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An in vitro release study of indomethacin from nanoparticles based on methyl methacrylate/glycidyl methacrylate copolymers

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Abstract Indomethacin was coupled onto some macromolecular nanostructures based on methyl methacrylate copolymers with glycidyl methacrylate and tested as a model drug. The polymeric matrices were synthesized by radical emulsion copolymerization with and without the presence of a continuous external magnetic field of 1500 Gs intensity. Mathematical analysis of the release data was performed using Higuchi, Peppas–Korsmeyer equations. NIR chemical imaging (NIR-CI) was used to provide information about the spatial distribution of the components in the studied nanostructures. This opportunity was used to visualize the spatial distribution of bioactive substances (indomethacin) into the polymeric matrix, as well as to evaluate the degree of chemical and/or physical heterogeneity of the bioactive samples. The release rate dependence on the synthesis conditions as well as on the chemical compositions of the tested polymeric systems, it was also evidenced.

1 Introduction

A huge variety of controlled release systems has been proposed over the last two decades; among them, the simplest system is the polymeric matrix device, where the drug is dispersed within a polymer network [1–5]. The studies performed onto the controlled release systems have been developed especially to increase the drug pharmacological action and reduce their side effects. The basic concept is that a controlled rate of drug release from the dosage form may be adjusted through the ability of drug absorption and its retaining. Polymers are used as carriers for the delivery of drugs, proteins, targeting moieties, and imaging agents [6]. The challenge lies in the design of macromolecular chains nanoparticles effectively able for coupling the bioactive substance and their future release over an extended period of time to achieve a clinical response [7–14].

There is a continuous need to design efficient synthetic methods to obtain polymeric matrices capable for better coupling of different compounds. In this context, polymers nonconventional synthesized in a continuous external magnetic field were developed [15–27].

In one of our previous papers the adsorption of bovine serum albumin (BSA) onto the surfaces of poly(methyl methacrylate) and of methyl methacrylate copolymer with 2,3 epoxypropyl methacrylate, it was investigated [28]. The polymeric matrices were obtained through radical emulsion polymerization with and without the presence of a continuous external magnetic field (MF) of 1500 Gs intensity. Two types of surfactant agents were used for polymers' synthesis: a classic one sodium lauryl sulphate (SLS) and β-cyclodextrin (CD). The protein adsorption was conducted in the presence as well as in the absence of MF, by varying the coupling conditions, respectively, the temperature, pH and albumin/polymer ratio. The study underlines the assistance of MF during the adsorption process, materialized into growth of the BSA adsorbed quantity. Thus, MF presence during adsorption determines the doubling of the BSA adsorbed quantity onto the surface of polymers prepared in the MF. The adsorption process was also related on the tensioactive substances used for the polymeric matrices synthesis. The higher content of the adsorbed BSA corresponded to polymers with CD instead of SLS. The fact was attributed to the catalytic activity of

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the magnetic field, which determines the molecules distortions, the growth of distance interactions and the modifications of the angles between bonds, with benefit effect upon adsorption.

The possibility to use β-cyclodextrin (CD) as biocompatible tensioactive and an electromagnetic field in order to improve the kinetic parameters of the radical emulsion copolymerization of methyl methacrylate (MMA) with 2,3-epoxypropyl methacrylate (GMA) was initially subject of study. [29] The research underlined the coupling possibilities of the MF influence—growth of the reaction rate and conversion explained through radical pairs mechanism—with a combination of the 'cage' effect and 'conformational control' afforded by CD. The presence of MF and CD during the syntheses leads to an increase of T_g and thermal stability for polymers.

Also, the polymerization in the presence of cyclodextrin (CD) complexes opens an alternative route to simply polymerize, in water, without using organic solvents. The supramolecular structures formed between cyclodextrins and polymers have inspired interesting developments of novel supramolecular biomaterials. The properties of CD inclusion complexes in aqueous solution have served as important models for the attainment of knowledge relevant to hydrophobic interactions, such as those determining some of the biological systems critical properties, i.e., the selectivity and the catalytic efficiency of the enzyme action [30].

The present investigation was focused on aspects about the drug release mechanism from the MMA/GMA copolymer matrices, using the indomethacin as the drug model.

The structure of the copolymers with drug before and after the indomethacin release was identified by FTIR-ATR spectroscopy. Near-infrared chemical imaging (NIR-CI) was used to visualize the spatial distribution of the chemical compounds in a sample (providing a chemical image). Mathematical analysis of the release data was performed using Higuchi, Korsmeyer and Peppas equations. The drug release kinetic was correlated on the copolymers composition and the magnetic field presence during the polymeric matrices preparation.

2 Experimental section

2.1 Materials

Methyl methacrylate (MMA) (c > 99 wt%, Merck) and 2,3-epoxypropyl methacrylate (GMA) (c > 97 wt%, Fluka) were freshly distilled before use. β-cyclodextrin (CD) from Fluka vacuum dried at 80°C for 12 h were used as tensioactive agent. Sodium lauryl sulphate (SLS) from Sigma, purity >95 wt%, was used without further purification. Potassium persulphate-KPS was twice recrystallized from twice distilled water. The indomethacin from Fluka BioChemika, purity >99.0%, was selected as model drug. In all the experiments twice distilled water was used.

2.2 The microspheres preparation

The polymeric particles, respectively poly(methyl methacrylate-co-2,3-epoxypropyl methacrylate) were synthesized through emulsion polymerization reaction: classic (C) and in the presence of a continuous external magnetic field (MF) of 1500 Gs, by the previously described procedure [26, 27].

The reactions were made in the same conditions for the both variants of synthesis with or without the MF: 0.8 wt% KPS—the initiator; 3 wt%, CD or SLS as surfactant; comonomers/water ratio 1/4; similar vessel shape; same reaction parameters.

The synthesized compounds were precipitated in methanol, purified by reprecipitation in methanol from acetone solution, dried under vacuum at room temperature for 48 h and stored in desiccators.

Table 1 presents the code of the polymers tested as matrices in the drug delivery system.

2.3 Methods of investigations

2.3.1 The polymeric nanoparticles characterization

The particle size, ζ potential and electrical conductivity were determined on a Malvern Zetasizer Nano ZS instrument (Table 2).

The *particle size* was determined by using a *dynamic light scattering technique*. The system uses non-invasive back scatter (NIBS) technology wherein the optics are not in contact with the sample, back scattered light being detected. This is the system for which the Mie method is applied over the whole measuring range from 0.6 nm to 6 μm. The particle size dimensions in the ranges of 200–500 nm are also sustained by SEM micrographs (Microscop SEM Philips XL 20).

The ζ *potential* was appreciated from the electrophoretic mobility (μ) using the Smoluchowski relationship,

$$\zeta = \eta\mu/\varepsilon, \quad \text{where } k\alpha \gg 1$$

where η—viscosity, ε—dielectric constant of the medium, k and α are Debye-Hűckel parameters. The determinations were made in solution (1% concentration) at 7.2 pH (adjusted with NaOH, on Autotitrator Malvern MPT2) and at 37°C. Each determination was made three times and their average value it is presented.

Table 1 The samples description and code

Description	Code
PMMA-co-GMA; monomers ratio: 97/3; classic emulsion polymerization; SLS surfactant	MMA/GMA 97:3 C-SLS
PMMA-co-GMA; monomers ratio: 97/3; emulsion polymerization in MF; SLS surfactant	MMA/GMA 97:3 MF-SLS
PMMA-co-GMA; monomers ratio: 75/25; classic emulsion polymerization; SLS surfactant	MMA/GMA 75:25 C-SLS
PMMA-co-GMA; monomers ratio: 75/25; emulsion polymerization in MF; SLS surfactant	MMA/GMA 75:25 MF-SLS
PMMA-co-GMA; monomers ratio: 97/3; classic emulsion polymerization; CD surfactant	MMA/GMA 97:3 C-CD
PMMA-co-GMA; monomers ratio: 97/3; emulsion polymerization in MF; CD surfactant	MMA/GMA 97:3 MF-CD
PMMA-co-GMA; monomers ratio: 75/25; classic emulsion polymerization; CD surfactant	MMA/GMA 75:25 C-CD
PMMA-co-GMA; monomers ratio: 75/25, emulsion polymerization in MF; CD surfactant	MMA/GMA 75:25 MF-CD

Table 2 Physico-chemical characteristics of unloaded particles: ζ potential, conductivity (mS/cm) and the Swelling degree (α)

Sample	Z average (nm)	ζ (mV)	Conductivity (mS/cm)	α_{max} (%)
MMA/GMA 97:3 C-SLS	370	-21.2 ± 0.6	0.038 ± 0.001	188 ± 3.4
MMA/GMA 97:3 MF-SLS	420	-26.6 ± 0.7	0.03 ± 0.001	$113 \pm .5.67$
MMA/GMA 75:25 C–SLS	430	-19 ± 0.4	0.058 ± 0.002	98.3 ± 2.1
MMA/GMA 75:25 MF–SLS	480	-21 ± 0.6	0.044 ± 0.002	68.7 ± 2.97
MMA/GMA 97:3 C-CD	200	-11.2 ± 0.3	0.038 ± 0.001	39.3 ± 1.9
MMA/GMA 97:3 MF-CD	230	-13 ± 0.4	0.03 ± 0.001	30 ± 1.5
MMA/GMA 75:25 C-CD	280	-9 ± 0.4	0.058 ± 0.002	35 ± 1.3
MMA/GMA 75:25 MF-CD	320	-11 ± 0.3	0.044 ± 0.002	28 ± 1.75

2.4 Preparation of indomethacin loaded particles

The indomethacin loaded particles were prepared by a solvent evaporation method. The polymers (100 mg) were swelled in 10 ml chloroform solution containing a known amount of indomethacin. Before this experiment we check the swelling capacity of pure polymers in chloroform vapours at 20°C and 2 Torr. The absorbed organic solvent was determined by weighing the samples, at various intervals of time, with a precision electronic balance (A&D Co. Ltd. HR 200). The results were presented before [29]. Table 2 presents also the correspondingly maximum swelling degree of the samples.

The mixture polymeric particles/indometachin/chloroform was maintained at constant stirring for 24 h. Then, the samples were dried at 30°C and 2 Torr until the chloroform was completely removed (checking by FTIR spectra). Figure 1a–d present the SEM micrographs (Microscop SEM Philips XL 20) of MMA/GMA 75:25 C-CD and MMA/GMA 75:25 MF-CD samples before and after the indomethacin loading. There are evidently the differences between the matrices before and after their loading with the bioactive substance.

2.5 The release study in vitro

The drug release study was carried out using the USP padle (apparatus II) method with a dissolution tester (ERWEKA Dissolution Testers) at 50 rpm, pH = 7.2 and 37°C temperature. Thus, the dried particles (approx. 300 mg of microcapsules from each formulation) loaded with indomethacin was immersed in the phosphate buffer solution. It was used 700 ml of dissolution medium as chamber volume containing potassium dihydrogen phosphate, KH_2PO_4 (0.2 M); monohydrogen phosphate (K_2HPO_4 0.2 M) and water. Time was recorded as soon as the microcapsules were put into the dissolution vessels. A two ml sample solution was withdrawn from each vessel at appropriate time intervals (1, 3, 5, 10, 15, 20, 25, 30, 40, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360 min and after that at each 120 min until 5040 min) for the analysis of drug release. Two ml of fresh phosphate buffer solution previously heated to 37°C was immediately added to the dissolution medium for compensating the sampling. The dissolution study was carried out for three samples from each formulation. The amount of the indomethacin was determined spectrophotometrically (Perkin Elmer spectrophotometer) at 319 nm.

The structure of the studied compounds before and after the indomethacin release was confirmed through *ATR-FT-IR spectra* (FT-IR VERTEX BRUKER) (Fig. 2).

It is well known the 1740–1630 cm^{-1} region corresponds to the carbonyl stretching absorption which is one of the strongest IR absorptions. As it can be saw from Fig. 2, the characteristic bands are excellent presented in

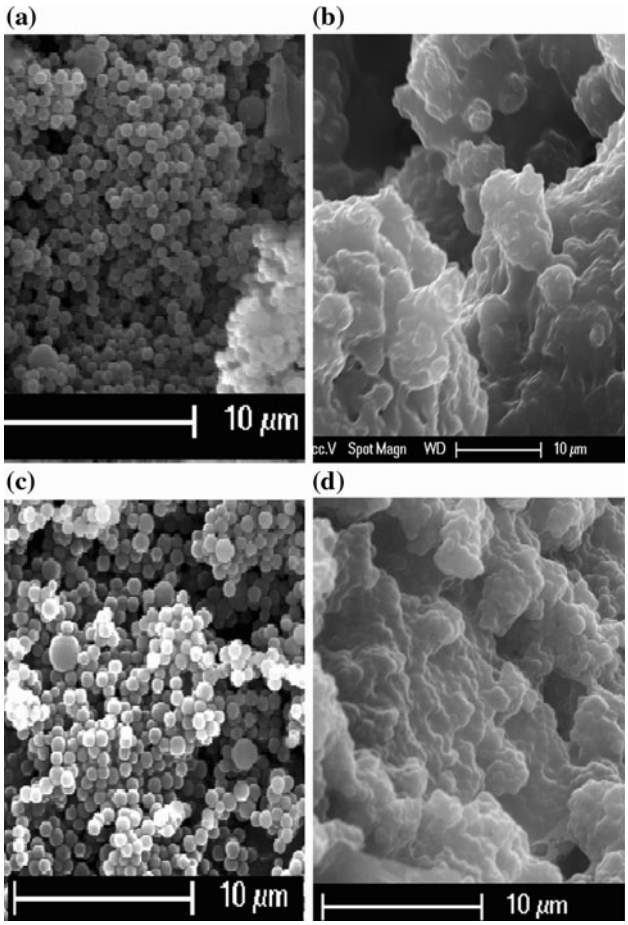

Fig. 1 SEM micrographs for : MMA/GMA 75:25 C-CD sample before (**a**) and after (**b**) the indomethacin loading; MMA/GMA 75:25 MF-CD sample before (**c**) and after (**d**) indomethacin loading

the spectra of the bioactive systems (the bands at 1650, 1690 and 1735 cm^{-1}) and there are diminished after the indomethacin release (the bands around of 1690 cm^{-1} are missing).

Near infrared chemical imaging (NIR-CI) data were collected on a SisuCHEMA device which employs SPECIM's hyperspectral imaging technology in the NIR (1000–2500 nm) range and the EVINCE as powerful chemometrics and the image processing software package. EVINCE allows to process the image data and to explore the spectral and spatial information as well as classifying and quantifying the image content. Also, they can be built spectral calibrations and prediction models for the specific chemical imaging applications. The contrast in the chemical images are compared by methods using the intensity of a single wavelength, the peak-height ratio of two wavelengths, the correlation coefficient with a reference spectrum and the principal component analysis (PCA). The correlation coefficient method was also compared with the partial least squares (PLS-DA) regression for further homogeneity investigations.

3 Results and discussion

3.1 Evaluation of the homogeneity using statistical analysis by NIR-CI

The application of NIR as a fast and nondestructive alternative method for the quantification of excipients within the polymeric drug delivery systems, such as implants, films and microspheres has been reported in the literature [31–33]. Near-infrared chemical imaging (NIR-CI) provides information about the spatial distribution of the components comprising the sample. The opportunity to visualize the spatial distribution of the included substances throughout the sample enables the determination of the degree of the chemical and/or physical heterogeneity within a given sample [31–39]. The chemical images as data acquisition, and visualized as three-dimensional block of data, are used for analysis techniques such as principal component analysis (PCA), principal component regression (PCR), partial least squares (PLS) modeling, and partial least squares-dynamic analysis (PLS-DA) through Evince software. The qualitative and quantitative information are derived from the pixels' counting and analysis of the statistical distributions of the classification results.

Figure 3 present the score images derived from the indomethacin component class. In the score images, the pixels with higher and lower score values are indicated by white and dark code colors, respectively. The code color in the most region of the score images is gray, the intermediate color between white and dark colors. The predominantly gray score images evidences the homogeneity distribution of drug in the polymeric matrix. Thus, the code color allows the qualitative differences between the particles loaded with drug and the particles after the releasing of the bioactive substance (the code color of the polymeric matrices loaded with drug is more appropriate to the indomethacin code color and the code color of the particles after release are much closer to the code color of the polymeric matrix).

PLS-DA calculations in the both classification and concentration modes are also performed through the Evince software. The predicted values of the spatially averaged contents of indhomethacin into the polymeric matrices after the drug release, derived from the PLS-DA, are presented in Table 3. The quantitative results obtained from the NIR-CI evaluation were compared with the results obtained by dissolution studies.

A relative good correlation between the two methods of investigation is observed from Table 3.

The NIR-CI analysis allows also, the determination of the prediction errors explained by the homogeneity of the indomethacin into the polymeric matrix, indicated by the standard deviation (STD) values, which are summarized in

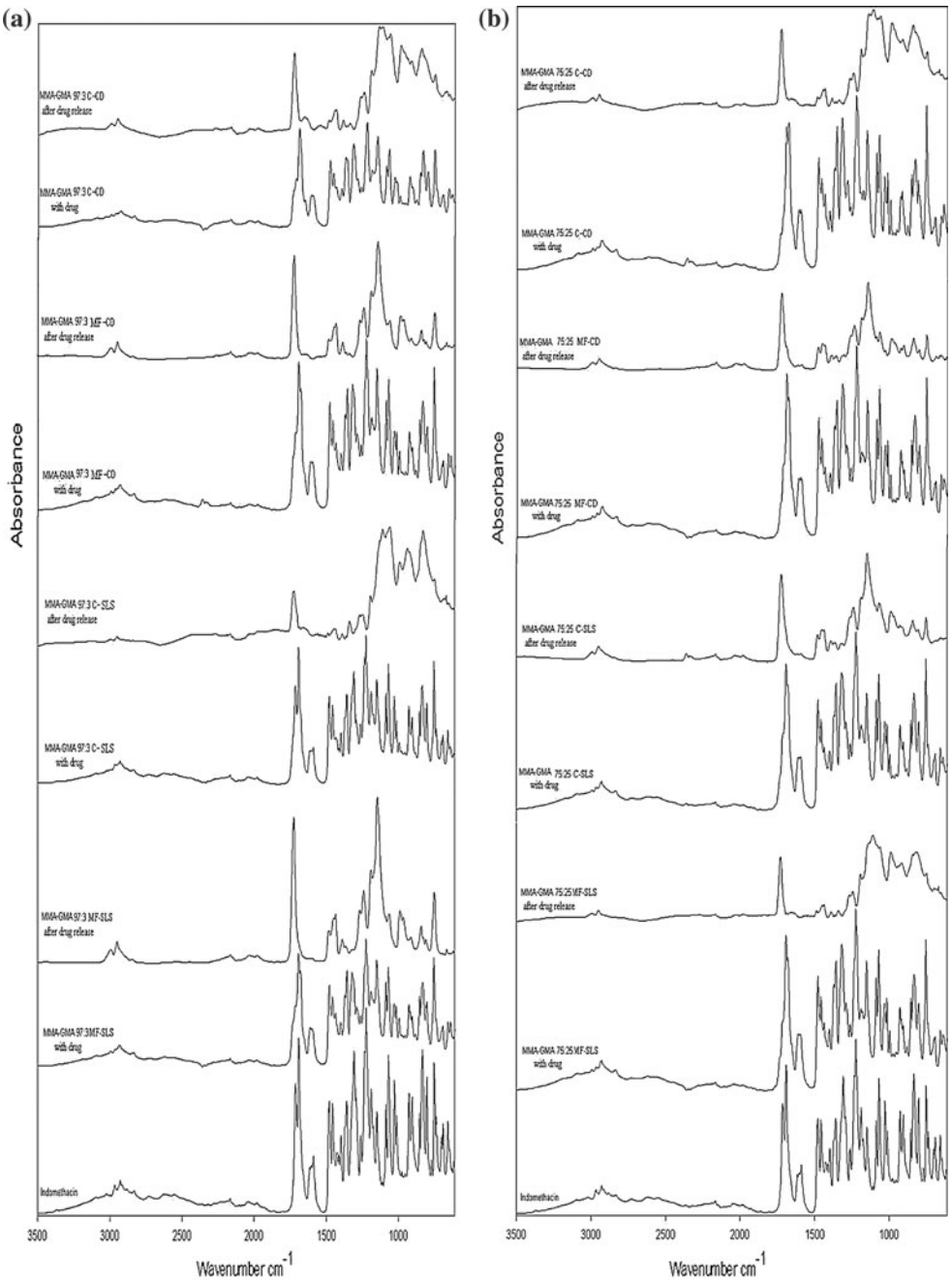

Fig. 2 FT-IR spectra of the polymeric matrix (copolymer), bioactive product (copolymer + drug) and bioactive product after release: **a** formulation with 3% GMA, **b** formulation with 25% GMA

Table 4. The STD values of the score image histogram are the same with the standard errors of the prediction (SEP) for the response variable in the result of Evince software. A histogram for the distribution of intensities (score values) in the score image, which includes the statistical information, is a powerful evaluation tool. Thus, a good sharing of the drug into the polymeric matrix evidences a normal distribution.

The quantitative measure is established by calculating the standard deviation of the distribution of pixel intensities as represented by the histograms of the PLS score images. An ideal distribution must be a narrow curve; conversely, a curve with a large breadth indicates a wide range of concentration values, leading to a high degree of heterogeneity. This behavior it is not properly for the drug release meaning an irregular release profile, with lag and burst effects resulting from drug clusters and voids.

In order to confirm the reproducibility of the data after the indomethacin release the samples were examined in three different locations (by three times data acquisition) and the data were analyzed by the PLS-DA model of Evince software. The three histograms of the indomethacin

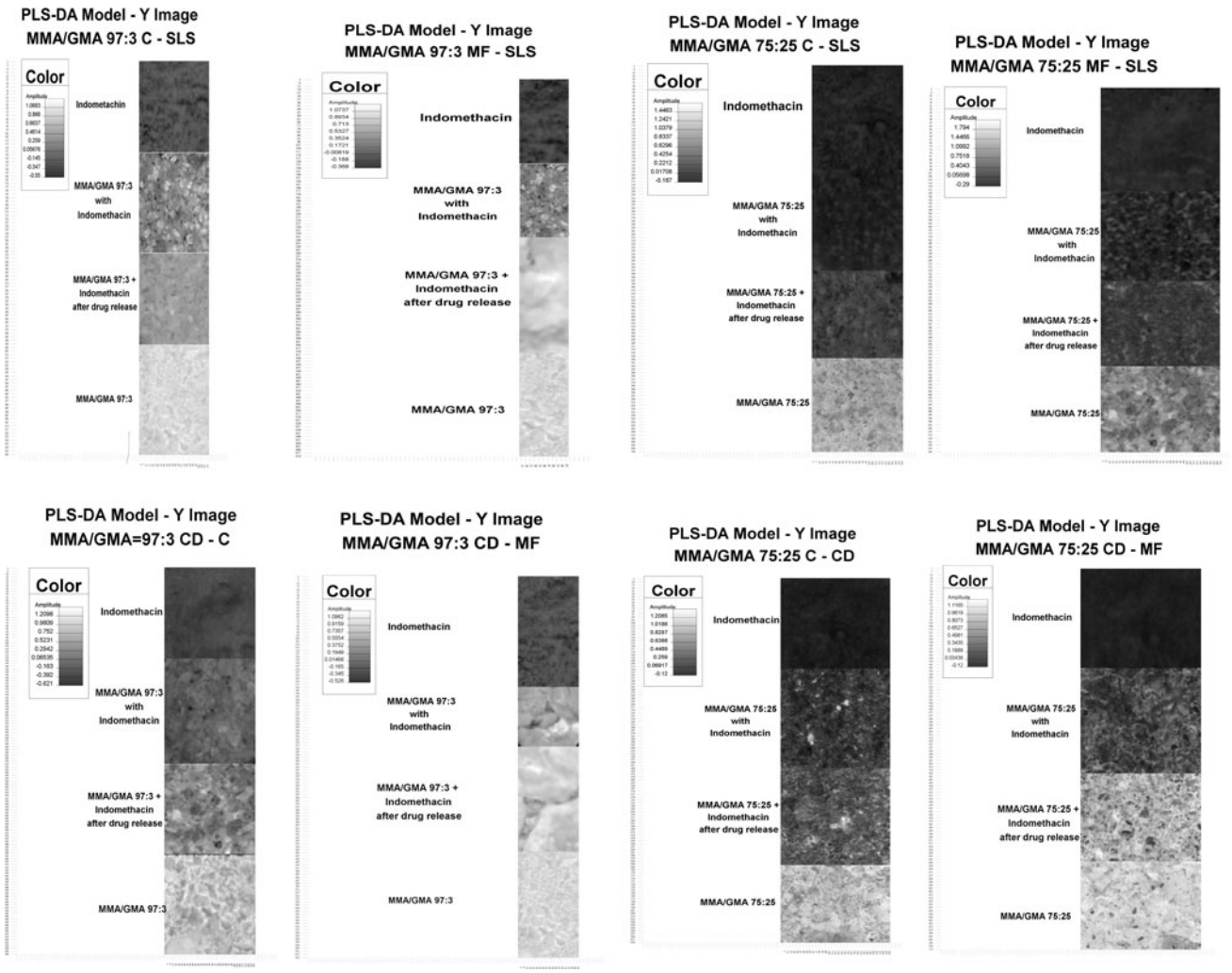

Fig. 3 Score images of the indomethacin dispersion into the polymeric matrices

Table 3 The predicted values of the released indomethacin from the matrix by the NIR-CI and dissolution studies

Samples	Indomethacin release %	
	NIR-CI analyses	Dissolution studies
MMA/GMA 97:3 C-SLS	78 ± 19.7	81 ± 2.4
MMA/GMA 97:3 C-CD	73 ± 3.8	87 ± 2.6
MMA/GMA 97:3 MF–SLS	48 ± 10.6	48 ± 1.5
MMA/GMA 97:3 MF-CD	61 ± 9	63 ± 1.9
MMA/GMA 75:25 C-SLS	87 ± 9.6	91 ± 2.8
MMA/GMA 75:25 C-CD	84 ± 8.8	91 ± 2.8
MMA/GMA 75:25 MF-SLS	65 ± 6.4	66 ± 2
MMA/GMA 75:25 MF-CD	56 ± 6	57 ± 1.7

scored images in the polymeric matrices are illustrated in Fig. 4. The STD values of the histogram are summarized in Table 4. The good reproducibility for the running and the good homogeneity of the studied samples are evidenced.

3.2 In vitro dissolution studies

As it was expected, the release kinetic of the bioactive product was influenced by the structure of the polymeric matrices which is in direct dependence with the conditions of the macromolecular chains preparation. Thus, the release rate was slower from the bioactive systems having as matrices the polymeric samples prepared in the MF presence (Fig. 5a, b).

The explanation for this behavior is based on the magnetic field effect which can be perceived as a dual action exerted on the one hand on the dynamics of molecular movement and on the other hand on the dynamics of radical spins. [15–18, 24] As it is well known beside the magnetokinetic modifications brought to the evolution of the chemical radical processes, the magnetic field influences the properties of the resulting compounds obtained through unconventional methods. The changes in the properties of the structures prepared or maintained in the magnetic field are attributed to the catalytic effect of the field on the molecules that can be

Table 4 The STD (%) values of the histogram and the reproducibility of the experiment from the score images of the samples after the release of the indomethacin

Polymeric matrix	Experiment*	Released indomethacin (%)	STD (%)
MMA/GMA 97:3 SLS C	REPROD 1	76.8	19.74
	REPROD 2	76	21.3
	REPROD 3	81	17.88
MMA/GMA 97:3 SLS MF	REPROD 1	46.2	10.57
	REPROD 2	46.2	10.63
	REPROD 3	51.8	10.63
MMA/GMA 97:3 CD C	REPROD 1	73.8	4.38
	REPROD 2	72.5	3.79
	REPROD 3	72.7	3.5
MMA/GMA 97:3 CD MF	REPROD 1	62.3	9.4
	REPROD 2	61.3	9.2
	REPROD 3	60.6	8.8
MMA/GMA 75:25 C SLS	REPROD 1	87.4	9.9
	REPROD 2	86.9	9.7
	REPROD 3	87	9.37
MMA/GMA 75:25 MF SLS	REPROD 1	67.2	8.75
	REPROD 2	65	6.3
	REPROD 3	63.1	4.14
MMA/GMA 75:25 CD C	REPROD 1	84.4	8.77
	REPROD 2	81.2	8.1
	REPROD 3	85.3	9.5
MMA/GMA 75:25 CD MF	REPROD 1	56.2	6.07
	REPROD 2	56.4	6.1
	REPROD 3	55.9	5.92

* REPROD 1, 2, 3 meaning the experiment number

reshaped through growing of distance interactions and modification of angles between bonds. Also, the improvement of the strength constant is owing to the inductive and electromeric effects increased in the new conditions of field. Thus, a better coupling between the polymeric matrix and the bioactive substance takes place and as consequence a slower release of the drug will be registered.

The surfactant nature used during the polymeric matrices syntheses influences also the release kinetic.

The release data at different interval of time presented in Table 5 evidence a more rapidly discharge of the drug up to 2100 min in the case of the polymeric matrices with 3% GMA in the composition, relative to the samples with 25% GMA, no matter the used surfactant or the presence or the absence of the MF during the synthesis. This behavior indicates that the drug release was controlled by the diffusion from the network. Also, the release behavior from the bioactive structure with 3% GMA into the polymeric matrix composition reached a plateau from 2600 min. This fact is explained by the possibility to entrap a higher amount of the indomethacin into a network with large meshes but also to release more rapidly the drug.

The drug release from the matrix with 25% GMA occurs up to 4200–5100 min. This behavior is attributed to the network with smaller meshes owing to the higher cross-linker amount. Thus, the drug is better entrapped into the polymeric network and the release is slower. This activity is also sustained by the swelling behavior into the organic solvent of the studied polymeric samples (Table 2) [30]. It was mentioned a decrease of swelling with the increase of the GMA amount as well as in the case of the polymeric structures prepared in the MF presence; these aspects were previously discussed, in detail [30].

From Fig. 5 and Table 5, there is observed the bioactive systems with polymeric matrices prepared in the MF presence—no matter of the surfactant nature—present a slower rate of the drug release. This behavior is also sustained by the reduced capacity of swelling of the polymeric matrix synthesized in the MF presence (Table 2). It can be concluded that P(MMA-co-GMA)(75/25) prepared in the MF presence responds better to the imposed conditions for a matrix of a retard system.

3.3 The kinetic of drug release

As it was mentioned before, there is assumed the drug release has a diffusion-controlled release process. For a better understanding of the release mechanism, the data got

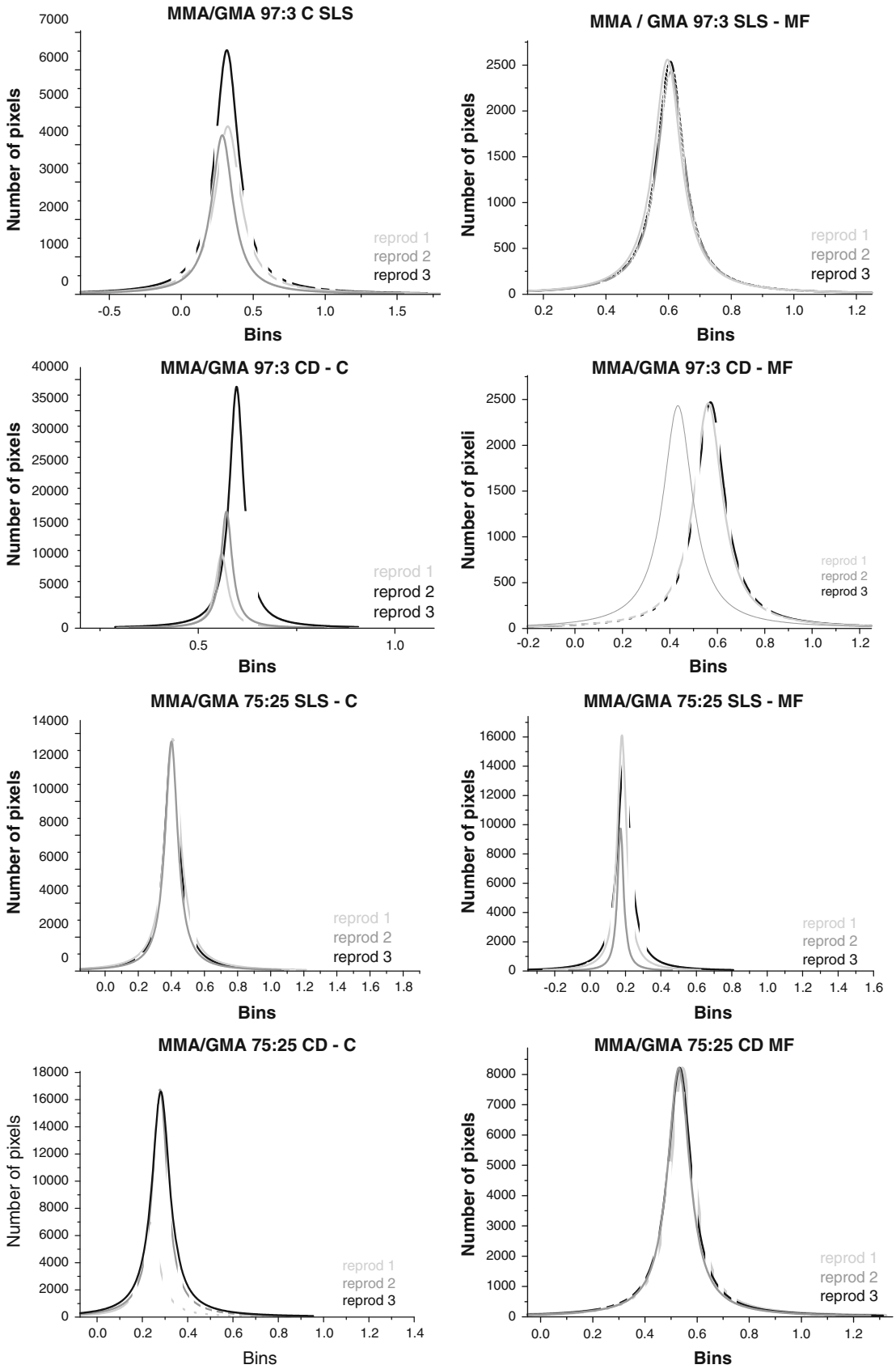

Fig. 4 The histograms derived from the score images for the samples after the release of the indomethacin

from the in vitro release of the indomethacin from the polymeric matrices synthesized with SLS or CD as surfactants were fitted according to the Higuchi (1) [40, 41] and Peppas–Korsmeyer Eq. 2 [42, 43] and the dissolution data $\{M_t/M_\infty < 0.6\}$ are evaluated.

As it is well known, the *Higuchi model* describes the fraction of the released drug from a matrix proportional to square root of time:

$$M_t/M_\infty = k_H t^{1/2} \quad (1)$$

where M_t and M_∞ are the cumulative amounts of the drug released at t moment and respectively infinite time, and k_H is the Higuchi dissolution constant that incorporates the characteristics of the macromolecular network system and the drug. If the Higuchi model of drug release (i.e., Fickian diffusion) is obeyed, then a plot of M_t/M_∞ versus $t^{1/2}$ will be straight line with k_H the slope [44].

Korsmeyer–Peppas model (Power Law) describes the drug release from the polymeric system accordingly to

$$M_t/M_\infty = k' t^n \quad (2)$$

$$\log[M_t/M_\infty] = \log k' + n \log t \quad (2')$$

where M_t and M_∞ are cumulative amounts of the drug released at the t moment and infinite time, respectively, k is the constant that defines the characteristics of the polymer network system and n is the diffusional release exponent indicative for the mechanism of the drug release for drug dissolution. The n value characterizes the different release mechanisms. For Fickian diffusion $n = 0.5$ and for non-Fickian transport n is between 0.5 and 1.0. It was further postulated that the drug release from slabs becomes independent of time and reaches zero-order release known as Case II transport. When other shapes such as cylinders or spheres are analyzed, Case II transport occurs as n approaches 1.0 ($n \sim 1.0$) due to the geometry of the system. In such cases, a diffusional exponent $n = 1.0$ is indicative of non-Fickian transport. The transport mechanism occurring at $n > 1.0$ constitutes a super Case II transport

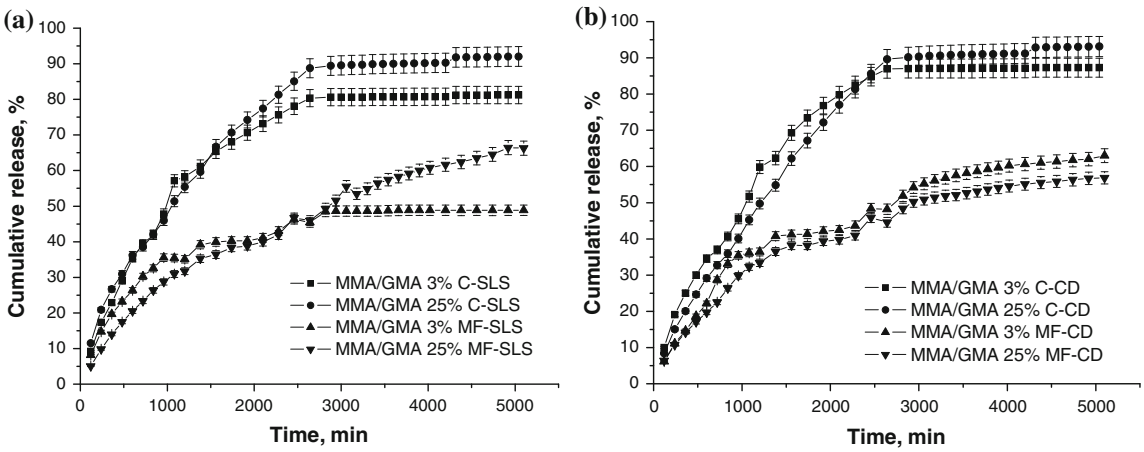

Fig. 5 The profile of the indomethacin in vitro release from the polymeric matrices synthesized with SLS as surfactant (**a**) and with CD as surfactant (**b**)

Table 5 The released indomethacin related to the polymeric matrix characteristics

Time (min)	Released indomethacin from the sample (%)							
	MMA/GMA 97:3 SLS C	MMA/GMA 97:3 SLS MF	MMA/GMA 97:3 CD C	MMA/GMA 97:3 CD MF	MMA/GMA 75:25 SLS C	MMA/GMA 75:25 SLS MF	MMA/GMA 75:25 CD C	MMA/GMA 75:25 CD MF
120	9.2	8.1	10	6.1	9	5.07	8.43	6.1
600	35.4	26.32	34.6	22.17	35.2	20.5	29.12	19.7
1200	58.2	35.7	59.85	36.44	55.45	31.7	49.77	33.25
2100	73.2	41.09	79.8	42.42	72.8	40	77	39.76
2640	80.3	45.43	87	59.5	88.75	46	89.6	44.6
4080	80.7	48.6	87.1	60.25	90.2	60.8	91	54.6
5200	81.2	48.9	87.3	63	92.05	66.3	93.1	56.9

Table 6 Drug release kinetic parameters

Formulation	Higuchi equation		Peppas–Korsmeyer equation		
	k_H ($min^{-0.5}$)	R^2	n	k (min^{-n})	R^2
MMA/GMA 97:3 SLS C	0.075	0.967	0.516	0.0027	0.979
MMA/GMA 97:3 SLS MF	0.048	0.953	0.405	0.0028	0.97
MMA/GMA 97:3 CD C	0.054	0.962	0.55	0.0543	0.985
MMA/GMA 97:3 CD MF	0.014	0.972	0.57	0.0477	0.952
MMA/GMA 75:25 C SLS	0.0167	0.97	0.64	0.054	0.991
MMA/GMA 75:25 MF SLS	0.0102	0.992	0.65	0.027	0.99
MMA/GMA 75:25 CD C	0.0461	0.977	0.77	0.021	0.997
MMA/GMA 75:25 CD MF	0.0081	0.985	0.55	0.0175	0.981

However many other authors have also reported a drug diffusion mechanism from acrylic/methacrylic matrices [1, 45, 46].

From the evaluation of the k_H and k' rate constants, it is confirmed the higher dissolution rate from the P(MMA-co-GMA) (97:3) matrices. It is also confirmed a slower release of the drug from the polymeric matrices synthesized in the MF. The bioactive samples with 3%GMA present a good fitting to Higuchi equation and n values between 0.405 and 0.57 according to Peppas–Korsmeyer equation, which indicates a drug release mechanism controlled mainly by Fickian diffusion.

The best agreement of the fitted indomethacin dissolution profiles from polymeric samples with 25% GMA according to the mentioned kinetic models was obtained with the Peppas–Korsmeyer equation (Table 6). The correlation coefficient (R^2) is closely to 1 and the release exponent "n" is higher than 0.5. It was concluded that the release mechanism is more complex than the Fickian diffusion.

4 Conclusions

The polymeric compounds based on the methyl methacrylate copolymers with 2,3-epoxypropyl methacrylate—in the ratio of 97/3 and 75/25%, respectively—have been tested as matrices for the preparation of the bioactive systems where the model drug was indomethacin.

The polymers were synthesized through classic radical emulsion polymerization with sodium lauryl sulphate or β-cyclodextrin as tensioactive substances and also, by nonconventional route in the presence of a continuous electromagnetic field. Both, the chemical composition and the synthesis conditions have affected the coupling as well as the release of the drug. Thus, the presence of the magnetic field during the polymer synthesis induces the molecules distortions with the growth of the distance interactions and the modifications of the angles between the bonds, with effect upon the drug coupling as well as the bioactive substance release.

The homogeneity of the prepared bioactive systems was appreciated through near-infrared chemical imaging as non-destructive method of analysis. It was observed the relative homogenous distribution of the drug into the polymeric matrix. The predicted values of the spatially averaged contents of indomethacin in the polymeric matrices after the drug release derived from PLS-DA were in good agreement with the data obtained from the dissolution test.

The study also confirmed the diffusion release as the predominant mechanism for the samples with the reduced amount of GMA. The increasing of the GMA content affected the drug release, thus a more complex mechanism of release than Fickian diffusion being possible.

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