**Simple design of chemically crosslinked plant oil nanoparticles by triazolinedione-*ene* chemistry**

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ABSTRACT: Plant oils, one of the most abundant source of fatty acids and derivatives thereof, have never been used as starting compounds to prepare chemically crosslinked nanoparticles. In this report, we demonstrate a simple approach for the preparation of chemically crosslinked nanoparticles (PONPs) in minutes, starting from a range of available plant oils (used as renewable starting materials) and, using triazolinedione (TAD)-ene reactions. The size of the PONPs can be controlled (Dh = 140 -260 nm) by varying different reaction parameters. The thermal stability (25oC - 80oC) of these nanoparticles in solution was demonstrated. This study can contribute significantly to the future design of different chemically crosslinked nanoparticles using triazolinedione chemistry for various applications.

**1. Introduction**

Sustainable and simple design of materials is of great concern for both academic and industrial research.[[1-4](#_ENREF_1)] One of the many aspects of sustainable chemistry is to replace petrochemically derived products by renewable alternatives. [[5-7](#_ENREF_5)] Recently, the preparation of nanoparticles from renewable resources (e.g. lignin based) is gaining a lot of interest.[[8](#_ENREF_8), [9](#_ENREF_9)] During the last decades, plant oils and derivatives thereof, appear as one of the most promising renewable resources for the preparation of biobased polymers and materials but they were less reported in context of nanoparticles.[[10-12](#_ENREF_10)] . In a few reports, oils - including plant oils, essential oils and their derivatives - were used as encapsulating agents for the preparation of lipid based particles (LPs).[[13-17](#_ENREF_13)] LPs are an important class of nanomaterials for their use in different kind of applications, such as drug delivery, imaging, therapeutics etc.[[18-24](#_ENREF_18)] From synthetic viewpoint, there are many advantages to use plant oils as a building block for organic nanoparticles, such as (i) plant oils are not (or less) toxic and in general biocompatible, (ii) the presence of inherent ester functionalities, will make the final nanoparticles degradable, (iii) they are easily affordable, and among them many are non-edible oils (such as castor oil), (iv) they are the most abundant sources of fatty acids.

The main problems regarding the use of crude oils for the preparation of nanoparticles are on the one hand the low reactivity of available functional groups that can be addressed to crosslink oils in emulsions with the formation of stabilized plant oil nanoparticles (PONPs) and on the other hand the complex chemical composition of crude oils. Chemical crosslinking of the constituent building blocks within the nanoparticles is a common technique to enhance their structural integrity and stability during applications. Chemically, plant oils mainly contain triglycerides of different unsaturated and saturated fatty acids, in which the most common reactive sites are substituted double bonds from unsaturated fatty acids, which are difficult to link by most conventional chemical reactions.

In this context, we aimed to solve those issues by making use, for the first time in the area of colloidal particles, of the powerful triazolinedione-based chemistry that has been reviewed very recently by us.[[25](#_ENREF_25)] 1,2,4-Triazoline-3,5-dione (TAD), being one of the strongest dienophile and enophile in organic synthesis, reacts fast - within seconds to hours, depending on the nature of unsaturation - with mono or polyunsaturated hydrocarbons and conjugated dienes via Alder-*ene* and Diels-Alder reactions respectively.[[26](#_ENREF_26)] In the context of plant oils, the potential of TAD-*ene* reactions was very recently demonstrated by Türünç et al. [[27](#_ENREF_27)] They showed that crude plant oils could be crosslinked in a few minutes with the formation of fatty acid based polymeric networks (plant oil foils) by reacting crude oil with bifunctional TAD-compounds.

TAD-based reactions were less explored in water due to restricted stability of TAD (hydrolysis within 10-15 minutes in neutral water).[[28](#_ENREF_28), [29](#_ENREF_29)] In spite of this, the fast reactivity of TAD inspired various research groups to study and use the TAD-based reactions in water, especially as efficient click-like reactions for bioconjugation.[[30](#_ENREF_30), [31](#_ENREF_31)] Additionally, Syrgiannis et al. showed that 4-phenyl-1,2,4-triazoline-3,5-dione (4-phenyl TAD) can significantly react with low molecular weight alkenes, such as 2-methyl-2-butene in the presence of water (as a cosolvent).[28]Those experiments inspired us to explore the potential of these type of reactions in colloidal science. Moreover, a very recent tutorial review, describing the importance and future directions on using 'green chemistry' for nanoparticle synthesis, further explains in detail the significance of the actual research effort.[4]

Herein we report a fast, straightforward method for the preparation of chemically crosslinked PONPs by nanoprecipitation, starting from commercially available plant oils and using TAD-ene reactions (Figure 1). For the current work, the nanoprecipitation technique, based on the so-called Ouzo effect[[32](#_ENREF_32), [33](#_ENREF_33)], was chosen for the following reasons: (i) the rapid and spontaneous emulsification technique is advantageous considering the fast TAD-ene reaction kinetics, (ii) the reaction conditions used in this process are similar to those reported in recently explored organic reactions [28], (iii) simple, one step procedure, (iv) elimination of the potent toxicity that comes from surfactants or co-stabilizers and (v) the avoidance of high energy ultrasonification methods.



**Figure 1:** Schematic depiction of the crosslinking reaction between plant oils and MDI-TAD for the formation of plant oil nanoparticles (PONPs).

The size of the nanoparticles was controlled by changing both the solvent ratio and the ratio of plant oils and MDI-TAD. The stability of the cross-linked particles is addressed by checking their diameter by dynamic light scattering (DLS) as a function of both temperature and time.

**2. Experimental section**

**2.1. Materials-** 4,4’-methylene-bis-(phenyl isocyanate), ethyl carbazate (97%), hydrogen chloride in ethanol and all solvents were purchased from Aldrich and used as such. Castor oil was purchased from a local pharmacy (SA Aca Pharma NV) and other plant oils (pumpkinseed, sunflower, hazelnut and olive oil) were purchased in a local supermarket (see Table SI 2 for the unsaturation degree of the used plant oils). All products were used without any pre-treatment or purification.

**2.2. Instruments**

NMR spectra were recorded with a Bruker AVANCE (300 MHz and 500 MHz) FT-NMR spectrometer. DMSO-d6 was used as solvent.

The hydrodynamic size of particles was measured by DLS, which was performed using a Malvern Zetasizer Nano Series running DTS software and operating a 4 mW He–Ne laser at 633 nm. Analysis was performed at an angle of 173°. The same instrument was used to measure the zeta potential. All samples (concentration = 0.1 mg/mL) were analyzed in triplicate to ensure reproducible data. In general, the measurements were performed at 25oC, unless reported otherwise.

Scanning electron microscope (SEM) analysis is performed on a JEOL JSM-5600 instrument. The SEM analysis is performed using a secondary electron detector. Two drops of the diluted emulsion (concentration ~ 0.1 mg/ mL) was dried on a silicon wafer to analyze the nanoparticles by SEM. Prior to analysis, all samples are coated with a thin gold layer using a plasma magnetron sputter coater.

Transmission electron microscopy (TEM) analysis is performed using a JEM- 2200FS FEG-TEM (Jeol), operated at 200 keV, and equipped with an in-column omega filter to reduce chromatic aberration. Energy dispersive X-ray (EDX) spectroscopy was used to analyze the chemical composition in scanning TEM mode (STEM). One drop of a diluted colloidal solution (~ 0.1 mg/ mL) was dried on a carbon coated copper grid to analyze the particles by TEM.

Differential Scanning Calorimetry (DSC) thermograms were recorded using a TA Instruments Q2000 DSC with autosampler option and Refrigerated Cooling System (RCS). Nitrogen gas was used as purge gas. The samples were studied in TAi Tzero Hermetic aluminium sample pans and at a scan rate of 10 K min-1 . Thermogravimetric analysis (TGA) was performed using a Mettler-Toledo TGA/SDTA 851e equipment. Samples (4 - 5 mg) were heated in a nitrogen atmosphere with a heating rate of 10 K min-1 going from 25 oC to 800 oC. For the analysis of the thermograms, the STARe software of Mettler-Toledo was used.

**2.3 Synthesis**

**Synthesis of 4,4’-(4,4’-diphenylmethylene)-bis-(1,2,4-triazoline-3,5-dione) (MDI-TAD)**

4,4’-(4,4’-diphenylmethylene)-bis-(1,2,4-triazoline-3,5-dione) (MDI-TAD) was synthesized in three steps as described elsewhere.[27]

**Synthesis of plant oil nanoparticles (PONPs)**

Stock solutions of plant oil (50 mg) in acetone (1 mL) and MDI-TAD (50mg) in acetone (3 mL) were prepared separately and thereafter mixed and stirred for 3 minutes at room temperature (~20oC). After that, 20 mL water was added to the mixture of plant oil and MDI-TAD with a stirring rate of 400 rpm. The emulsion was formed instantaneously and the red colour disappeared completely within 2 minutes. The emulsion was stirred for 15 more minutes and thereafter acetone was removed from the emulsion using a rotary evaporator. A series of plant oil nanoparticles were prepared in a similar way and the details of the reaction parameters are described in Table 1.

**Table 1:** Experimental conditions for the synthesis of plant oil nanoparticles.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Purpose** | **Experiment** | **Plant oil used** | **Plant oil (mg) [acetone (mL)]** | **MDI-TAD (mg) [acetone (mL)]** | **Mixing time (tmix) (seconds)** | **Water (mL)** |
| Model experiment with different oils (procedures described in experimental part | 1\* | Castor oil | 50 [1] | 50 [3] | 180 | 20 |
| 2 | Olive oil | 50 [1] | 50 [3] | 180 | 20 |
| 3\*\* | Pumpkin oil | 50 [1] | 50 [3] | 180 | 20 |
| 4 | Sunflower oil | 50 [1] | 50 [3] | 180 | 20 |
| 5 | Hazelnut oil | 50 [1] | 50 [3] | 180 | 20 |
| Study of the influence of acetone:water ratio on the preparation of nanoparticles | 6 | Castor oil | 50 [1] | 50 [3] | 180 | 5 |
| 7 | Castor oil | 50 [1] | 50 [3] | 180 | 10 |
| 8 | Castor oil | 50 [1] | 50 [3] | 180 | 16 |
| 9\* | Castor oil | 50 [1] | 50 [3] | 180 | 20 |
| 10 | Castor oil | 50 [1] | 50 [3] | 180 | 25 |
| 11 | Castor oil | 50 [1] | 50 [3] | 180 | 30 |
| Study of the influence of plant oil:MDI-TAD ratio on the preparation of nanoparticles | 12 | Castor oil | 25 [0.5] | 50 [3] | 180 | 17.5 |
| 13\* | Castor oil | 50 [1] | 50 [3] | 180 | 20 |
| 14 | Castor oil | 50 [1] | 25 [1.5] | 180 | 12.5 |
| 15 | Castor oil | 50 [1] | 16.7 [1] | 180 | 10 |
| 16 | Castor oil | 66.5 [1.3] | 16.7 [1] | 180 | 11.5 |
| Study of the influence of mixing time (tmix) on the preparation of nanoparticles | 17 | Castor oil | 50 [1] | 50 [3] | 30 | 20 |
| 18 | Castor oil | 50 [1] | 50 [3] | 60 | 20 |
| 19 | Castor oil | 50 [1] | 50 [3] | 120 | 20 |
| 20\* | Castor oil | 50 [1] | 50 [3] | 180 | 20 |
| 21 | Castor oil | 50 [1] | 50 [3] | 240 | 20 |
| 22 | Pumpkin oil | 50 [1] | 50 [3] | 30 | 20 |
| 23 | Pumpkin oil | 50 [1] | 50 [3] | 60 | 20 |
| 24 | Pumpkin oil | 50 [1] | 50 [3] | 120 | 20 |
| 25\*\* | Pumpkin oil | 50 [1] | 50 [3] | 180 | 20 |
| 26 | Pumpkin oil | 50 [1] | 50 [3] | 240 | 20 |

\* and \*\* indicate entries with same experimental setup.

**3. Result and discussions**

**3.1. Synthesis and characterization of the nanoparticles from castor oil**

For the initial study, the preparation of PONPs was investigated in detail for castor oil, known to be chemically the most pure plant oil. Primarily, castor oil is composed of the triglyceride of monounsaturated ricinoleic acid (Fig. 1, 85% - 95%, source dependent). After this proof of concept study, the synthetic procedure has been repeated on four other plant oils as well, i.e. olive, pumpkin, sunflower and hazelnut oil (section 3.4).

To prepare the PONPs, stock solutions of plant oils, such as castor oil, and an aromatic bifunctional triazolinedione compound [4,4-(4,4-diphenyl-methylene)-bis-(1,2,4-triazoline-3,5-dione; MDI-TAD, Figure 1] in acetone were prepared separately, and then mixed in several ratios (see table 1) for 3 minutes prior to the addition of water. The time, allowed to mix the plant oil and crosslinker before the addition of water into the reaction mixture, was defined as 'mixing time’ (tmix). A systematic study revealed that a minimal mixing time is prerequisite to obtain a homogeneous solution of plant oil and MDI-TAD and get a good control in both size and dispersity of the prepared PONPs later on (Table SI 1). It is important to note that the reaction between the plant oil and MDI-TAD immediately started as soon as they were mixed, which initiated the network formation slowly but instantaneously. After 3 minutes, water was added to the mixture, and the emulsion formed spontaneously. The reaction was finished within 2 minutes after the addition of water as can be visualized by the disappearance of the deep red colour of MDI-TAD, resulting in the formation of chemically crosslinked PONPs. After stirring the emulsion for an additional 15 minutes, acetone was removed by vacuum and a colloidal solution containing the crosslinked plant oil nanoparticles was obtained. As shown by DLS, the hydrodynamic size of the nanoparticles can be tuned within the range of dh = 140 - 260 nm by changing different reaction parameters (section 3.2). Moreover, the emulsions were found to be stable for at least 2 months (Table SI 2).

For the whole study, while reporting the ratio of the reactants (Table 1, plant oils: MDI-TAD), we used their weight and thus not their mole ratio of the ene functionalities in relation to MDI-TAD. This choice is based on (i) the complex chemical compositions of the plant oils, and (ii) nature of the TAD-ene reaction, i.e. a ene-function actually results in another ene-function after reaction. For this reason, striving for a 1:1 ene:TAD mole ratio for a given oil is not useful. On the other hand, with a fixed mass ratio, the chemical composition of the particles can be controlled on the level of the constituents.

In order to confirm chemical reactions between the plant oils and MDI-TAD during the formation of the PONPs by NMR, the emulsions were prepared using D2O and then dried. The solid nanoparticles were washed with deuterated acetone and thereafter dispersed in deuterated DMSO. Analysis of the PONPs by 1H-NMR shows the presence of broad signals (expected for crosslinked structure) for both the aliphatic protons of the fatty acid residues (δ = 0.8 - 1.8 ppm) and the phenyl protons from MDI-TAD (δ = 7.1- 7.5 ppm) (Figure 2). In addition, the newly generated urazole protons (NH) were found at δ = 9.8 ppm and the protons attached to double bonds were also visualized at δ = 5 - 6 ppm, confirming the reaction between plant oils and MDI-TAD in the nanoparticle.



**Figure 2:** 1H NMR spectra of castor oil and corresponding crosslinked PONP (experiment 1, Table 1).

The castor oil based nanoparticles were also characterized by DLS, which showed the formation of particles with low polydispersity (PDI = 0.07) with an average hydrodynamic diameter of 155nm (Figure 3A). To demonstrate the thermal stability of the cross-linked PONPs in solution, the hydrodynamic radius of these nanoparticles was measured at three different temperatures, respectively at 25oC, 50oC and 80oC (Figure 3A, Table SI 3). The observation of the same hydrodynamic diameter and size distribution (Figure 3A) of these nanoparticles in this temperature window supported the fact that the PONPs were formed as a result of chemical crosslinking between MDI-TAD and plant oils, and thus not only because of the inherent presence of physical crosslinking of the attached urazole groups (H-bonding) at lower temperatures (< 75°C).[[34](#_ENREF_34)] [[35](#_ENREF_35)]



**Figure 3:** Characterization of the PONPs: (A) Contin plots from DLS (intensity average distribution at 3 different temperatures), (B) SEM images, (C) TEM images. TEM images (D) and corresponding STEM-EDX analysis of (E) carbon, (F) nitrogen and (G) oxygen indicate an even crosslinking of the plant oil network by the MDI-TAD crosslinker (\* TEM studies were performed using a carbon coated copper grid).

To visualize the size and shape of the PONPs, the particles were analyzed by both SEM and TEM (Figure 3B and 3C). The SEM- images confirmed the presence of spherical PONPs with an average diameter (d) of 153 nm with a size distribution of 0.07, as measured by image analysis on 500 nanoparticles (Figure SI 1). Sphericity of the nanoparticles (dmin / dmax) was calculated from SEM images, by analyzing 50 individual nanoparticles. For the PONPs obtained from castor oil, this calculated sphericity was 0.94. To understand the elemental composition of the PONPs in more detail, STEM-EDX analysis of the nanoparticles was performed (Figure 3D to 3G), which confirmed the presence of C, N and O as main elements, as a result of the TAD-adduct formation ( also Figure SI 2 and 3). The colloidal stability of these nanoparticles is ascribed to their negative zeta potential (- 40 mV), which appeared as a result of the deprotonation of acidic urazole groups (pKa ~ 5.3) at pH ~ 6.7 (Figure SI 4). [[36](#_ENREF_36)]

**3.2. Effect of experimental parameters on the particle size**

To study the influence of different reaction parameters on the formation of nanoparticles in more detail, the ratio of water and acetone on the one hand and the ratio of plant oils and MDI-TAD on the other hand has been varied. To understand the influence of the water: acetone ratio, we always used similar concentrated stock solutions of plant oil and MDI-TAD. In all cases stable emulsions containing PONPs with low polydispersity (PDI = 0.14 - 0.06) and dimensions in the range between dh = 260 nm - 150 nm were obtained. The diameter and polydispersity of the formed nanoparticles can be decreased by increasing the relative amount of water until a certain minimum was reached (dh ~ 155 nm and PDI ~ 0.07) (Figure 4A). Nanoparticles with this diameter were formed in a reproducible way when the volume ratio of water and acetone is 4:1 or higher. Indeed, further increase of the amount of water did not significantly change the diameter of these particles. Considering the above results, the ratio of water:acetone was always kept constant at 5:1 to understand the effect of the amount of crosslinker (MDI-TAD) used.

At different ratios of castor oil to MDI-TAD, it was found that the average size of the nanoparticles increased from about 135 to 200 nm when lowering the amount of MDI-TAD (Figure 4B). This observation can be explained by the fact that a lower amount of crosslinker resulted in a smaller degree of crosslinking and thus less structural integrity, leading to higher degree of swelling. The soft nature of these nanoparticles can also be visualized from the SEM image, when the ratio of plant oils to MDI-TAD is 3:1 or higher (Figure SI 5).



**Figure 4:** (A) Effect of the volume ratio of water and acetone on the size of the castor oil based nanoparticles (on the right side relevant contin plots from DLS), (B) Effect of the weight ratio of castor oil and crosslinker on the size of the nanoparticles (on the right relevant contin plots from DLS).

**3.3** **Thermal analysis of the solid dried castor oil nanoparticles**

In an earlier publication from our group, it was reported that the introduction of an aromatic crosslinker increases the rigidity of the crosslinked plant oil networks (foils), which resulted in an increase of the glass transition temperature (Tg). [27] In order to understand the thermal properties of the crosslinked nanoparticles and compare with the previous reported ones, the dried castor oil based PONPs (ratio of castor oil: MDI-TAD = 1:1, water: acetone = 5:1) were subjected to Differential Scanning Calorimetry (DSC) and Thermo-gravimetric analysis (TGA). As shown in figure 5A, the nanoparticles exhibited broad Tgs. The mid point Tg is 85 oC (comparable to the crosslinked foils - reported as 75 oC [27]). The TGA thermogram (Figure 5B) confirmed excellent thermal stability (no/negligible mass loss) of the nanoparticles till 250 oC.



**Figure 5:** (A) DSC (2nd heating) and (B) TGA thermograms of the castor oil based PONPs.

**3.4 Preparation of nanoparticles from other plant oils**

As mentioned earlier, the above described synthetic procedure has been repeated on four other plant oils as well, i.e. olive, pumpkin, sunflower and hazelnut oil. These oils were chosen based on their difference in chemical composition, more specifically the nature of unsaturation - olive and hazelnut oil have a higher percent of monounsaturation whereas the pumpkin and sunflower oil contains higher percentages of polyunsaturated fatty acids (Table SI 4). The nanoparticles prepared from different oils using the same procedure were characterized by DLS, as described in Table 2.

**Table 2:** Characterization of the nanoparticles prepared from different plant oils (ratio, plant oil : MDI-TAD = 1:1)

|  |  |  |  |
| --- | --- | --- | --- |
| **Used plant oil (degree of unsaturation)** | **Diameter (dh) [error#] (nm)** | **PDI [error#]** | **Zeta potential (mv)** |
| Olive (~ 85%) | 185 [± 6] | 0.11 [± 0.02] | -30 |
| Pumpkin (~77%) | 172 [± 8] | 0.08 [± 0.03] | -35 |
| Sunflower (~ 88%) | 178 [± 10] | 0.07 [± 0.05] | -33 |
| Hazelnut (> 90%) | 175 [± 10] | 0.09 [± 0.04] | -35 |

# Each experiment was performed in triplicate to determine the error. All samples were analyzed in triplicate, thus in total 9 measurements were done before reporting

The prepared nanoparticles from different oils were also visualized by SEM, which confirmed the formation of stable spherical nanoparticles (similar to castor oils), with an average diameter ~ 170 -180 nm (Figure SI 6). This study confirmed the applicability of this procedure, irrespective of the nature of fatty acids and their composition as long as a substantial amount of double bonds are present.

**4. Conclusion**

TAD-ene reactions were used to develop a simple, one-pot approach for the preparation of surfactant-free crosslinked nanoparticles in minutes, starting from crude, readily available plant oils. The size of these PONPs was decreased by increasing the ratio of water to acetone. For castor oil as plant oil source, the hydrodynamic diameter reached a minimum (dh ~ 155 nm) when the ratio of water and acetone was 4:1 or higher. On the other hand, the size of the nanoparticles increased by decreasing the amount of the used MDI-TAD crosslinker. Thermal stability of these colloidal PONPs was confirmed by DLS to temperatures up to 80°C. Furthermore, the nanoparticles still contain a significant amount of double bonds, as evidenced by 1H-NMR, because of the nature of the TAD-ene reaction. These double bonds would allow further modification of these nanoparticles as a function of the envisaged applications. [[37](#_ENREF_37), [38](#_ENREF_38)] Because this synthetic procedure was shown to be applicable for the preparation of nanoparticles from triglycerides of a wide range of fatty acids, it is expected that this procedure will allow to prepare cross-linked nanoparticles for different targeted applications from other double-bond containing building blocks.

**Supplementary information:** Details of DLS data, SEM images, details of elemental analysis by STEM-EDX mapping and a blank experiment were given in SI.

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