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Development of affinity polymeric particles for the removal of 4-dimethylaminopyridine (DMAP) from active pharmaceutical ingredient crude streams using a green technology

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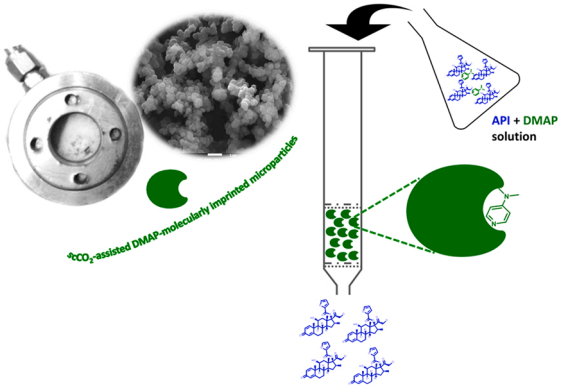
HIGHLIGHTS

- DMAP- molecularly imprinted polymer was developed using $scCO_2$ technology.
- DMAP-MIP was synthesized for cleanup DMAP impurity from pharmaceutical mixtures.
- Polymer particles were obtained in high yield as dry powder.
- MIP particles were able to remove 18.3 μmol DMAP/g pol from a 104 ppm DMAP solution.
- 1004.6 μmol DMAP/g API were removed by MIP from a solution containing DMAP + API.

GRAPHICAL ABSTRACT



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ABSTRACT

Polymeric particles with affinity for 4-dimethylaminipyridine (DMAP) were developed by molecular imprinting using supercritical carbon dioxide ($scCO_2$) technology, for cleanup of this potentially genotoxic impurity from crude mixtures of Active Pharmaceutical Ingredients (APIs). DMAP-molecularly imprinted polymer (DMAP-MIP) and the respective control, the non-molecularly imprinted polymer (NIP) were produced by free radical polymerization using methacrylic acid as monomer, ethylene glycol dimethacrylate as crosslinker and AIBN as free-radical initiator in $scCO_2$. The materials were obtained in high yield and were characterized chemically, physically and morphologically. Their extraction efficiency was evaluated by dynamic binding experiments using two solutions: i) a solution containing 104 ppm DMAP solution; ii) model pharmaceutical mixture containing 104 ppm of DMAP and 1018 ppm of Mometasone furoate (API). Particles were able to remove 18.3 μmol DMAP/g

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polymer from a 104 ppm DMAP solution (i) and 1004.6 μmol DMAP/g API (ii). In addition, high recoveries of both DMAP and API were obtained, above 99%.

1. Introduction

4-dimethylaminipyridine (DMAP) is widely used as catalyst in several types of organic reactions, such as sulfonylation, acylations, silylations [1], esterifications [2], and amino group protections [3]. Furthermore, DMAP is present in the manufacturing of Active Pharmaceutical Ingredients (APIs), being considered a potentially genotoxic compound [4]. Since 2006 pharma authorities, Food and Drug Administration (FDA) and European Medicinal Agency (EMA), have issued recommendations on the pharmaceutical impurities admissible values, in particular on genotoxic content in pharmaceutical drugs, due to the potential negative effects on human health. These guidelines impose limits on content of impurities in final drug product at ppm levels [5].

DMAP is a typical API impurity since it is used in many methane sulfonylation reactions used in API manufacturing [6]. The final crude mixtures of APIs should be free of impurities such as reactants, intermediates, by-products, and degradation products [7]. Typically, the pharma industry takes advantage of the well implemented purification processes to remove different types of API contaminants, such as re-crystallization [8], chromatography [9], nano-filtration [10] distillation [11], extraction, resins, activated carbon powder treatments [12], or combinations of these processes as multi-step/hierarchical purification processes. However, most of them lack specificity for impurities removal without simultaneous loss of API, use large quantities of organic solvents, which make these strategies costly, demanding and time-consuming. About 50–80% of API manufacturing costs are due to purification processes [13]. Highly specific, cheap, efficient, robust and less intensive solutions for the specific extraction of genotoxic compounds from unpolished solutions are potentially of interest to the pharma industry [7].

High affinity materials can be designed by Molecular Imprinting Techniques (MITs), a synthetic approach that takes advantage of the molecule which the affinity is wanted - the template, or a structurally similar surrogate, to assemble recognition sites by establishing precise bonds with the polymeric matrices. A template-monomer complex is formed during the polymerization process, which is “frozen” by a crosslinker under a porogenic solution, within a 3D porous structure [14]. The recognition sites are built for a perfect match between the template and the matrix, which are specifically designed to be complementary in size, shape and functional groups, acting as *lock-and-key* systems. These affinity materials typically present binding constants comparable to natural receptors. Their low cost of preparation is another significant competitive advantage of synthetic receptors. Moreover, they can work under harsher temperature and pressure conditions than natural materials as well as having low reactivity to strong acids and bases and organic solvents [15–17].

Several types of affinity-scavengers based on molecularly imprinted polymers (MIPs) were reported by conventional processes using organic solvents, for removal of genotoxic compounds, such as acetamide and arylsulfonates [6], 1,3-diisopropylurea [18], 4-aminopyridine [19], 2-aminopyridine [20], benzhydrol [21], methyl p-toluenesulfonate,24 (2RS)− 2-[[2-[[[(1E)− 5-methoxy-1-[4(trifluoromethyl) phenyl] pentylidene] amino] oxy] ethyl] amino] butanedioic acid [22], p-nitroaniline [23], and DMAP [24,25].

MIPs are obtained in these cases as bulk materials which need to be crushed and sieved and at the end of the process, only a small fraction is used. Hence, part of the bulk material produced is unusable and useless. Moreover, large quantities of organic solvents are used in the process, which makes the process unwieldy, arduous and time-consuming. To overcome this intensive processing, new alternative solvents and new clean or solvent-free chemical synthesis approaches have emerged with environmentally beneficial characteristics that replace conventional methods.

Supercritical carbon dioxide ($scCO_2$) is a green solvent that replaces conventional organic solvents to obtain ready-to-use affinity polymeric materials as dry and free-flowing white solids with controlled morphology, in high yields, easy-to-handle, without any additional drying or purification steps. Utilization of this technology, therefore makes cost-efficient and timesaving procedures available. Drug delivery, switchable devices, extraction of natural products from natural resources, removal of an oxidized impurity from diesel and removal of genotoxic compounds are some of diverse fields where this technology [26–33] has already shown its potential, conforming to the development of Green Process Engineering [34].

Herein, it is reported an environmentally-friendly strategy to produce affinity polymeric particles for DMAP, a genotoxic impurity, using methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA), focused on API purification processes. The physical properties of the polymeric particles were assessed, in a dynamic manner by solid phase extraction (SPE), both with a DMAP solution and a simulated model of a crude pharmaceutical solution containing DMAP and mometasone furoate as API (DMAP+API), which mimics the late purification stage of the API. Mometasone furoate (API) is a corticoid commonly applied in a topical way to treat skin irritation caused by eczema or psoriasis or, via inhalation to treat allergic rhinitis and asthma pathologies [13]. The chemical structures of 4-dimethylaminopyridine (DMAP) and mometasone furoate (API) are presented on Fig. 1.

2. Materials and methods

2.1. Materials

4-Dimethylaminopiridine (DMAP, 99% purity) was purchased from Acros (Geel, Belgium), Methacrylic acid (MAA, 99% purity), ethylene glycol dimethacrylate (EGDMA, 98% purity), dichloromethane (DCM), methanol (MeOH) and Hydrochloric acid (HCl) were acquired from Sigma-Aldrich (Lyon, France). Azobis (isobutyronitrile) (AIBN, 98% purity) was supplied by Fluka (Seelze, Germany). Acetonitrile (ACN) was purchased from Carlo Erba (Cornaredo, Italy). Supelclean SPE cartriges (TM LC-Ph SPE Tubes 3 mL) were supplied by Supelco (Lyon, France). Formic acid and orthophosforic acid (85%) were acquired from Merck (Lyon, France). Hovione FarmaCiencia SA (Loures, Portugal) gently provided Mometasone furoate as API. Carbon dioxide was

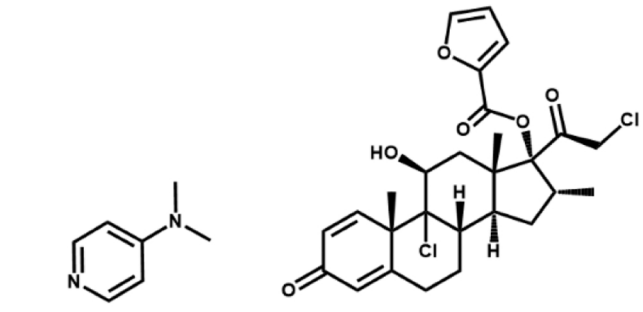

Fig. 1. Structures of 4-dimethylaminopyridine (DMAP) and Mometasone furoate (API).

obtained from Air Liquide (Lisbon, Portugal) with purity better than 99.998%. All chemicals were used without further purification. Ethyl-acetate (EtOAc) was acquired from LabChem (Loures, Portugal).

2.2. Synthesis of DMAP-affinity polymeric particles in $scCO_2$

DMAP-MIP copolymer was produced in $scCO_2$ by free radical precipitation following a methodology previously reported [27]. Basically, in a typical synthesis, 1 mmol of DMAP (template molecule), 4 mmoles of MAA (functional monomer), 20 mmoles of EGDMA (crosslinker) and the AIBN (radical initiator, 1 wt% of total monomers used) were introduced in a 33 mL stainless steel high-pressure cell equipped with two aligned sapphire windows and a Teflon™ coated magnetic stir bar. The cell was submerged in a thermostated water bath at 65 ºC (optimal AIBN initiation conditions) and temperature control was made through an open bath circulator Julabo Ed with stability ± 0.1 ºC. Carbon dioxide was loaded up to 21 MPa and polymerization reactions occurred during 24 h under stirring. At the end of the reaction, the polymer was slowly washed with a fresh stream of $scCO_2$ for 1 h to remove unreacted reagents. The non-imprinted polymer (NIP), a control material, was produced using the same procedure but in the absence of template molecule.

2.3. $ScCO_2$-assisted DMAP desorption

Template desorption from the matrices is a crucial step in molecular imprinting in order to provide empty binding sites for further rebinding processes. $ScCO_2$ has already proved to be able to remove the template from imprinted matrices due to the high diffusivity, typically with an efficiency 10-fold higher than with traditional organic solvent processes [14]. $ScCO_2$-assisted DMAP desorption was carried out by packing the 1 g of pre-synthesized polymer in a tubular reactor (ID 7 mm, 15 cm length), coupled to a 33 mL stainless steel high-pressure cell containing a co-solvent [27], 3 mL of DCM. Both high pressure reactors were immersed in a thermostated water bath at 40 °C and CO_2 was bubbled through the cell containing the co-solvent (bottom to top) and the mixture CO_2-DCM was passed through the tubular reactor. The system was loaded up to a pressure of 20 MPa. The polymer was then slowly washed for 3 h in continuous mode with fresh high-pressure CO_2 to remove all the template and co-solvent from the matrices. The residual amount of DMAP entrapped within polymer was evaluated by crushing 20 mg of DMAP desorbed polymer and stirring for 3 days with 3 mL of DCM at room temperature. Quantification of the template released was carried out by HPLC.

2.4. Evaluation of the performance of the polymeric DMAP-affinity particles by dynamic binding tests

Solid-phase extraction (SPE) experiments were carried out in duplicate in a SPE apparatus coupled to a vacuum pump. For that, 50 mg of both DMAP-MIP and NIP were loaded and packed in 3 mL SPE syringes. Initially, columns were conditioned with 2 × 15 mL of DCM each and their performance was evaluated in two different ways: i) 5 mL of a solution containing only genotoxic compound (104 ppm DMAP) in DCM was placed on the column and then exhaustively washed with DCM; ii) 5 mL of a solution containing API (1018 ppm) and DMAP (104 ppm) in DCM was treated in the same way. The SPE syringes were then washed exhaustively with DCM, ACN and ethyl acetate, sequentially, and the eluate collected and analyzed by HPLC as described below.

2.5. Characterization methods

Scanning electron microscopy (SEM) analysis was assessed through in a Hitachi S-2400 instrument, with an accelerating voltage set to 15 kV. The samples were gold-coated and fixed on aluminum stumps using carbon adhesive tape. Specific surface area and pore diameter of the polymers were determined by N_2 adsorption according to the Brunauer-Emmett-Teller (BET) method. An accelerated surface area and porosimetry system (ASAP 2010 Micromeritics, Norcross, Georgia, USA) was used under nitrogen flow. Dry polymers were degassed under nitrogen atmosphere at 70 ºC for approximately 12 h prior to measurement. Fourier transform infrared spectroscopy (FTIR) measurements were carried out using a Perkin Elmer Spectrum BX FTIR (Waltham, Massachusetts, EUA) (16 scans and 1 cm^{-1} resolution between the 4000 cm^{-1} and 700 cm^{-1}). Samples were produced by preparing tablets containing a finely ground powder of a small quantity of each sample of polymeric particles (DMAP-MIP and NIP) mixed with dehydrated KBr (1:5 mass ratio). Morphologi G3 (Malvern, UK) equipment was used to determine particle size of the affinity particles. The samples were dry-dispersed using an integrated dispersion unit using the following conditions: sample volume 13 mm^3; injection pressure: 0.4 MPa; injection time: 40 ms; Setting time: 120 s; optic selection 50 x. Triplicated dispersions were analyzed.

2.6. HPLC quantification of DMAP and API

Quantification of DMAP and API was carried out using High Performance Liquid Cromatography (HPLC) [35]. A Merck L-7100 HPLC system containing an L-7400 UV detector, D-7000 processor interface and a XT Maraton autosampler was used. The wavelength for the UV detection was 250 nm for both compounds. The isocratic mobile phase was prepared with ACN and 1.5% w/v aqueous ammonium acetate buffer in the ratio 45:55 (% v/v), pH 3.8 (adjusted with orthophosphoric acid). Separations were carried out at 25 ℃ using a Symmetry C8, 150 × 3.9 mm, 5 μm, stainless steel analytical column supplied by Waters (Milford, Massachusetts, USA). A flow rate of 1.0 mL/min was employed to perform the analyses. The DMAP (0.61–122 ppm) and the API (6.5–1300 ppm) samples were run for analysis using a loop volume of 25 μL.

3. Results and discussion

3.1. Material characterization

The produced copolymers were collected in high yields (> 90%, calculated gravimetrically), as white dry-powders, which is in agreement with precipitation polymerization in $scCO_2$ as previously described [31,36]. All the samples showed a similar morphology. A typical SEM image of the particles is shown in Fig. 2. Materials are obtained as aggregated discrete nano-sized particles in contrast to the much larger

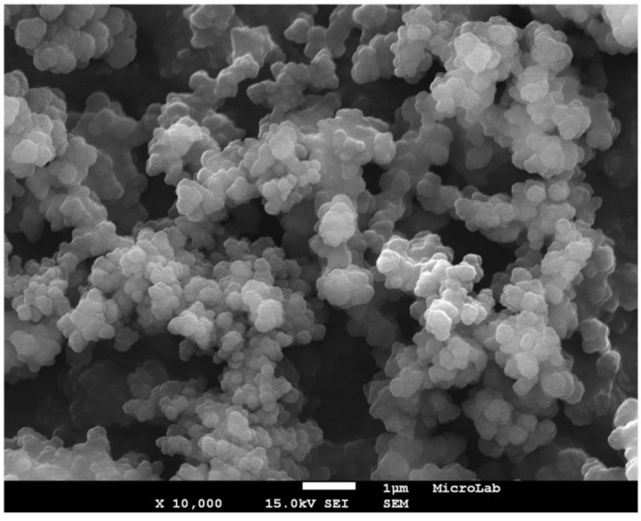

Fig. 2. SEM image of DMAP-affinity polymeric particles.

particles typically reported for conventional molecular imprinting, which have to be ground and sieved before utilization [31,36].

FTIR analysis (Fig. 3) showed the following bands: 3590 cm^{-1} (OH stretch); 1748 cm^{-1} and 1732 cm^{-1} (C═O stretch). Both DMAP-MIP and NIP presented similar spectra and indicate efficient incorporation of carboxylic acid groups into MAA-based polymeric matrices [27].

Physical characteristics of the DMAP-affinity polymeric particles were also evaluated by nitrogen adsorption experiments. They exhibit higher surface area, pore volume and pore size than the control polymer. Both copolymers presented type-II curves [27], which is indicative of the presence of mesopores.

Table 1 shows the average particle size, acquired from Morphologi G3. No significant differences were found in average particle size, between DMAP-MIP sample and its control. Accordingly to the literature, the particle's dimension is strongly dependent on their solubility in the $scCO_2$ phase and on the precipitation conditions from the supercritical phase [27]. The data obtained suggest that both polymeric particles were produced by similar processes, in particular, suggesting that the increase of DMAP content on the polymer reaction step does not influence significantly the average particle size, pore volume and average pore diameter of the copolymer particles, as described previously [37,38]. MIP generally presents higher BET surface area than NIP which reflects the different specific interactions stablished during the polymerization.

3.2. Dynamic binding experiments on DMAP polymeric particles

The dynamic binding experiment results presented in Fig. 4 showed that DMAP polymeric particles (MIP) adsorb DMAP at a level 1.44 times higher than NIP. Takeuchi et al. [24] were the first to explore affinity polymers for DMAP utilizing halogen bonding-based binding sites as Lewis acids with affinity for the neutral Lewis base, DMAP. DMAP-affinity particles were produced in an organic solvent, $CHCl_3$, by a non-covalent imprinting strategy and free radical polymerization where 2,3,5,6-tetrafluoro-4-iodostyrene was the monomer selected, styrene the co-monomer and divinylbenzene the crosslinker. The polymer obtained was ground and sieved (a common procedure in the conventional methodologies) to yield polymer particles with a medium size below 32 μm. These authors performed static binding experiments using 10 mg of this fraction, in 1 mL of a 250 μM (30.54 ppm) solution of DMAP in ACN, removing 3.8 μmol DMAP/g polymer. Further Esteves et al. [25] also reported the use of acrylate-based affinity polymers for DMAP by conventional methods using different compositions of Template:Monomer:Crosslinker (T:M:C) and two different methodologies: i) the polymerization process was carried out at 40 °C during 12 h and then the temperature rose up stepwise each 30 min in 5 °C increments until a temperature of 65 °C was reached and held for additional 4 h; ii) the polymer reaction was performed at 65 °C for 16 h. Copolymers were further crushed and sieved and the fraction with a particle size of 38–63 μm (obtained as a small percentage of the total MIP) was used for affinity measurements. Passing 1.5 mL of a solution containing 100 ppm

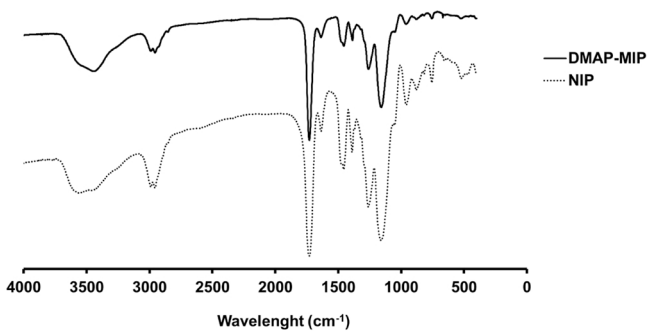

Fig. 3. FTIR spectra of DMAP imprinted and non-imprinted polymer.

Table 1
Physical features of DMAP-affinity polymeric particles produced.

Sample	BET surface area ($m^2.g^{-1}$)[a]	Porosity volume ($cm^3.g^{-1}$)[a]	Average pore diameter (nm)[a]	Average particle size diameter (μm)[b]
Control	26.1 ± 0.7	0.03 ± 0.00	4.2 ± 0.5	3.4 ± 0.3
DMAP-MIP	46.7 ± 1.3	0.07 ± 0.01	5.7 ± 0.7	3.2 ± 0.3

[a] Duplicated samples.
[b] Triplicated samples.

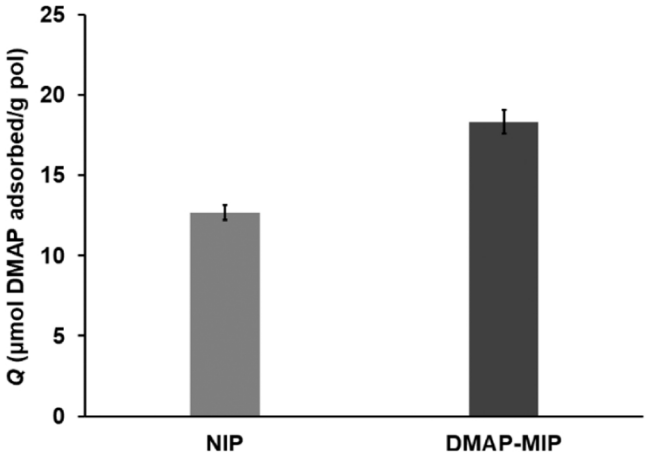

Fig. 4. Dynamic binding experiments on DMAP-MIP and NIP particles.

of DMAP through a column containing 50 mg of this MIP fraction resulted in the removal of 60–95% of DMAP, corresponding to 14.8 and 23.4 μmol DMAP/g polymer.

Herein, we provide a new green and alternative strategy to obtain DMAP-affinity polymeric particles which are able to adsorb higher amounts than those previously reported in the literature, 18.3 μmol DMAP/g polymer.

Fig. 5 shows that the HPLC method was efficient for the separation of DMAP and API.

Fig. 6 summarizes the results obtained for the Solid Phase Extraction (SPE) for DMAP-MIP and NIP, in which it was demonstrated that MIP was able to remove 1004 μmol DMAP/g API over 900.3 μmol DMAP/g API from NIP. In addition, higher recoveries of both, DMAP and API were obtained, above 99% (*see* Fig. 6**b**).

Esteves et al. [25] used a combination of two processes, organic

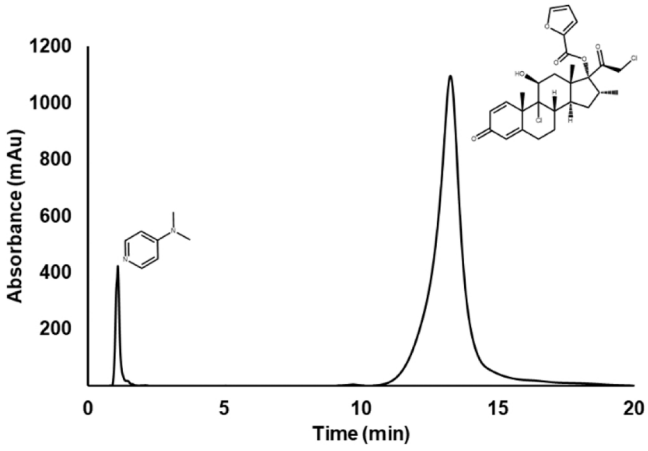

Fig. 5. HPLC chromatogram of DMAP polymeric particles, 25 μL of a model solution of DMAP and API (104 ppm + 1018 ppm).

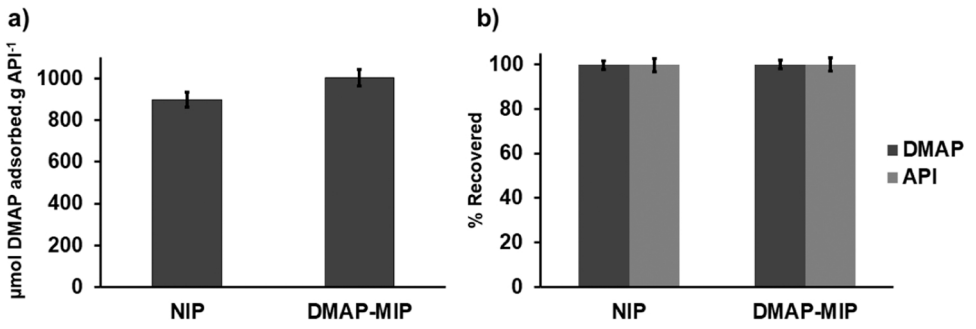

Fig. 6. Solid phase extraction results of DMAP-MIP and NIP particles for DMAP and API: a) µmol of DMAP adsorbed per gram of API and b) % Recovered.

solvent nanofiltration (non-specific) followed by SPE-MIP (specific) to explore removal of DMAP from an API. This procedure allowed to remove from 2.4 to 13 µmol DMAP per gram of API.

Typically, DMAP content on API dosage required is below 60 µmol DMAP per gram of API. Our methodology delivers in a single-step an efficient way to remove higher amounts of DMAP per gram of API, 1004 µmol DMAP per gram of API in comparison to other reported approaches.

Overall, the DMAP-MIP produced under $scCO_2$ was able to compete with conventional strategies in terms of physical characteristics and performance evaluation. The obtained material presented unique features, as aggregated discrete nano-sized particles in contrast to the much larger particles typically reported for conventional molecular imprinting process, which have to be ground and sieved before their utilization. In this green methodology, the use of organic solvents was drastically lower, and in the end of the reaction, there was no need for further purification steps, decreasing the steps involved in the MIP preparation.

4. Conclusions

Affinity polymeric particles were successfully designed towards DMAP in supercritical CO_2 environment for use as a SPE affinity adsorbent material for potential use in API purification processes. Polymeric particles were obtained as a free-flowing material, easy-to-handle and pack. Moreover, DMAP-affinity polymeric particles were characterized by morphological, chemical and physical analyses. The results obtained showed clearly that our technology provides a green, sustainable and effective way to produce polymeric particles with ability to selectively remove DMAP from a crude pharmaceutical mixture. DMAP-affinity particles were able to remove 18.3 µmol DMAP/g polymer from a 104 ppm DMAP solution and 1004.6 µmol DMAP/g API, with high recoveries of DMAP and API (> 99%).

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

The authors are unable or have chosen not to specify which data has been used.

Acknowledgments

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