion/t	MW	1.30	1.8
	Thermal	0.02	0.03
$r_1 \times r_2$	MW	0.152	1.38
	Thermal	0.032	2.17

consecutive homopolymerization, while this value for DIPF/NBA system suggest a random distribution of the monomeric units along the polymeric chain, with some preference for NBA monomer addition.

Living radical polymerization is a chain polymerization in which the kinetic chain carriers are radicals and chain transfer and termination reactions are absent. It is appropriate to clarify that there has been considerable debate about the correct terminology to use for these systems [27]. However, the term "reversible-deactivation radical polymerization" (RDRP), as an encompassing terminology, was recommended by IUPAC in 2010 [28]. Various RDRP techniques are currently available to produce polymers with well-defined structure, dispersity and average molecular weight. It is beyond the scope of this review to introduce a detailed description of the mechanism involved in each of the RDRP methodologies, which can be found in excellent articles and reviews published [29–32].

Matsumoto and coworkers deeply studied the homo and copolymerization of DIPF under different controlled polymerization mechanisms [33]. Nitroxide-mediated radical polymerization (NMP), uses a radical initiator and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) to produce an active and stable radical to control the reaction. The authors carried out DIPF polymerization with and without TEMPO obtaining similar M_n, under both conditions. These results suggested that the homopolymerization ran out of control, which could be due to insufficient initiation. The polydiisopropyl fumarate (PDIPF) was also performed by atom transfer radical polymerization (ATRP) technique, employing two different commercial ligands. This mechanism involves the generation of radicals via an organic halide undergoing a reversible redox process catalyzed by a cuprous halide-based transition metal compound. The cuprous halide is bound to a ligand that promotes its solubilization in the organic reaction system. Although in all cases the molecular weight increases with the reaction time, indicating a control of polymerization, the reaction conversions did not exceed 30%. The authors suggest that Cu (II) (persistent metallo-radical that reduces the steady-state concentration of propagating radicals and minimizes normal termination) is accumulated, and the bimolecular termination occurs suppressing the polymerization. Other polymerization mechanisms, such as organotellurium mediated-living radical polymerization (TERP) and reversible chain transfer catalyzed polymerization (RTCP) were assayed. PDIPF was obtained with controlled molecular weight and molecular weight distribution, but M_n was less than 10^4 and the dispersity was 1.3–1.7; in addition, the reaction conditions were limited.

Given this performance, reversible addition-fragmentation chain transfer (RAFT) polymerization was tested. The RAFT mechanism controls the reaction by the use of a chain-transfer agent (CTA), appropriately selected according to the nature of the monomer [34]. PDIPF was produced using 2-(methoxycarbonyl)-2-propyl dithiobenzoate (MDB) and MAIB as CTA and initiator, respectively. Although a deviation from the theoretical M_n value was observed from 60% conversion, as can be seen in Fig. 4, the reaction conversions reached more than 80% and M_n values close to 10^4 g/mol.

Although it was not possible to obtain PDIPF by RAFT mechanisms with M_n greater than 10^5, the spectroscopic characterization of polymers obtained indicates that the final chain contains the dithiobenzoate moiety end from CTA. Thus, that polymer was used as the macro-CTA agent for block copolymer synthesis, using 2-ethylhexyl acrylate (EHA) as second monomer. After 20 h of reaction it was possible to obtain a block copolymer with narrow dispersity, 13×10^3 M_n values (in accordance to theoretical ones), 68% conversion and the percentage molar monomer composition of DIPF in the block copolymer was approximately 50%. The conversion results were corroborated by size exclusion chromatography (SEC) and nuclear magnetic resonance (NMR) and together indicate a good control of the copolymerization reaction using the macro-PDIPF.

Matsumoto and coworkers also tested the copolymerization between macro-CTA and tetraethylene glycolmonoacrylate (TEGA) monomer, but a variation was observed between the theoretical and experimental values of M_n, which could indicate transfer reactions on the long and
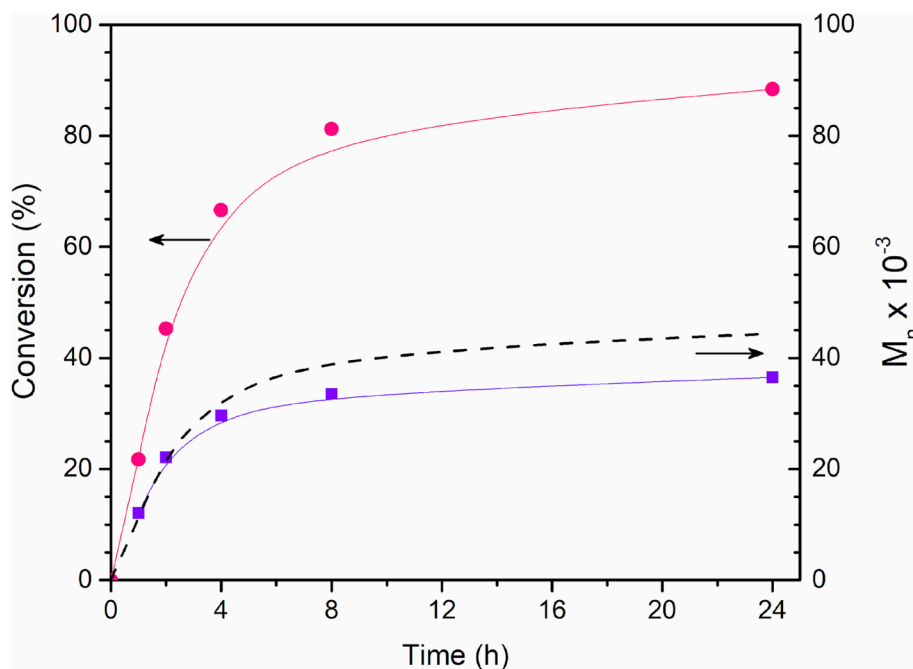
Fig. 4. Plots of Conversion and Mn versus time for the RAFT polymerization of DIPF in bulk at 80 °C, [DIPF]/[MDB] = 250 and [MAIB]/[MDB] = 0.35 M ratio. The dashed line indicates the theoretical M_n values. (Adapted from Ref [33] with John Wiley and Sons permission).

hydrophilic pendant chain of the repeating unit of the second monomer [33]. Both block copolymers were colored (due to the presence of CTA at the end of the structure), which was removed by treating the polymers with a reducing agent. The copolymer structure (corroborated by NMR and Fourier-transform infrared spectroscopy, FTIR) and the molecular weight (corroborated by SEC) were not modified. In addition, reverse copolymerization (from macro-DIPF as CTA) were tested but the process was less efficient.

Takada et al. also synthesized AB and ABA block copolymers employing DIPF and HEA monomers by RAFT mechanisms, using an adequate CTA for each case [35,36]. The yellow polymers were discolored by reaction with n-butylamine in order to improve the coloration and other optical properties of the transparent polymers. However, the molecular weight after that reaction shows an additional peak with a value twice the original molecular weight, suggesting that coupling reactions between the ends of the polymeric chains occurred during the reduction process.

In addition, other copolymers including fumaric monomers, with different structural characteristics have been obtained by Sato et al [37]. The authors synthesized graft copolymer with a flexible backbone and rigid branches (Fig. 5). First, the macromonomer was produced by addition-fragmentation chain transfer (AFCT) to obtain PDIPF macromonomers (PDIPF MM), and then PDIPF MM was copolymerized with ethyl acrylate by conventional radical polymerization to obtain the graft copolymer. From the synthesized polymers, films were obtained that turned out to be transparent from ultraviolet (UV) to visual regions and showed a microphase separated structure.

2.1. Properties

The polymethylene structure of polydialkyl fumarate (PDRF) was deduced by ^{1}H and ^{13}C NMR spectroscopy, while its partially crystalline structure was analyzed by X-ray diffraction studies [5,38]. Further evidence of crystalline order and orientability was provided by the X-ray experiments which showed one equatorial (11.16 Å) and two meridional (4.81 and 2.40 Å) reflections respectively, which suggest a cylindrical structure with 13 Å in diameter [39], in agreement to the aforementioned results.
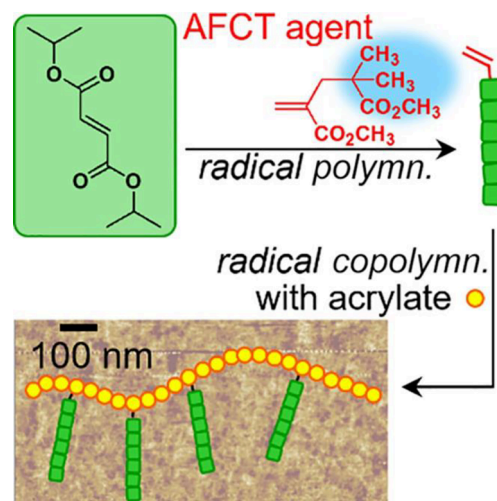

Fig. 5. Graphical illustration of the procedure development for graft-copolymer synthesis. (Reproduced from [37] with John Wiley and Sons permission).

The polymerization mechanism of DRF was elucidated through the analysis of the stereochemical structure of homo- and copolymers by means of ^{13}C NMR spectroscopy [40–42]. Tacticity studies suggest a preferential formation of *meso* diads by double bond opening during the propagation step, essentially leading to an atactic structure.

Solution properties of DIPF and diethyl fumarate (DEF) polymers were undertaken with the intention of substantiating the less flexible nature of fumarate homopolymers [43,44]. It is known that *a* parameter of Mark-Houwink-Sakurada equations, which links the intrinsic viscosity [η] of a polymer solution to the viscosity average molecular weight (M_η), is dependent on the shapes of macromolecules in solution. Thus, a value of 0.98 in benzene or tetrahydrofuran (THF) at 30 °C was found for PDIPF, while this value decreased to 0.87 for polydiethyl fumarate (PDEF), at the same conditions. These results indicated that the rigidity of the chain sensitively depends on the bulkiness of the ester groups.

Analysis of several PDRF by DSC revealed that most of this type of

polymer does not show a glass transition temperature (Tg) below their degradation temperature [6,15,23]. However, in some of them it was possible to show this transition, which was attributed to the motion of ester groups along the macromolecular main chain. This Tg could be modulated by the effect of the comonomer, as demonstrated in different cases [25,45].

For a large number of applications of polymeric materials it is necessary to know their degradation temperature, as well as the processes involved. This the case of important industrial practices such as reactive extrusion or injection for thermoforming, sterilization processes of biomaterials, or during functionalization reactions of synthetic or natural polymers, to mention a few examples. Bearing in mind these premises, studies of thermal degradation of fumaric homo and copolymers have been undertaken. All fumarate homopolymers exhibited high temperature of thermal degradation, as evidenced by thermogravimetric analysis (TGA) [5,6]. PDIPF as well as PDMF and polydiethyl fumarate (PDEF) degrade at 250 °C in one step, being the alcohol and the corresponding monomer the main degradation products. On the other hand, tertiary alkyl esters, such as polydi-*tert*-butyl fumarate (PDtBF) and polymethyl-*tert*-butyl fumarate (PMtBF) degraded by a two-step mechanism, the first of which was observed at 190 °C and corresponds to the elimination of isobutene, while the second stage occurs at 290 °C. Subsequently, the degradation of PDEF was analyzed in detail [46]. It was concluded that the polymer degrades above 200 °C by cleavage of the pendant ester group to produce ethylene and ethanol with the production of maleic anhydride moieties in the polymer residue, as shown in Fig. 6. Then, at temperatures above 300 °C the random main-chain scission of C–C bonds start to occur, leading to monomer release. All these products were verified by chromatographic and spectroscopic methodologies.

Similar degradation mechanisms were proposed for some copolymers of fumarate esters. Copolymers of di-n-docosyl fumarate (DnDF) with vinyl acetate and n-alkyl (meth)acrylates exhibited a single step degradation mechanism between 220 and 400 °C [47]. On the other hand, the thermal behavior of NBA and DIPF copolymers with different comonomer composition was studied by SEC and gas chromatography-mass spectrometry (GC–MS) [26]. All copolymers exhibited two-stage decomposition processes and showed higher initial decomposition temperatures (280–290 °C) than the corresponding homopolymers, which suggests higher thermal stability. From the analysis of degradation products a mechanism of decomposition including pending group and main chain scission initiated from the stable radical aromatic has been proposed.

Mechanical properties of PDIPF and copolymers with similar monomers were evaluated on membranes which thicknesses were in the range of 20–30 μm [24]. For PDIPF, elongation at break was very small; while an elastic modulus of 106.04 MPa was determined, suggesting a fairly inelastic and very brittle material, similar to methacrylic polymers. The inclusions of other fumarate comonomers with n-alkyl substituent increase the elongation at break but decrease the tensile strength.
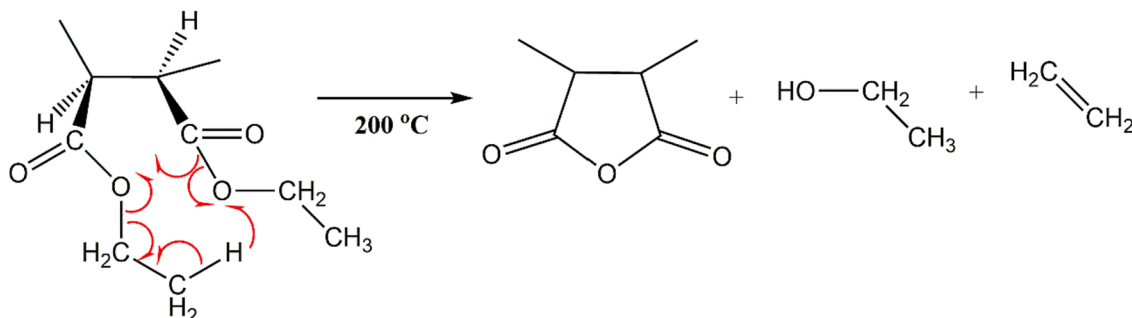
The ability of homo and copolymers of fumaric esters to form insoluble monolayers was analyzed on an aqueous subphase [23]. The behavior of some DRF and fumaramides, as well as that of its copolymers with electron withdrawing comonomers was analyzed. Due to the rigidity of the polymer backbone it was found that the long hydrophobic chains interfere with spreading, but hydrophilic groups located in the polymer shell favor spreading. Besides, the best monolayer features were not obtained for the most hindered and thus most rigid homopolymers, but for the more flexible homo- and copolymers.

Very interesting properties of styrene and fluoroalkylfumarate (FAF) copolymers were analyzed due to the interest of modifying polymer surfaces by attaching other functional molecules [48]. The incorporation of the fluoroalkyl group in the macromolecular structure confers high hydrophobicity, even at low concentrations of this group. Through partial hydrolysis it is possible to generate carboxylic groups that would potentially allow the surface union of biomolecules.

The thermoresponsive behavior of membranes prepared from dioctyl fumarate-N-isopropylacrylamide copolymers (DFN) with different compositions was thoroughly analyzed using DSC and transmittance measurement [49]. The thermo-sensitive behavior can be easily adjusted by varying the copolymer composition and a different behavior was observed from other studied systems, because in this case, the low critical solution temperature (LCST) increases when a greater amount of the hydrophobic monomer is incorporated into the copolymer. These results have been attributed to several factors such as hydrogen bonding, hydrophobic-hydrophilic interactions, composition, and chain stiffness, due to the inclusion of a bulky monomer (1,2-disubstituted ethylene). The membranes were completely transparent at low temperature and became opaque above their LCST. This observation is a macroscopic evidence of phase transition, as it can be seen in the image inset of Fig. 7.

It was also very interesting to observe that thermoresponsive behavior significantly influences the swelling capacity, superficial hydrophilicity, and cellular response. Both cell viability and osteoblastic cell differentiation were dependent on the surface topography and the hydrophilic–hydrophobic state in which the materials are at body temperature. Thus, these properties could be very useful for various applications in the field of regenerative medicine.

3. Applications

Knowledge of the properties of fumaric homo and copolymers has prompted the development of new materials designed for different applications in various technological fields. Among them, biomaterials stand out for their applications in biomedicine as well as in energy areas, such as those linked to road and oil engineering.

3.1. Biomedical applications

Polyesters derived from fumaric acid have been firstly synthesized by Mikos's group and their applications directed to biomedical field have experienced significant development over the last 30 years [50,51]. In
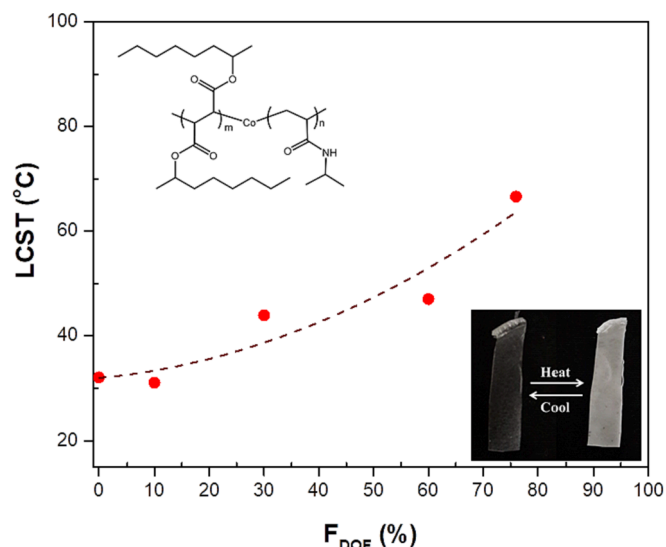

Fig. 6. Schematic illustration of the partial degradation mechanism of PDEF.

Fig. 7. LCST values in function of dioctyl fumarate (DOF) content in the copolymer (F_{DOF}). Insert: copolymer structure and scaffold image after and before ~~of~~ the phase transition.

contrast, the use of homo- and copolymers derived from fumaric ester obtained through chain polymerization, with a polymethylene backbone structure, is more recent.

Particularly, for in tissue regeneration applications, films of PDIPF and polydicyclohexyl fumarate (PDCHF) were prepared, and their biodegradation and biocompatibility were analyzed to develop scaffolds which can support osteoblastic growth [52]. The studies were carried out with two cells lines (UMR106 and MC3T3E1 osteoblastic lines), and compared with two polyester films: poly-β-propiolactone (PBPL) and poly-ε-caprolactone (PCL). It was found that these cells grow adequately on all polymeric matrices, albeit with some preference for the polyesters, Fig. 8.

Biodegradation studies of PDIPF labeled with a chromophore, showed that this material can be degraded by RAW264.7 macrophages demonstrated by the decrease of the average molecular weight at 21 days. Morphological change on cells was observed, from a rounded monocytic appearance to an activated phagocytic phenotype as can be seen in Fig. 9. These results suggested that this polymer can be degraded by a phagocytic process through an oxidative and not hydrolytic mechanism, as was also observed for other polymers containing a C–C catenary structure [53].

To improve the mechanical properties of PDIPF, a mixture of PDIPF

and PCL, compatibilized by ultrasound, was prepared and several properties analyzed [54]. The mechanical properties of this blend were comparable to those of the trabecular bone and the biological studies showed no evidence of cytotoxic effects. In addition, the biocompatibility assay demonstrated that osteoblasts plated on the compatibilized blend adhered to and proliferated more than homopolymers. Later, this compatibilized mixture was used to develop scaffolds with improved properties of osteoconductivity and osseointegration by electrospinning as well as nanocomposites with nanohydroxyapatite, all of which led to biomaterials suitable for bone tissue engineering [55–57].

A borax cross-linked scaffold based on partially hydrolyzed diisopropyl fumarate-vinyl acetate copolymer (PFVH) and chitosan directed to osteochondrondral tissue engineering was developed and its properties and potential applications in osteocartilaginous regeneration analyzed [58]. Fig. 10 presents the illustration of this system.

The results demonstrated that the borax cross-linked scaffold exhibited hydrogel behavior with appropriate mechanical properties for bone and cartilage tissue regeneration, without evident signs of cytotoxicity when evaluated in an in vitro system. These studies were later extended to show that this biomaterial can be nanostructured using anodized aluminum oxide (AAO) templates [59]. Nanorod-like scaffolds with a diameter comparable to those of collagen fibers of the bone matrix (170 and 300 nm) were obtained. These matrices allowed the adhesion and proliferation of bone marrow progenitor cells (BMPC) and chondrocyte cells without inflammatory response on in vitro assay, as outlined in the Fig. 11.

Microspheres of natural microgel were prepared based on this biomaterial as an innovative three-dimensional support for bone marrow mesenchymal stem cells (BMSCs) culture in 3D environments, expanding the range of possible applications in regenerative medicine [60]. It was found that the BMSCs grew in this system with a proliferation rate like the 2D culture but growing in biomimetic microenvironments which promotes the formation of aggregates with multidirectional cell–cell interactions. This material proved to be very versatile in terms of its design capacity according to the intended application.

Subsequently, two families of functional fumaric copolymers based on DIPF and poly(ethylene glycol) methyl ether methacrylate (OEGMA) or N-isopropylacrylamide (NIPAM) were prepared by conventional radical and RAFT polymerization to obtain linear or star architectures, respectively [61]. The TGA analysis proved that the branched star copolymer was thermally less stable than its linear counterpart, without observing significant differences in the maximum decomposition temperature according to the architecture of the copolymers.

The biocompatibility and cytotoxicity studies carried out with Raw macrophages cells, showed that none of the materials obtained exhibit
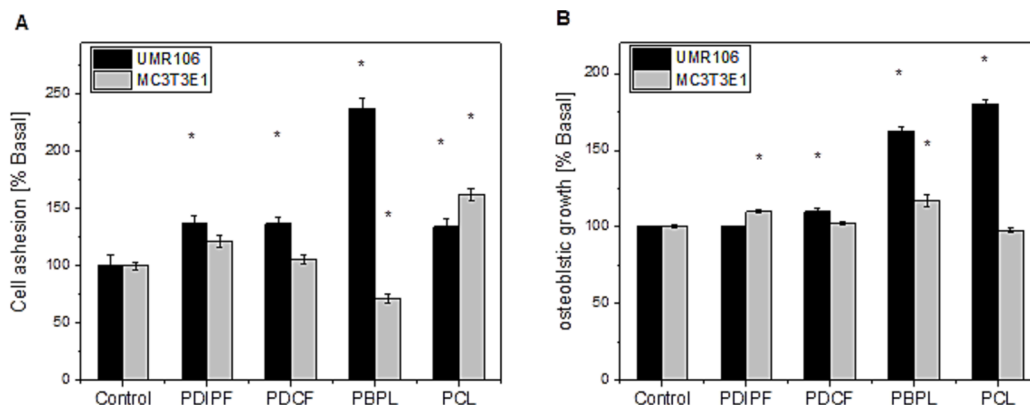

Fig. 8. Adhesion (A) and proliferation (B) of osteoblasts on culture plates (as control) or polymeric scaffolds. Cells were plated on a polystyrene control dish or on different polymeric matrix-coated dishes and incubated for 1 h (A) or 48 h (B). Results are expressed as a percentage of basal. Each bar represents mean $\pm$ sem (standard error measurement) * p < 0.05. (Adapted from Ref [52] with John Wiley and Sons permission).
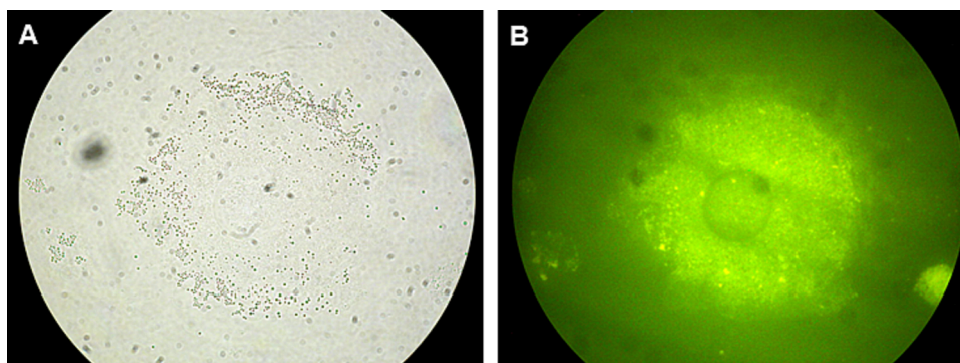
Fig. 9. RAW264.7 macrophages growing on labeled PDIPF. Cells were cultured on a fluorescent PDIPF matrix for 20 days. Light (A) and fluorescent (B) microscopy revealed the presence of fluorescent particles included in the cytoplasm of activated macrophages. Obj. 40x (Reproduced from Ref [52] with John Wiley and Sons permission).
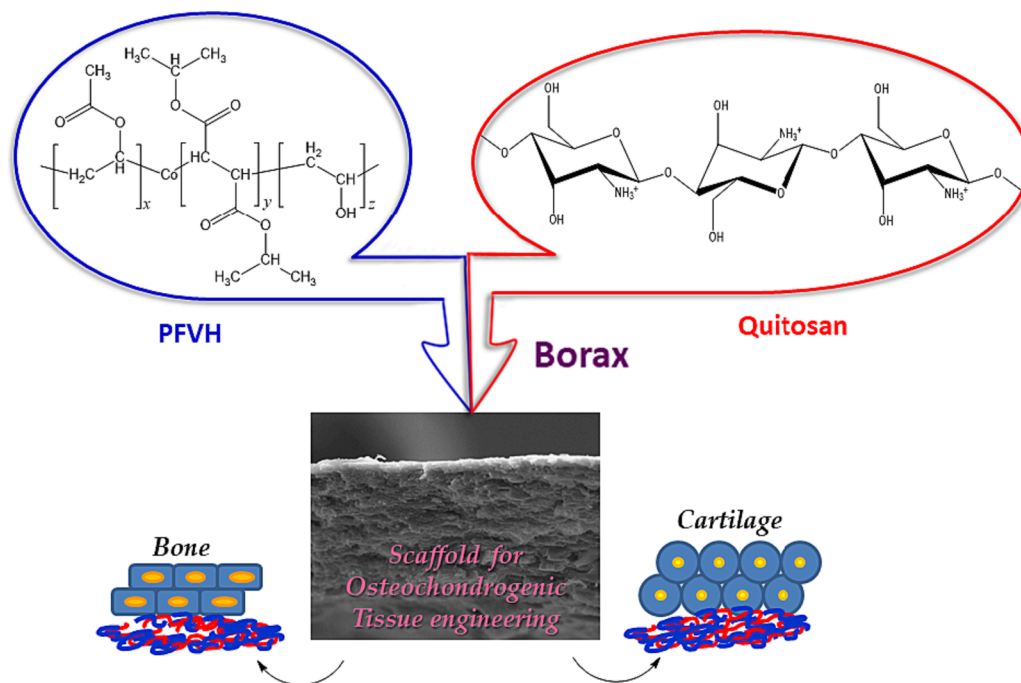

Fig. 10. Schematic representation of scaffold development for osteochondrogenic tissue engineering by combination of PFVH and chitosan.

cytotoxicity, although the cells grew better on the matrices prepared by casting of copolymers including NIPAM, indicating an improved interaction of these cells with the surface of this material. Fig. 12 summarizes these findings.

Based on these previous developments, another fumaric copolymer was synthesized starting with DOF and N-isopropylacrylamide (NIPAM), using two azo initiators (AIBN and MAIB), which exhibited different initiation efficiency [62]. The copolymer prepared exhibited different macromolecular characteristic: for the same mole fraction of DOF in the feed (f_1 value), a higher DOF content in the copolymer was found when MAIB was used as initiator, due to the lower reactivity of the DOF with respect to NIPAM and the highest reactivity of initiation of the primary radicals generated by MAIB. In addition, the morphological characteristics of scaffolds obtained from two samples (with similar composition) prepared by casting and electrospinning were analyzed, noting that the composition influenced the surface roughness more significantly in the samples prepared by casting, Fig. 13. On the other hand, 3D fibrous scaffolds were obtained by electrospinning methodology, consisting of random fibers of similar diameters (3 μm) with high porosity.

Adhesion, proliferation and osteoblastic differentiation studies carried out with BMPC cells showed greater cellular viability on materials obtained by electrospinning technique. Although all scaffolds exhibit good osteogenic capacity, it was significantly increased on materials with more fumaric content and more homogeneous surface (by casting technique). These results suggested that all the biomaterials have excellent characteristics to be applied in bone tissue regeneration although the fibrous membranes will allow a better flow of nutrients.

Finally, a new hybrid biomaterial that combines a fumaric terpolymer with a biopolymer (chitosan, Ch) was prepared [63]. The terpolymer was synthesized by radical polymerization based on DIPF, vinyl benzoate (VBz) and 2-hydroxyethyl methacrylate (HEMA). The best relationship of DIPF:VBz:HEMA was 5:4:1, which allowed efficient interaction with chitosan through cross-linking with borax to achieve stable scaffolds. The 1:3 ratios of polymers (Ch/terpolymer) with 4% borax allowed us to obtain the best membrane. Both physical appearance and SEM images showed excellent compatibility between both polymers, which was verify by DSC analysis, Fig. 14.

These characteristics together with the swelling capacity (140% at equilibrium), good mechanical properties (elastic modulus, tensile strength and elongation at break, were 1.0 ± 0.2 MPa, 0.20 MPa $\pm$ 0.03,
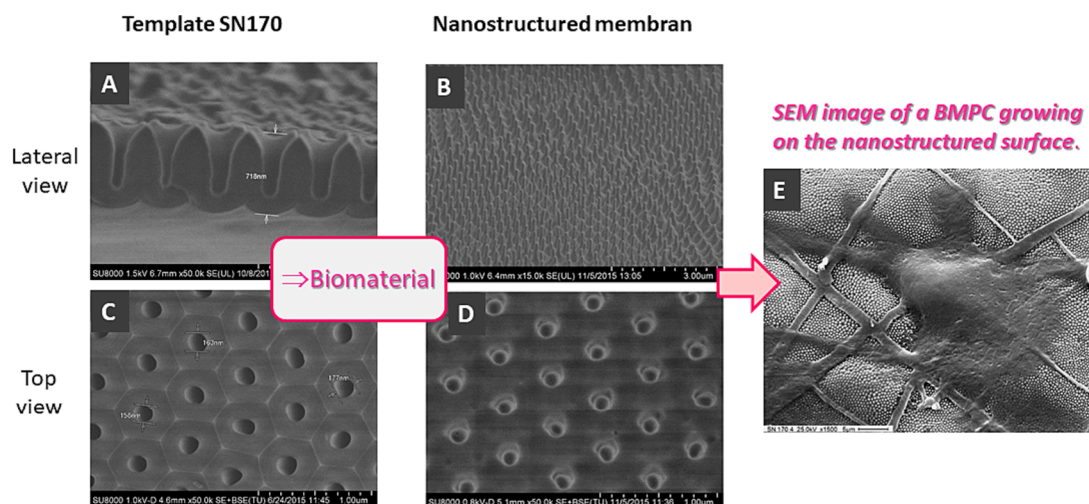
Fig. 11. Scanning electron microscopy (SEM) images of template NS170 and nanostructured membrane: 3D lateral view (A, B) and top view (C, D); SEM image of a BMPC growing on the nanostructured surface (E). (Adapted from Ref [59] with John Wiley and Sons permission).
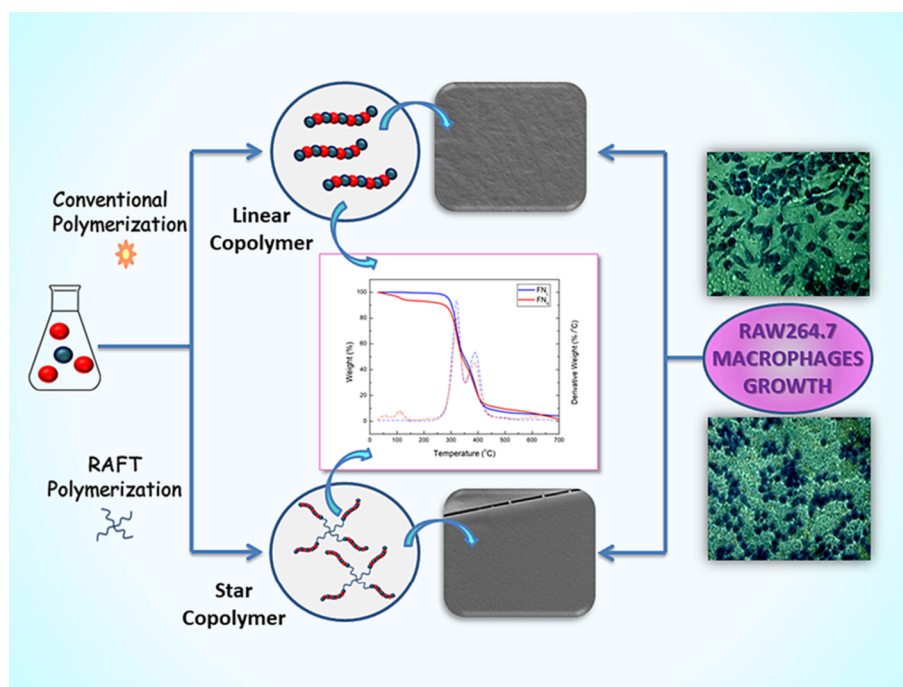

Fig. 12. Synthesis, characterization and cytotoxicity evaluation of poly(DIPF-co-NIPAM) scaffolds. (Reproduced from Ref [61] with John Wiley and Sons permission).

and 4.8 ± 1.5%, respectively) and good biocompatibility, without evidence of cytotoxicity suggested that the designed material could be applied in scaffolds for osteochondral engineering.

Fumaric copolymers were also employed in other biomedical applications such as transdermal drug delivery systems (TDDS). Pasqualone et al. synthesized copolymers from vinyl acetate (VAc) and DIPF or DOF, respectively. The characterization of VAc/DOF copolymer membranes suggested that swelling, mechanical and superficial properties are adequate for this application [64]. Particularly, copolymers with VAc: DOF (60:40) compositions were employed to design a risedronate (R) delivery system to be used for treatment of osteoporosis. The membrane obtained exhibited good flexibility, transparence and high homogeneity as can be seen in Fig. 15. The kinetic of drug release was initially burst, reaching the plateau at the first hour or at 96 h, for 6% or 12% w/w of R, respectively. Under both conditions a 70% drug release was observed,

suggesting that this system could be useful for osteoporosis treatment without adverse effect [65].

3.2. Energy applications

Some alkyl fumarate-vinyl acetate copolymers (DRF-co-VAc) of different molecular weight were prepared based on behenyl fumarate (docosanol, C22) in order to study the structural effect on the efficacy as flow improver/pour point depressant on the three Indian waxy crude oils [66]. The crude oils were characterized by its wax (12%) and asphaltene (<0.5%) contents. It was found that highest molecular weight copolymer is the best additive for crude oils having a broad range of normal paraffins and lower average carbon numbers, while the addition of the lowest molecular weight copolymer resulted in the best efficacy for crude oils containing a narrow range of normal paraffins
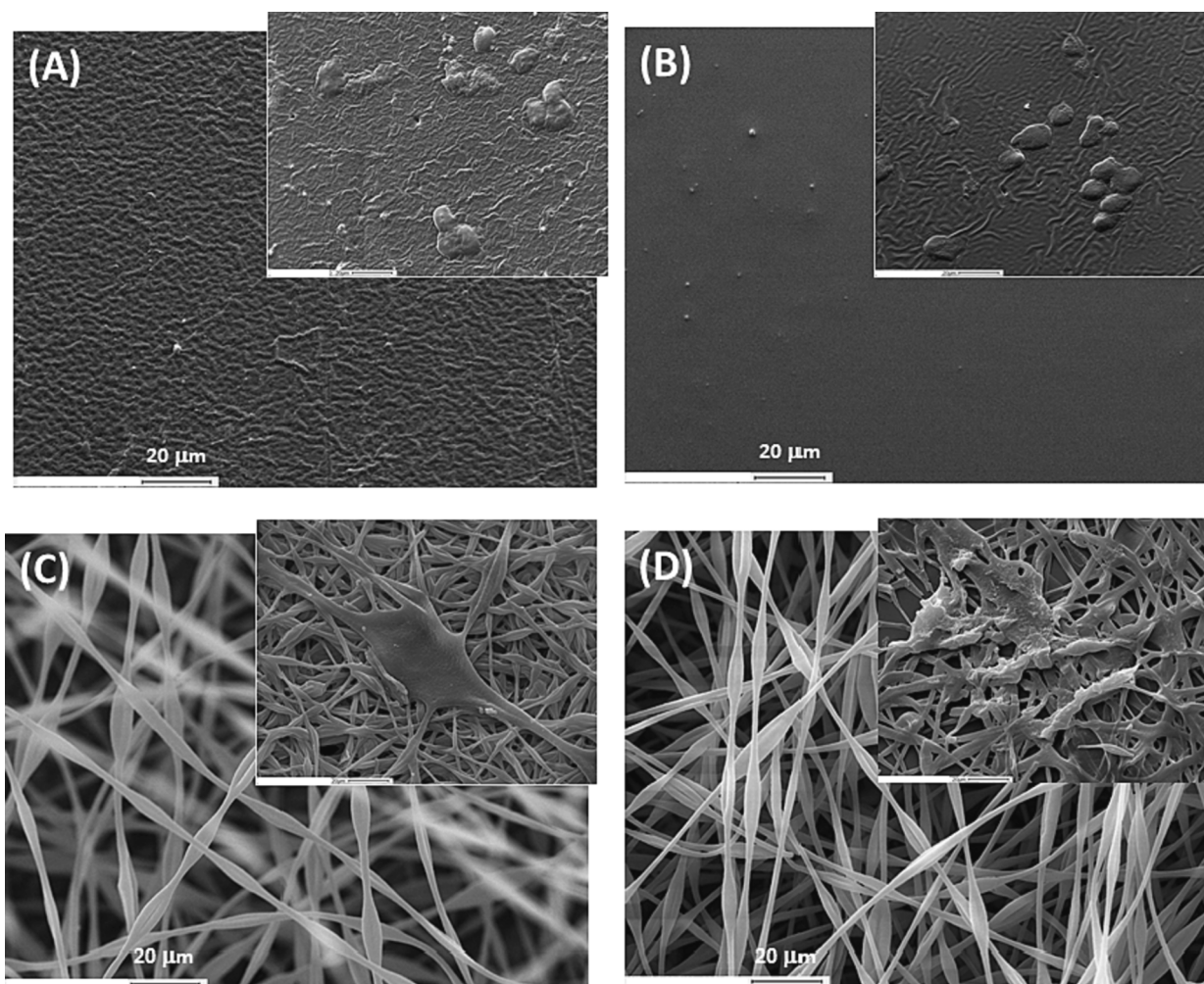
Fig. 13. SEM images showing the surface morphology of scaffolds: (A) and (B) solution-cast films of copolymers with 10 and 30% fraction molar of DOF, respectively; (C) and (D) fibrous scaffolds formed by electrospinning of copolymers with 10 and 30% fraction molar of DOF, respectively. Insert images show BMPC growing on each surface (24 h). Magnification 500 ×.

with higher average carbon numbers.

Later, n-dioctadecyl fumarate (DODF) and vinyl acetate copolymers were prepared and their properties as flow improvers for viscous oil and residual oils were analyzed [67]. The DODF content in the copolymers was between 45.9 and 97.8 mol%, and M_n were close to 10^4 g/mol. The authors found that the more the crystalline CH_2 number on the side chains, better the lattice match between copolymer and wax crystal structure of oils.

Copolymers of DRF (DRF, R = C6, C12, C18) and VAc or vinyl pyrrolidone (VP) were prepared and their effect as viscosity index and flow improvers was studied [68]. The copolymers including VP were more efficient than VAc copolymers, as well as those that included the highest chain length of the alkyl group.

An alternative for obtaining copolymers of 1,2-disubstituted ethylenic derivatives for those applications was subsequently proposed using maleic anhydride as precursor monomer [69]. The copolymers of octadecyl acrylate (ODA) and maleic anhydride (MA) were prepared and then esterified with dodecanol, as can be schematized in Fig. 16.

Copolymers with benzyl alcohol were also obtained. Both kinds of copolymers were tested as additives of waxy crude oil and their effects on the pour-point and rheological behavior were analyzed. It was concluded that the polymer containing aromatic rings showed the best performance, which decreased the pour point by 19 °C, the yield stress as well as the viscosity to a large extent.

Similar methodology was used for preparing copolymers of vinyl acetate and dodecyl, stearyl, or behenyl fumarate, used as petroleum additives and whose performance as pour point suppressant and flow improver for Egyptian waxy crude oil was evaluated [70]. It was observed that stearyl derivative copolymer with 1:2 feed ratio showed the best efficiency as pour point suppressant even at low concentration while octadecyl derivative copolymers with 2:1 feed ratio is effective as flow improver.

Subsequently, varied compositions of copolymers based on DOF and VBz with different molecular weights were synthesized and characterized [71]. These copolymers were used as additives at different concentrations to evaluate the effect of these variables on their performance as flow improvers in a waxy crude oil composed of paraffin with high average carbon number and a narrow carbon number distribution. Based on the DSC and rheological measurements, it was concluded that the copolymer of low molecular weight and high DOF content is more effective as flow improver, while polymers of higher molecular weight and VBz content produced an unwanted effect that worsened flow properties of waxy crude oil at low temperatures.

The fumaric copolymers were tested as asphalt modifiers, as well. Oberti et al., synthesized DOF and styrene copolymers with different monomer contents and molecular weight distributions to employ as asphalts modifiers, Fig. 17 [72]. The monomer selections were based on asphalt composition due to the fact that it has aromatic (compatible with styrene) and aliphatic (compatible with DOF) components. The reaction was carried out by radical polymerization employing AIBN as initiator
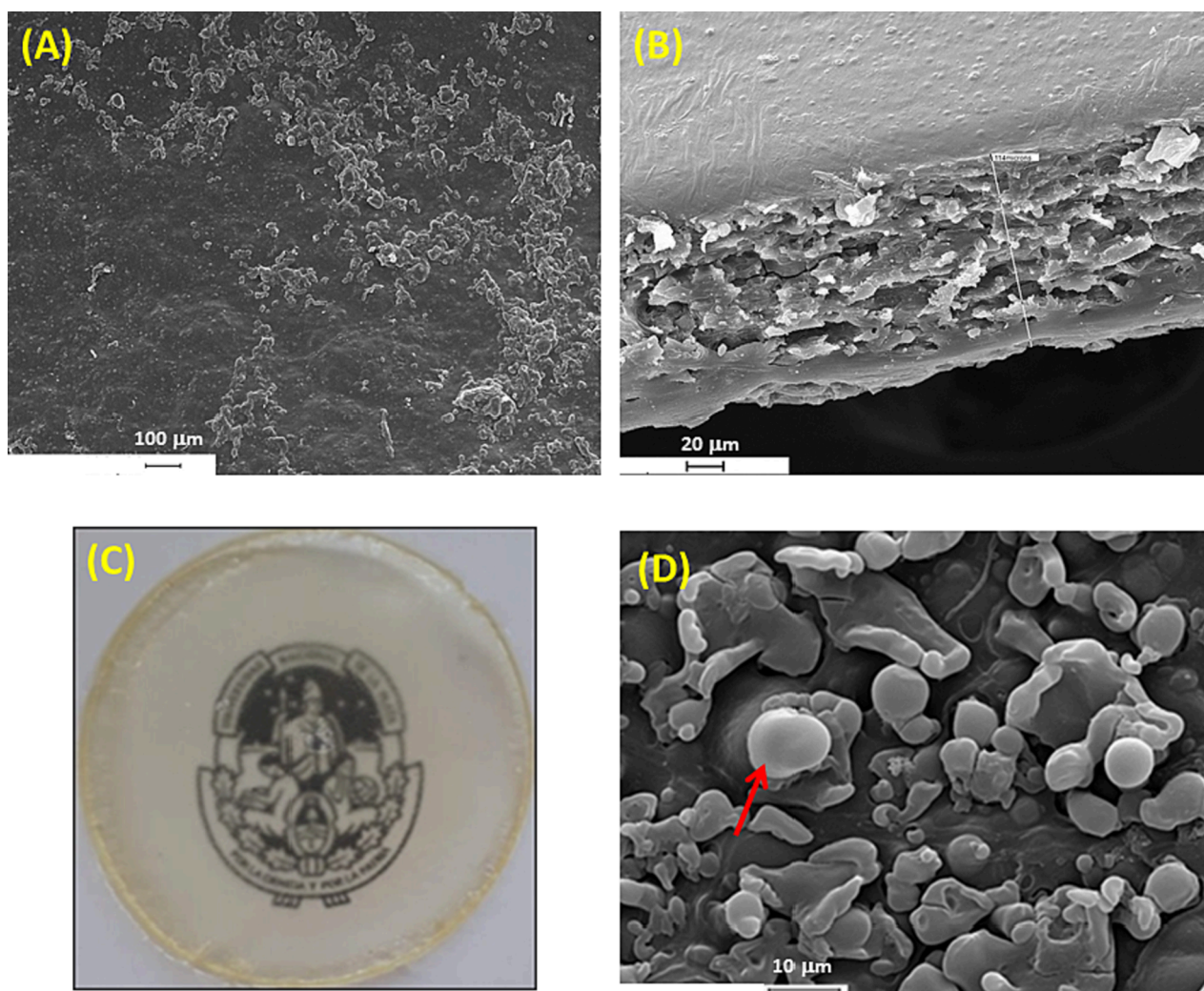
Fig. 14. SEM images of scaffold prepared from 1:3 ratios of chitosan/terpolymer with 4% borax: (A) surface and (B) cross section; (C) macroscopic aspect of membrane; (D) SEM image of RAW 264.7 cells (arrow indicates) growing on the surface of the membrane. Magnification x1000. (Adapted from Ref [63] with John Wiley and Sons permission).

and was performed with and without toluene as solvent. Spectroscopic characterization showed a 60%mol DOF in the copolymers and the molecular weight of the different copolymers varied between 45 and 118×10^3 g/mol. The original asphalts were modified with two different polymers contents and its properties (penetration, softening points, viscosities, and elastic recovery) were tested. The mix compatibility was analyzed by DSC analysis and fluorescence microscopy, observing bright spots (polymer) distributed on a dark homogeneous background (asphalt) in the last case. This indicated that only 60 min at 170 °C of mixing were necessary to make the synthesized copolymer compatible with the original asphalt. Another observation was that the copolymer with higher Mw produced a significant effect over viscosity of modified asphalts, however the polymer content did not produce any change over the final properties of the material.

4. Conclusions and future perspectives

Since the first basic research systematic studies on radical polymerization reactions carried out by Otsu and his group in the 1980 s, interest in polyfumarates has grown widely, opening up the doors to future research and promising applications. Likewise, the study of properties of this type of polymers has highlighted that their features are, in many cases, similar to those of polymers or copolymers derived from methacrylics esters, which would position them in the market as alternative

materials to these.

Fumaric homopolymers exhibit a more rigid chain than other ethylenic polymers with flexible chain and different reactivity of polymerization depending of initiator, (MAIB or AIBN). These characteristics give them particular properties that clearly differentiate them from other widely known polymers. Spectroscopic and crystallographic studies allowed determining a structure generally atactic. Regarding its thermal properties, it can be mentioned that Tg values are not generally observed; however if they exist, it can be modulated with the incorporation of a comonomer. In addition, the fumaric polymers usually begin to decompose around 200 °C in one or two stage processes. Another important property is its high elastic modulus and tensile strength, which gives it glassy properties, probably due to the rigidity of the chain.

It is concluded that, although these monomers have a low tendency to homopolymerize, their very particular and different characteristics from vinyl monomers constitute a challenge for the scientist trying to polymerize them. Thus several methodologies have been tested. Although emulsion polymerizations allow high molecular weights to be obtained, the conversion reaches a limit that cannot be exceeded. Gamma radiation was also used as the initiation system, but the polymerization times were very long (5 days). On other hand, microwave reactions showed a higher polymerization speed, achieving in some cases up to 60% conversion in only 20 min. In addition, the copolymerization of this type of monomers with other vinyl monomers under
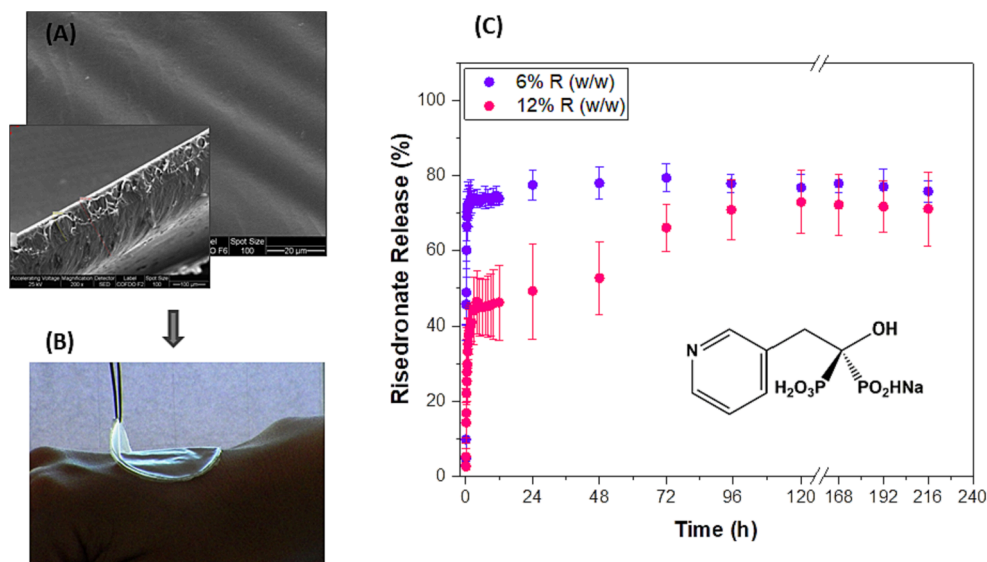
Fig. 15. (A):SEM micrography of membrane based on VAc:DOF copolymer, surface and cross section; (B) Photography of membrane adhered to human skin; (C) Release profiles of risedronate from membrane with different drug content (6% and 12% w/w). Insert: risedronate structure. (Adapted from Refs [64;65], with Springer and Elsevier permissions, respectively).
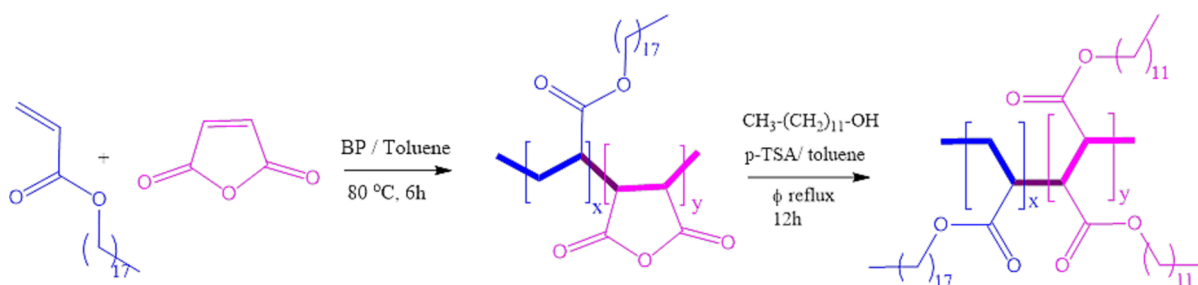

Fig.16. Schematic illustration of the synthetic methodology for prepared copolymers from octadecyl acrylate and maleic anhydride.
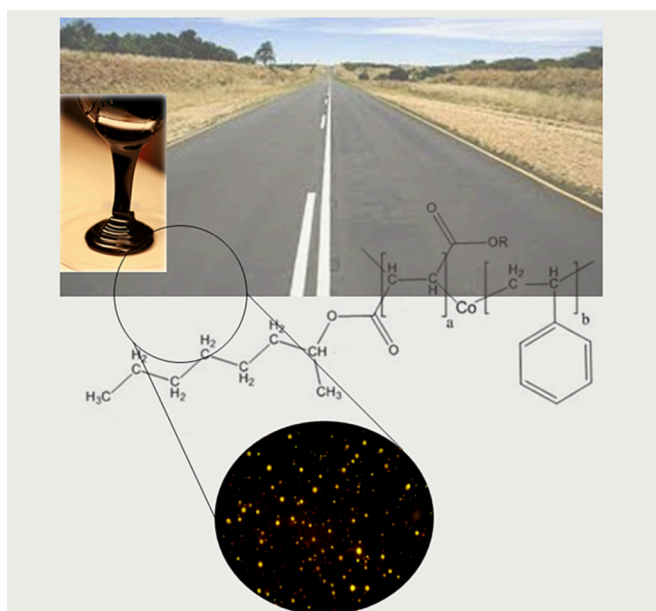

Fig. 17. Graphical illustration of fumaric copolymers as asphalt modifiers, including the microscopic morphology of a sample by fluorescence microscopy.

conventional radical polymerization is favored, particularly with monomers that have electron donating substituents as pendant chain, achieving copolymers with random structure. On the other hand, with the advent of new "living" radical polymerization methodologies, particularly ATRP, RAFT, and NMP, it has become possible to custom design new homo- and copolymers with easily controllable properties. In this way it has been obtaining block copolymers that include a fumaric comonomer, which had not been possible to synthesize previously, due to their low reactivity.

As presented in this review, these polymers have been used in recent years to design new materials for various applications, both in the biomedicine and energy field. Various fumaric homo and copolymers as well as combinations of these with other synthetic and natural polymers were tested in biological studies. *In vivo* assays showed that they are not cytotoxic and in most cases good cell adhesion and proliferation was found, although fumaric copolymers with lower Tg can hinder the cells proliferation used for bone regeneration assays. As has also been seen for other materials, the matrices obtained by electrospinning or with specific nanostructures favor the cellular response compared to other systems prepared by the solvent casting technique. Fumaric copolymers have also been used in drug delivery systems.

Other applications in which fumaric polymers have been used are as depressants of the petroleum pour point and as asphalt modifiers. In the first case, it was found that the greater the amount of crystalline CH_2 in the main chain, the interaction between the polymer and the wax of the crudes is better. On the other hand, the copolymers which presents in their structure both alkyl and aromatic components and higher

molecular weight allow adequately improve the asphalt.

However, beyond the uses so far developed, there are still several challenges to overcome to extend their future applications. One of them is the scaling of the most effective synthesis methods of this type of polymers in order to extend its application on an industrial scale. Another important aspect to improve is related to compatibility with other types of materials, such as ceramics, metals and petroleum derivatives, which would lead to the development of novel composite materials with better performance in their properties.

It is expected that in the near future fumaric homo and copolymers will be used in new applications, for example: the designing of new drug delivery systems, smart separation membranes or novel composite materials aimed at different areas of industrial interest, fields of application in which due to their properties they could be used efficiently.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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