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Preparation of PMMA Nanoparticles Loaded with Benzophenone-3 through Miniemulsion Polymerization

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Summary: The present paper analyzes the production of poly(methyl methacrylate) – PMMA – nanoparticles loaded with benzophenone-3 through miniemulsion polymerization. The obtained product is homogeneous and stable, allowing for preparation of photo-protective formulations. It is observed in particular that bezophenone-3 interacts with the reacting system, promoting the growth of the PMMA chains produced in miniemulsion.

Keywords: benzophenone-3; miniemulsion polymerization; nanoparticles; PMMA; sun filter

Introduction

Different materials are being employed for encapsulation of solar filters, in order to ensure decreased cutaneous absorption, increased sun protection factors (SPF), enhanced delivery control and improved photostability and safety.[1–4] Among these, polymer nanoparticles have received particular attention, due to additional therapeutical properties and enhanced stability both in biological fluids and during storage.[5,6]

Different techniques can be employed for production of polymer nanoparticles and encapsulation of biomedical compounds,[7] although miniemulsion polymerizations usually allows for production of more homogeneous and stable nanoparticles, easier encapsulation of active biomedical compounds (when they do not interact with the reacting system) and simpler process flowsheets.[8,9] In typical miniemulsion polymerization systems, an organic phase (which contains the monomer mixture, initiator and the compounds that must be encapsulated) is emulsified in water (which contains emulsifying agents and initiator) and is afterwards polymerized into the polymer nanoparticles. The original monomer droplets constitute the primary polymerization *loci* and behave as "nano-reactors". [8,9] The main advantage of the miniemulsion polymerization process is the capability to produce complex nanostructures in a single reaction step.[8,9]

Benzophenones constitute a class of sun filters that belong to the aromatic ketones group. Benzophenones have been used commercially as sun filters since the late fifties. Particularly, benzophenone-3 (BZ-3) (2-hydroxy-4-methoxybenzophenone or oxybenzone) is the commonest compound of this class.[10] BZ-3 is a lipophilic compound that is capable to absorb and dissipate UVA radiation very efficiently, although with lower intensity in the UVB region.[11] Particularly, the Brazilian Health Surveillance Agency (ANVISA) approves the commercial use of BZ-3 as sun filter in personal hygiene products, cosmetics and

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perfumes and these sun filters are marketed a long time ago. [12]

Sunscreen formulations prepared with polymer nanoparticles loaded with benzophenone-3 have already been studied by different authors. [13,14,15] The encapsulation of BZ-3 can be advantageous because it can prevent the absorption of the sun filter by the skin. However, the preparation of nanoparticles was carried out with previously obtained polymer materials, with incorporation of the sun filter into the polymer matrix during a second process stage. This can lead to additional production costs and lower encapsulation efficiencies. For this reason, in the present work nanoparticles containing benzophenone-3 are obtained in a single step through in situ incorporation during methyl methacrylate miniemulsion polymerizations.

Experimental Part

Materials

Methyl methacrylate (MMA, monomer) was supplied by Aldrich with minimum purity of 99.5%. Potassium persulfate ($K_2S_2O_8$, initiator) was supplied by Merck Indústrias Químicas with minimum purity of 99.5%. Sodium bicarbonate ($NaHCO_3$, buffer) was supplied by Proquimios with minimum purity of 99.5%. Sodium lauryl sulfate (SLS, surfactant) was supplied by Proquimios with minimum purity of 99.5%. Benzophenone-3 (BZ-3, encapsulated sun filter) was donated by Spectrum with minimum purity of 99%. Distilled water was used as the suspending medium in all polymerization runs. Hydroquinone (inhibitor used to halt the reaction) was supplied by Vetec Química Fina with minimum purity of 99%.Tetrahydrofuran (THF) was supplied by Spectro as HPLC grade and used for GPC analysis. All materials were used as received.

Production of PMMA Nanoparticles with BZ-3

The basic recipe used for preparation of sun filter nanoparticles is presented in Table 1. (As observed in the following paragraphs, the recipe was developed to allow for production of polymer latexes with long shelf stability.) Initially SLS, $NaHCO_3$ and $K_2S_2O_8$ solutions were prepared separately with distilled water and kept under stirring during 20 minutes at room temperature. Then, BZ-3 was dissolved in MMA. Afterwards, the initial organic emulsion was prepared by adding the previously prepared solutions into the reaction flask in the following order: (1) SLS aqueous solution, (2) $NaHCO_3$ aqueous solution, (3) distilled water and (4) the organic medium. After preparation of the mixture, the reaction system was kept under constant stirring at room temperature for 30 minutes. After that, the mixture was fed into a high shear homogenizer (APLAB-10/1.000 bar – Artepeças) for 20 minutes (10 cycles), with pressure losses ranging from 200 to 800 bar (miniemulsions were prepared with pressure losses of 200, 400, 600 and 800 bar), at a flow rate of 10 l/h. The emulsion temperature was monitored during homogenization and temperatures usually raised to 50 °C. The miniemulsion was then placed into a glass reactor and heated to the desired reaction temperature (80 °C). Finally, the $K_2S_2O_8$ solution (initiator) was added to the reactor, starting the

Table 1.
Miniemulsion polymerization recipe.

Components	Concentration
Solution of sodium lauryl sulfate	5.0 g of LSS + 50.0 g of distilled water
Solution of sodium bicarbonate	0.3 g of $NaHCO_3$ + 31.0 g of distilled water
Solution of potassium persulfate	0.6 g of $K_2S_2O_8$ + 31.0 g of distilled water
Additional distilled Water	115.0 g
MMA	100.0 g
Benzophenone-3	5.0 g

reaction. It is important to emphasize that foaming was not significant at the analyzed conditions.

Stirring control was performed with a programmable mechanical stirrer (IKA Labortechnik RW20D2Mn), kept at constant agitation speed of 1000 rpm. In order to avoid monomer loss, a top reflux condenser was connected to the reactor and kept at 10 °C. The finished product was dried with a lyophilizer (CHRIST BETA 1–16) operated at −50 °C and 0.4 mbar. The final volatile contents (including water) of prepared polymer products were always below 0.01 wt%.

Characterization

Monomer conversion was analyzed gravimetrically by drying samples (after addition of 0.1 wt% of hydroquinone) to constant weight in an oven (Quimis Q314 make) kept at 60 °C.

Particle size distributions were characterized through dynamic light scattering, with help of a Malvern Instruments Zeta Sizer Nano S instrument. Samples were prepared by introducing a drop of the polymer emulsion directly into the quartz cell filled with distilled water. Prior to use, the emulsion samples and the distilled water were carefully homogenized with Pasteur pipettes.

In order to characterize the morphology of the synthesized dry polymer nanoparticles, scanning electron microscopy (SEM) analyses were carried out with a JSM 5300 JEOL equipment. Photomicrographs were processed with a Zeiss image analyzer. Before being exposed to the electron beam, samples were metalized with gold under argon atmosphere at high vacuum.

In order to characterize the molar mass distributions of the final polymer materials, samples of 0.15 mg were initially dissolved in 3 ml of THF. Then, the obtained solutions were filtered with teflon membranes with pores of 0.45 μm. Afterwards, samples of 300 μl were injected into the chromatograph (VE 2001 Viscotek, equipped with four Phenomenex columns of 500, 10^3, 10^5 and 10^6 Å and a VE-3580 Viscotek refractometric detector). Analyses were carried out at 35 °C, using THF as the mobile phase. Calibration curves were built with polystyrene standards.

Light absorption analyses were performed to determine the amounts of sunscreen that were encapsulated. Analyses were carried out with a UV/Vis Perkin-Elmer spectrophotometer, using solutions prepared with 0.1 g of the polymer sample and 100 ml of ethanol. The standard solution was prepared with 0.01 g of BZ-3 in 100 ml of ethanol. Readings were carried out for maximum absorption wavelengths.

Results and Discussion

The obtained polymer latexes were stored in glass flasks and kept at room temperature for several weeks. Particle size analyses were performed regularly to characterize the stability of obtained products. Obtained polymer latexes remained homogeneous without phase segregation or change of average particle sizes for at least six months. This was due to the good stability provided by the SLS surfactant and the proposed recipe and also because of the very high monomer conversions attained during the reaction step. Particularly, Table 2 and Figure 1 show that the final particle size distributions were not very sensitive to modification of the pressure of the homogenization step.

MEV analyses (Figure 2) indicated the formation of spherical nanostructures with very regular diameters (as expected in typical miniemulsion reactions) and agreed well with the average diameters determined through light scattering analyses (Table 2). Dosing of sunscreens through UV analyses (Table 2) showed that incorporation of the sun filters was essentially equal to 100%, which allows for preparation of sunscreens with BZ-3 contents that are similar to other commercial formulations prepared with non-encapsulated BZ-3. Besides, the UV spectra indicated that the encapsulated filter remained integer after reaction.

Table 2.
Characteristics of products obtained at different reaction conditions.

Sample	P (bar)	Dp (nm)	IP	BZ-3 encapsulated (%)	Mn (g/mol)	Mw (g/mol)	Mw/Mn
Reaction 1	800	62	0.084	99.5	436×10^3	1206×10^3	2.77
Reaction 2	600	60	0.049	100.2	463×10^3	1290×10^3	2.79
Reaction 3	400	48	0.095	98.4	459×10^3	1297×10^3	2.83
Reaction 4	200	59	0.113	98.6	446×10^3	1253×10^3	2.81
PMMA	200	60	0.100	0.0	168×10^3	453×10^3	2.69

P – pressure loss; Dp – average particle diameter; IP – polydispersion index of the particle size distribution; Mn – number average molecular weight; Mw weight average molecular weight.

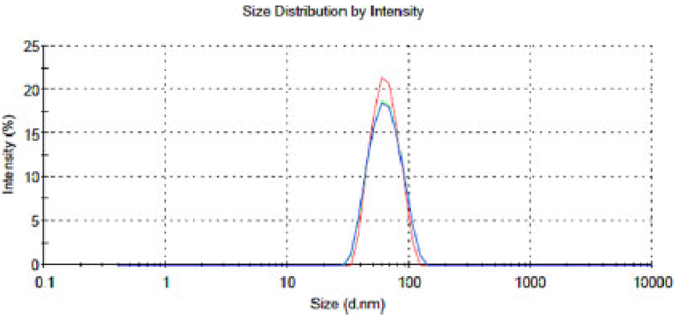

Figure 1.
Size distribution of the nanoparticles obtained in reaction 4.

It is interesting to observe that PMMA particles presented much higher molar masses in presence of BZ-3 (Table 2). This result indicates that the filter probably interacts with the polymerization process. As BZ-3 molecules present various oxygenated functional groups, it is reasonable to assume that BZ-3 might act as a reticulating agent. This hypothesis is reinforced by the fact that BZ-3 can promote MMA polymerization at low rates in the absence of initiator. Similar results were observed in

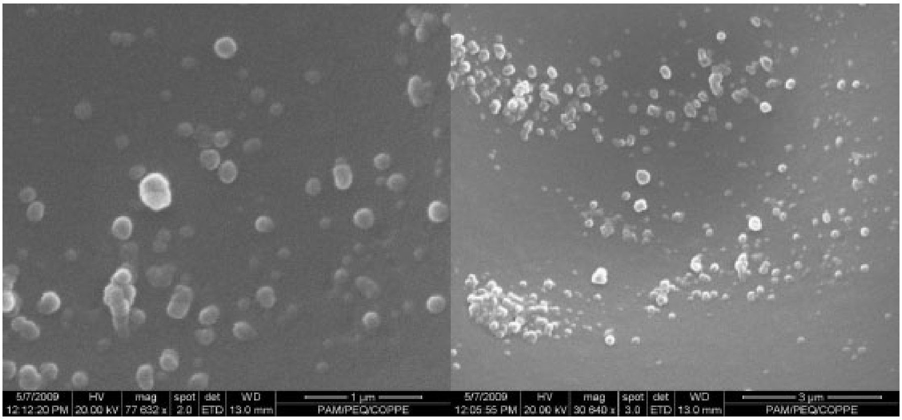

Figure 2.
Typical micrographs of PMMA nanoparticles loaded with BZ-3 (Reaction 4).

other studies, when MMA polymerizations were performed in presence of amoxicillin and doxorubicin.[16,17] In principle, this can be very advantageous, as the incorporation of BZ-3 into the molecular structure of the final polymer material can contribute with the reduction of BZ-3 absorption by the cutaneous tissue.

Conclusion

The results presented here show that it is possible to prepare PMMA nanoparticles loaded with benzophenone-3 in situ through miniemulsion polymerization reactions. The obtained product presents regular homogeneity and stability, enabling the utilization of the polymer nanoparticles in sunscreen formulations. It was noticed that benzophenone-3 interacts with the reacting medium and promotes the growth of the final PMMA chains.

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