A Survey of Synthesis Processes for N-doped Carbon Dots Assessed by Green Chemistry, Circular and EcoScale Metrics

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ABSTRACT

Six most promising lab-scale synthesis process methodologies for N-doped carbon dots (NCDs) are selected and compared in terms of green chemistry, circular and EcoScale/Good-Manufacturing-Practice metrics. We compare a new innovative route, the low-temperature plasma-enabled synthesis of carbon dots, *e.g.* from citric acid and monoethanolamine, to more-established literature processes, such as thermochemical processes, from the same or other materials. Along with this study, the advantages and disadvantages of each method are depicted in manifold sustainability facets. It is shown how recycling/reuse of non-converted starting materials and solvents can improve the sustainability profile. In addition, safety constraints, cost analysis, and energy consumption are considered. The analysis showed that the thermal process from citric acid and monoethanolamine gives the best performance with regard to the sustainability assessment chosen here. It has a material circularity indicator of 0.971, with an EcoScale factor of 56%, and an E-factor of 5.56. In continuation of those results, the paper shows how the low-temperature plasma using the same materials and the same recycling strategy can be improved to come closer to the performance of its thermal counterpart. It has the best energy efficiency, while lacking so far in mass efficiency. From this study, we learned more about which of these methods are most promising for scaling-up and industrial manufacturing of N-doped carbon dots.

KEYWORDS: green chemistry, circular and EcoScale metrics, laboratory-scale synthesis, large-scale synthesis, nitrogen-doped carbon dots

List of abbreviations

F_R	Fraction from recycled sources.
C_C	Fraction of mass to go into a composting process.
C_R	Fraction of mass to go into a recycling process.
E_F	Efficiency of the recycling process.
W	Mass [kg] of unrecoverable waste associated with a product.
W_0	Unrecoverable end-of-life waste [kg] through a product's material.
W_F	Unrecoverable waste [kg] generated when recycling.
LFI	Material flowing in a linear fashion.
F(X)	Utility factor built as a function of the utility *X* of a product.
MCI	Material Circularity Indicator.

INTRODUCTION

Carbonic nanomaterials such as nanodiamonds, fullerenes, carbon nanotubes, graphene sheets, and fluorescent carbon nanoparticles (Carbon Dots: CDs) have strongly emerged during recent years thanks to their many exciting properties. One of the key features of these novel nanomaterials is their optical properties, which can be customized by the nanoparticle size and shape.[1] Consequently, this typical characteristic of these nanomaterials leads to a variety of important applications in medicine,[2] agriculture,[3] electronics,[4] environment,[5] etc. However, despite being discovered serendipitously by (Xu *et al*.) in 2004,[6] carbon dots (CDs) has been considered as a stronger candidate for various applications due to their smaller particle size ranging from 1-10 nm in comparison with these carbon nanomaterials.[7] This class of fluorescent CDs is, apart from that, not only interesting due to their optical properties,[8] but also because of their high aqueous solubility, electronic properties as well as excellent biocompatibility and functionalizability.[8-13] Thanks to these outstanding characteristics, CDs have manifold uses as sensors (including chemo and biosensors),[14] catalysts, pesticides and fertilizers, chemical and bio-sensing, bioimaging, drug/gene delivery[15-17], and optoelectronic devices applications.[7, 18]

In an agri-tech context, CDs have been used as nanopesticides to enhance crop efficiency throughout various functionalities such as pesticide nanocarriers, pesticides, pathogen targeting, and phytopathogen detection.[19] This underlines the above-mentioned

arguments (pros/cons of CDs) at a real-life example of eminent importance for humankind, which we have compiled in a review paper.[20] Pesticides are extensively used in modern agriculture and are an effective and economical way to enhance the yield quality and quantity of vegetables, ensuring consequently food security for the ever-growing population around the globe.[21] The application of chemical pesticides is still preferred over all other alternatives to protect crops from yield loss.[22, 23] Presently, throughout the globe approximately 2 million tonnes of pesticides are used, from which 47.5% are herbicides, 29.5% insecticides, 17.5% fungicides and 5.5% other types.[21, 24] The top ten pesticide consuming countries in the world are China, the USA, Argentina, Thailand, Brazil, Italy, France, Canada, Japan and India. Moreover, it has been estimated that by the year 2020, the global pesticide usage will increase up to 3.5 million tonnes.[21, 25, 26] The downside of the extensive use of pesticides is soil and water pollution, as well as remaining contaminants in the crops, which finally enter the food chain. This poses threat to humans and the environment.[27] In order to tackle this issue, new research initiatives have developed new technologies and new materials (e.g. well-engineered CDs) to promote the development of safe and sustainable agro-systems. [20, 28]

In comparison with the first-generation metal quantum dots (QDs) (e.g. cadmium quantum dots) with regard to agriculture applications, CDs – considered as the second generation of quantum dots – are proved to be less toxic and more environmentally friendly.[8] In terms of the fabrication process, CDs synthesis is simpler than the (high-temperature) routes described for metal QDs, with the potential to lower production costs, keeping comparable optical properties and versatility for chemical modification and surface passivation.[29] Importantly, to enhance the typical properties of CDs, surface modification and passivation is one of the most effective functionalization approaches. Among surface functionalization strategies, doping of CDs with nitrogen (N-doped carbon dots, NCDs) has proven to be the most effective for tuning catalytic activity, electronic and optical properties.[30] Yet, the need for doping may rise the process complexity, costs and toxicity.[31] Thus, as a complementary bio-approach, different procedures for the synthesis of NCDs have been described using natural precursors such as milk[32] and soy milk,[33] peanut[34] and prawn shells,[35] grass,[36] silk,[37] seaweed,[38] mushroom[39] and Prunusavium fruit,[40] or biomass waste (orange peels,[41] lemon peels,[42] rice residue,[43] coffee ground,[44] etc.), but with limited production and quantum yields. Besides the mentioned performance functions of CDs and NCDs, those natural precursor based-nanomaterials have resistance to photobleaching, superior electron transfer ability, versatile surface engineering properties, outstanding colloidal stability, which limits their potentials in agri-tech applications.

The key to that is chemical process technology, which is also suitable at an industrial scale. Yang *et al.*[45] first synthesized CDs by facile, economical microwave pyrolysis in a household microwave oven within 7 min, with a production efficiency yield of 30%. Chen *et al.* [46]synthesized CDs at gram scale with a high yield (42%) by carbonization of sucrose with oil acid in one-step synthesis. Similarly, Hu *et al.* [47]developed a rapid thermal synthesis of NCDs from citric acid with a yield of 15% in 10 minutes. Hydrothermal methods have been also developed to increase CDs' production rate, *e.g.* Zhang *et al.* [48]conducted a green, versatile, and scalable route to prepare CDs at a large scale from commercial bee pollens with a high production yield of 30%. Other references use ultrasonic baths at 300W and 40 kHz during 24 hours at room temperature.[49] The latter uses a bombined effect of ultrasounds with thermal, since the temperature of the bath is also increased along 24 hours sonication. Yet, in this case, no extra heating energy is needed.

Other more sophisticated methodologies, such as thermal plasma, have been considered to produce CDs on a large scale; concerning the needs of the specialty functional materials (with many grams or few kilograms being 'large'). In this context, Kim *et al.*[50] carried out a size-controllable and low-cost fabrication method of graphene quantum dots (GQDs), using a thermal plasma jet with a production rate of 4 g/h. Microplasma, with its much smaller reaction volumes, has been considered as well, as process miniaturization might help to conduct a process in a more controlled way. Ma *et al.* [51]demonstrated the synthesis of NCDs via a microplasma-assisted process at atmospheric pressure, yet with a low yield of 0.4%.

This analysis makes clear that the yield and productivity rate has to be improved, if CDs syntheses should become industrial and be considered green. Otherwise, they produce much more waste relatively than a normal chemical process. Besides the yield, the use of environmentally friendly starting materials and process conditions is demanded; yet a high yield is even for those mandatory. Seeing the above state of the art, yield should be, at least, larger than 50%. The Circular Economy (CE) concept goal aims at re-using all compounds in a process and manufacturing lifecycle, while concurrently increasing their usage and reducing their waste. The European Commission has filed the EU Circular Economy Action Plan[52] (EU CEAP) as a top priority, with the aim of *'closing loops'* by greater re-use and recycling of materials. To quantify how close a process is to true circularity, circular metrics have been introduced by the Ellen MacArthur Foundation's CE100 program, where the Material Circular Indicator (MCI) has been used as a central metric.[53]

While CDs have so far hardly reached industrial scale, other nanomaterials have. True sustainability studies, beyond using bio-approaches or similar, are largely missing. This CDs process engineering study wants to close this missing link. Green chemistry and circularity metrics are used to assess the sustainability of thermal, microwave-assisted, hydrothermal, thermal plasma and microplasma methods for the synthesis of CDs (Figure 1). In this study, all processes were considered as closed systems, so secondary manufacturing or landfill costs were not considered to avoid the complexity of the study and not introducing too many possible alternatives to the proposed production circular loops.

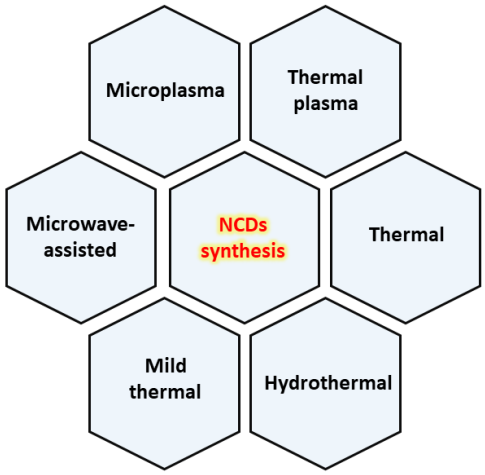

Fig. 1: Potential synthesis pathways of N-doped carbon dots (NCDs).

EXPERIMENTAL

The vast majority of the literature relevant for this paper are scientifically-curiosity oriented regarding the design and synthesis of new nanomaterials, and do not head for process-sustainability information concerning future industrial processes as we give. They investigate the use of various precursors, synthesis methods, characterization of synthesized CDs, and new applications of CDs. All of those studies were conducted at laboratory-scale while the possibility to produce CDs at a large scale is hardly explored, and the combination of lab-scale and higher scale publications could deliver leverages in working conditions due to scale-up.[54] All those research papers lack process data which are essential for this study (e.g. initial mass of starting materials, mass of products, production yields, etc.) and do not allow to make conclusions for a large-scale production of CDs. Table 1 and Table 2 show the underlines above and explains the reasons why selected papers are used in our manuscript.

Raw data from each scenario are collected from literature, including mass of starting materials and products, cost of materials, energy consumption, and reaction time. Based on that, a comparison of the calculation of green chemistry and circularity metrics is performed.

As CDs and other nanomaterials do not have a defined molecular structure, as low-molecular weight compounds have, and typically do not react by just one defined reaction mechanism, a yield as a percentage value of mole product per mole reactant cannot be defined; as common in chemical engineering. Rather a mass-rated yield, termed mass-yield, is used in the following; meaning the mass of nanomaterial produced per mass of key reactant. The latter is the one providing the carbon (and nitrogen) atoms and is not used in excess to other reactants. The list of six selected synthesis methodologies with specific parameters is shown in table 3.

Table 1. References of N-doped carbon dots with and without process information

Name of methodologies	**Our collected references**		**Other references with similar protocols**	
	Name of collected reference	**Relevant process information for this assessment**	**Reference**	**Missing process information for this assessment**
Hydrothermal	Zhang et al. (2015)	After synthesis, 0.3 g of CDs are obtained out of 1 g of starting materials.	Zheng *et al.* (2017)[55]	This report does not reveal the mass of obtained CDs.
			Han et al. (2020)[56]	This report does not reveal the mass of obtained CDs.
			Wang et al. (2018)[57]	This report does not reveal the mass of obtained CDs.
Microwave	Yang et al. (2017)	After synthesis, 3 g of synthe-sized CDs are obtained.	Liang et al. (2019)[58]	This report does not reveal the mass of obtained CDs.
			Gul et al. (2020)[59]	This report does not reveal the mass of obtained CDs.
			López et al. (2015)[60]	This report does not reveal the mass of obtained CDs.
Thermal	Chen et al. (2013)	After synthesis, 8.36 g of synthe-sized CDs are obtained.	Rimal et al. (2020)[61]	This report does not reveal the mass of obtained CDs.
			Ma et al. (2019)[62]	This report does not reveal the mass of obtained CDs.
			Wei et al. (2019)[63]	This report does not reveal the mass of obtained CDs.
	Hu et al. (2015)	After synthesis, 40.0 g of synthe-sized CDs are obtained.	Dong *et al.* (2014)[64]	This report does not reveal the mass of obtained CDs.
Thermal plasma	Kim et al. (2019)	After synthesis, 4 g of synthe-sized CDs are obtained.	Li et al. (2013)[65]	This report does not reveal the mass of obtained CDs.
Microplasma	Ma et al. (2020)	The yield of the reaction is 0.42%.	Carolan et al. (2017)[66]	This report does not reveal the mass of obtained CDs.
			Wang et al. (2015)[67]	This report does not reveal the mass of obtained CDs.
			Huang et al. (2014)[68]	This report does not reveal the mass of obtained CDs.

Table 2. References of N-doped carbon dots made by thermal methods with and without process information.

Compounds	Yield	Volumes	Process	Working conditions	Purification and NCD's features	Fluorescence	References
o-phenylenediamine 2,6-pyridinedicrboxylic acid	n/a	108mg 167mg	Thermal	180°C 4h	+ Purification by scratching the crucible and washing with water + Particle size 4.9 nm	365 nm QY = 34%	*69*
Carboxymethyl cellulose Polyethyleneimine	n/a	100mg 1mg	Hydrothermal	260°C 2h	+ Purification in three steps: (i) Centrifugation 10,000 rpm 12 min, (ii) Filtration 0.22µm, (iii) Dialysis membrane (1kDa) + Particle size 3.4 nm	465 nm QY = 44%	*70*
Pulp-free grapefruit juice Urea Water	n/a	20 ml 1.82 ml 20 ml	Hydrothermal	180°C 6h	+ Purification in three steps: (i) Centrifugation 5,000 rpm 15 min, (ii) Dialysis 3.4 kDa 48 h, (iii) Freeze-drying + Particle size 6.34 nm	365 nm	*71*
Silk Citric acid Water	n/a	160 mg 160 mg 4ml	Hydrothermal	200°C 3.5h	+ Purification in three steps: (i) Centrifugation 11,000 rpm 15 min, (ii) Dialysis 0.5 kDa 12 h, (iii) Freeze and vacuum drying + Particle size 5.6 nm	360 nm QY = 61%	*72*
4-aminophenol Water	n/a	500 mg 20 ml	Hydrothermal	200°C 20h	+ Purification in three steps: (i) Centrifugation 14,000 rpm 20 min, (ii) $CHCl_3$ addition and organic layer separation, (iii) Dialysis 1 kDa 24 h + Particle size 2.25 nm	340 nm QY = 45%	*73*
Gum tragacanth Ethylenediamine Water	n/a	1000mg 3.12mg 60 ml	Hydrothermal	180°C 10h	+ Purification in two steps: (i) Centrifugation 20,000 rpm 15 min, (ii) Freeze drying of the liquid fraction + Particle size 2 nm	436 nm QY = 66.7%	*74*
$Ti(SO_2)_2$ $H_2C_2O_2{\cdot}2H_2O$ *N*-ethylpiperazine	60 %	240 mg 252 mg 83µl	Hydrothermal	180°C 72h	+ Crystals washed with water and ethanol + Particle size 4 nm	n/a	*75*
Citric acid Ethylenediamine Water	63 %	2 g 0.7 ml 0.5 ml	Hydrothermal	110°C 4h	+ Water and methanol added for purification + Particle size 2.5 nm	365 nm QY = 73%	*76*
L-citrulline Water	n/a	500 mg 25 ml	Hydrothermal	220°C 12h	+Purification in two steps: (i) Centrifugation 17,000 rpm 40 min, (ii) Filtration 0.22µm. + Particle size 2.7 nm	350 nm QY = 33%	*77*
Ammonium citrate Triethylenetetramine Water	n/a	2.43 g 1.46 ml 10 ml	Microwave pyrolysis	800W 2 min (3 cycles of 1 min 800W)	+ For each cycle, 5 ml water addition + Purification in three steps: (i) Centrifugation 15,000 rpm 10 min, (ii) Filtration 0.22µm, (iii) Dialysis 1 kDa 48h + Particle size 7 nm	350 nm QY = 30%	*78*

NCDs process chemistry methodologies

NCDs process chemistry methodologies from the literature review (including hydrothermal, thermal, microwave, thermal plasma, and microplasma) are briefly described with a fabrication process diagram in the following sections.

Hydrothermal NCDs synthesis process (Scenario 1)

In this method (Figure 2), commercial pollen bees are well-dispersed into water under sonication.[48] Then, the resulting pollen solution is transferred into a Teflon-lined stainless-steel autoclave and heated up to 180 ^{0}C for 24 h, and cooled down to room temperature before undergoing vacuum filtration. Finally, the synthesized carbon dots are stored at 4 ^{0}C for characterization and applications. 1 g bee pollen costs about 0.07 Chinese yuan, equivalent to about 0.01 US dollar. At least 3 g of CDs can be prepared from 10 g input of the raw material, giving a mass-yield of ≈30% (w/w).

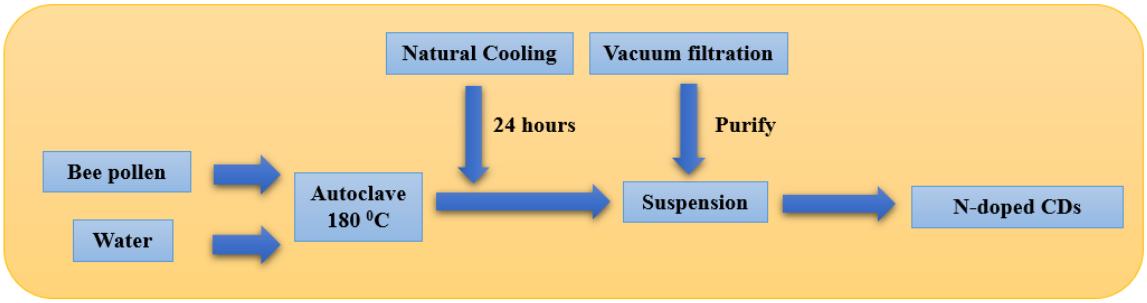

Fig. 2: Hydrothermal NCDs synthesis process from pollen bees.

Thermal NCDs synthesis process (Scenario 2)

In this method (Figure 3), precursors are heated up without using water as a solvent during reaction, since oleic acid performs as a solvent.[46] Sucrose and oleic acids are rapidly mixed and transferred into a three-neck flask at 215 ^{0}C to allow 5 minutes reaction. Thereafter, the mixture is purified and extracted by using water and hexane. Finally, the extracted products are dialysed using a 0.5 kDa membrane before freeze-drying, giving a mass-yield of 42%.

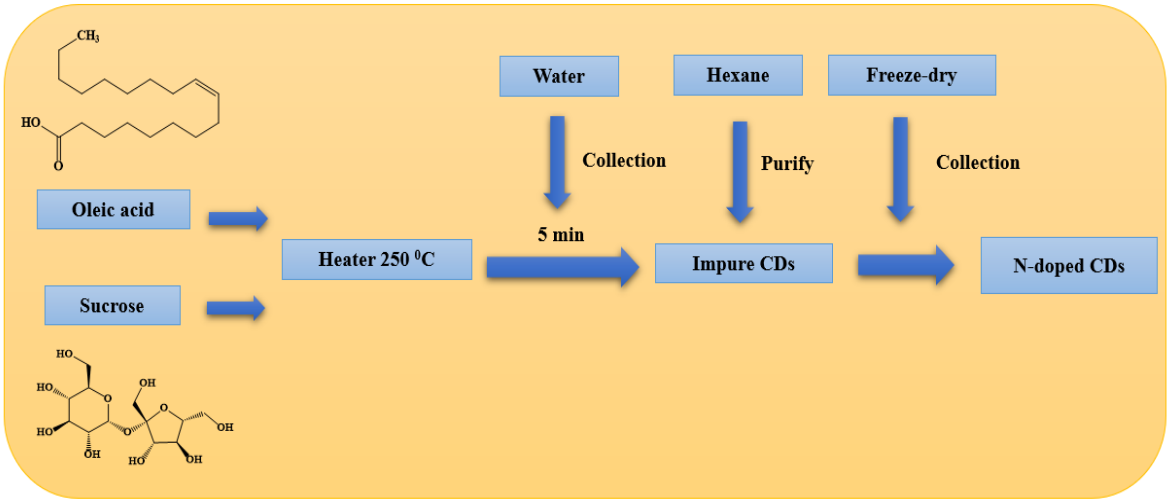

Fig. 3: Thermal NCDs synthesis process from oleic acid and sucrose.

Thermal NCDs synthesis process (Scenario 3)

In this method (Figure 4), citric acid and monoethanolamide (MEA) are mixed under mechanical stirring, and then heated up to 170 ^{0}C.[47] Soon after, the mixture becomes a transparent solution, turning also from colourless to yellow, indicating the generation of NCDs. The solvent removal is conducted under a vacuum oven to obtain 40 g of products.

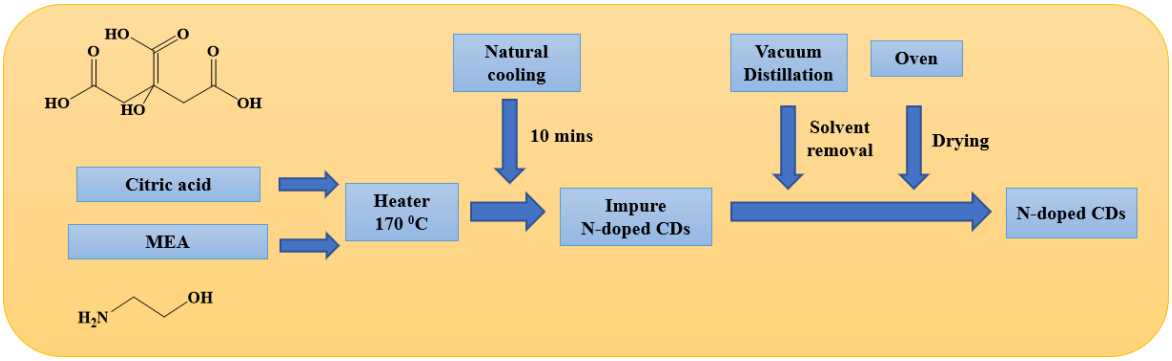

Fig. 4: Thermal NCDs synthesis process from citric acid and monoethanolamide.

Microwave-assisted NCDs synthesis process (Scenario 4)

This method (Figure 5) uses household microwave equipment for heating.[45] 4,7,10-trioxa-1,13-tridecane-diamino (TTDDA) and glucose are mixed well in distilled water under sonication. Then, the obtained solution is heated for 7 mins, obtaining an aqueous solution with a concentration of CDs of 20 mg/mL, which is freeze-dried. The mass-yield is 30%.

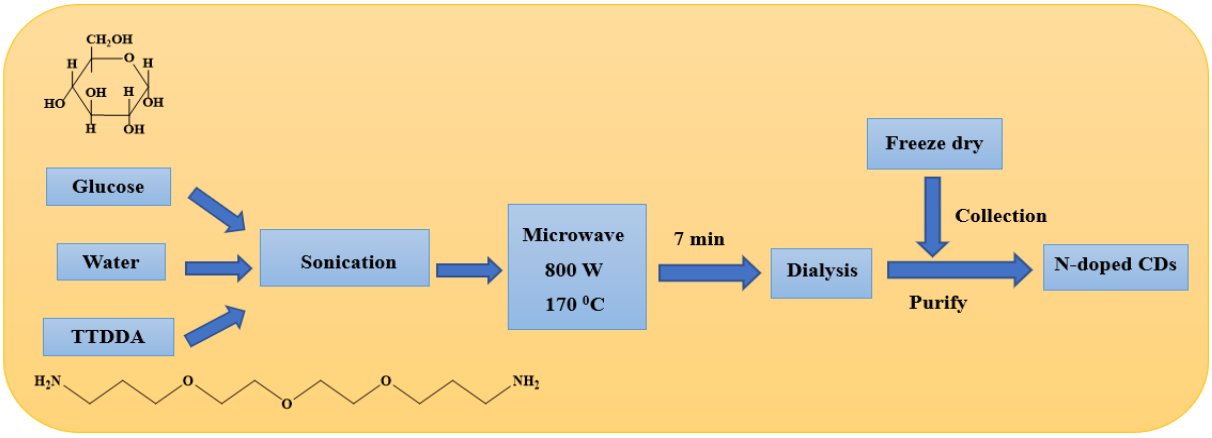

Fig. 5: Microwave-assisted NCDs synthesis process from glucose and 4,7,10-trioxa-1,13-tridecane-diamino (TTDDA).

Thermal plasma NCDs synthesis process (Scenario 5)

Thermal plasma is generated by applying a high voltage of 3 kV between a zirconium-containing tungsten cathode and a copper anode (Figure 6).[50] The thermal plasma jet is operated by a direct voltage with a current of 200 A. A carbon atomic beam is generated by injecting a large amount (2.5 L/min) of ethylene gas continuously into an argon plasma. The beam flows then through a carbon tube (5, 10 or 20 cm in length depending on the desired size of CDs) attached to the anode and then is dispersed into a chamber. The CDs are made by gas-phase reaction. The production rate of the carbon soot is 40 g/h at a 2.5 L/min injection rate. While the carbon soot is dispersed in ethanol by sonication, isolated CDs are dispersed in ethanol by stirring.

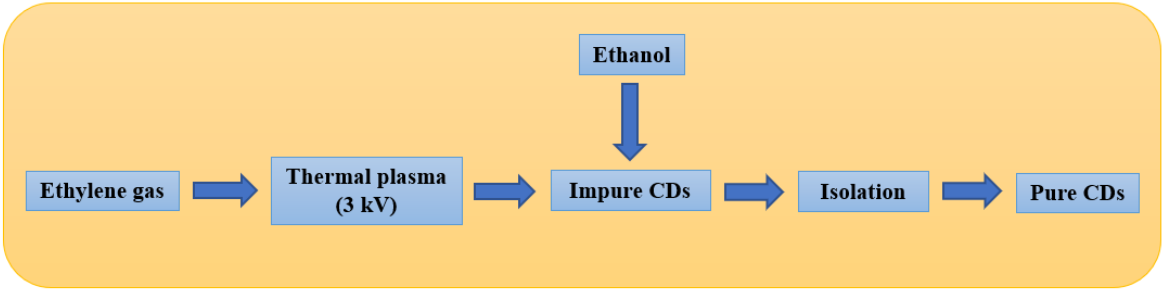

Fig. 6: Thermal NCDs synthesis process from ethylene.

Low-temperature microplasma–assisted NCDs synthesis process (Scenario 6)

A second low-temperature plasma-assisted method uses citric acid and ethylene diamine dissolved in deionized H_2O (Figure 7).[51] The resulting solution is transferred into a self-designed quartz reactor, where microplasma is applied to the solution for 20 minutes. The product is purified by dialysis and freeze-dried. This procedure has a mass-yield of 0.4%.

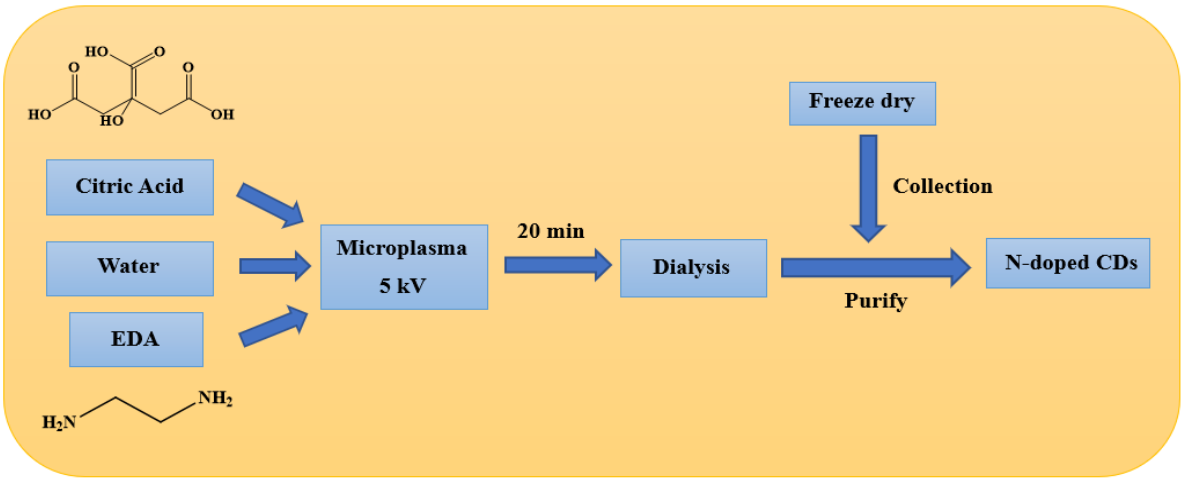

Fig. 7: Microplasma-assisted NCDs synthesis process from citric acid and ethylenediamine (EDA).

Table 3. Methodologies for NCDs process synthesis.

Scenario	Precursors	Cost *(Sigma-Aldrich)*	Density (kg/dm^3)	M_w (g/mol)	Power /heat	Purification method	Reaction time (min)	QY (%)	Particle Size (nm)	Mass of product (g)	Reference
1	Rapeseed flower Bee pollen (1 g) 40 ml (H2O)	$12.58/kg 0	n/a 1.0	180.2 18.0	180 ^{0}C	Vacumm filtration	1440 *(24 h)*	9.1	From 1 to 2	0.3	Jia Zhang *et al.*
2	Oleic acid (40 ml) 20 g Sucrose 40 ml (H2O) Hexane *(Extraction solvent)*	$32.14/L $52.46/kg 0 $94.84/L	0.895 1.59 1.0 0.659	282.5 342.3 18.0 86.2	215 ^{0}C	Solvent extraction	5	21.6	1.84	8.36	Bisang Chen *et al.*
3	30 g Citric acid 230 mL MEA	$67.22/kg $42.96/L	1.66 1.01	192.1 61.1	170 ^{0}C	Vacumm distillation	10	40.3	3.5	39.96	Yaoping Hu *et al.*
4	Glucose (5g) TTDDA (5 g) H_2O (80 mL)	$42.18/kg $159,83/kg 0	1.56 1.005 1.0	180.2 220.3 18.0	800 W	Dialysis	7	n/a	7	3	Yuzhao Yang *et al.*
5	Ethylene gas (150 L) 177 g	$20.77/kg	1.18	28.1	600 kW.h	Ethanol isolation	60	13.5	10	4	Juhan Kim *et al.*
6	Citric Acid (1g) EDA (0.6 mL) Water (10 mL)	$67.21/kg $37.69/kg 0	1.66 0.9 1.0	192.1 60.0 18.0	30 W	Dialysis	20	9.9	5.98	0.007	Xing Tong Ma *et al.*

Green chemistry metrics studies

Roschangar *et al.*[79] proposed a way to group Green Chemistry (GC) metrics. Following this, herewith the GC metrics are grouped along with the four reaction mixture ingredients: NCDs raw material, auxiliary reagent(s), solvent, and water. Particularly, PMI and PME are considered to be related to "water" assessment, while MI, MP and E-factor are relevant to "solvent" ingredient.[79] RMI and EMY are used to assess "auxiliary reagents", while RME, AE, and CE are related to "raw material" assessment.[79]

GC Metrics for NCDs Raw Materials

Reaction mass efficiency (RME)

Reaction mass efficiency (RME) measures the mass of product divided by the total mass of raw materials, expressed as a percentage. RME does not account for the solvent used. [80, 81]

$$RME\ (\%) = \frac{Mass\ of\ product\ x\ 100}{Total\ mass\ of raw\ materials} \quad (1)$$

Carbon economy (CE)

Carbon economy is the mass of carbon in the product divided by the total mass of carbon in the raw materials, expressed as a percentage.[80]

$$Carbon\ Economy\ (CE\ \%) = \frac{Carbon\ in\ product\ x\ 100}{Total\ carbon\ in\ raw\ materials}\ (2)$$

Atom economy (AE)

Atom economy is the metrics, which relates the molecular weight of the product to that of the reactants, expressed as a percentage. Thus, it is a measure of the relative loss of molecular weight (atoms) of the process, which generates waste.

$$Atom\ Economy\ (AE\ \%) = \frac{MW_{product}\ x\ 100}{MW_{reagents} + MW_{raw\ materials}}\ (3)$$

GC Metrics Related to Solvents

E-factor (E)

The E-factor is the amount of waste produced considering all process components, including reactants, catalysts, and solvent, yet excluding water, relative to the mass of the final product. [52, 82] A higher E-factor means more waste is generated; the ideal E-factor is zero.

$$E\text{-}factor\ (E) = \frac{Total\ mass\ of\ waste}{Mass\ of\ final\ product}\ (4)$$

Mass Productivity (MP)

Mass Productivity relates the mass of the product to the mass of all input materials. The latter would include reactants, catalysts, solvent, and even water.

$$Mass\ Productivity\ (MP\ \%) = \frac{m_{product}\ x\ 100}{m_{input\ materials}} \quad (5)$$

Mass Intensity (MI)

Linked with the previous metrics, Mass Intensity is an inversely defined metrics as to the Mass Productivity.

$$Mass\ Intensity\ (MI\ kg.kg^{-1}) = \frac{m_{input\ materials}}{m_{product}} \quad (6)$$

Solvent Intensity (SI)

Solvent Intensity is the Mass Intensity only considering solvent flows.

$$Solvent\ Intensity\ (SI\ kg.kg^{-1}) = \frac{m_{solvents}}{m_{product}} \quad (7)$$

GC Metrics related to Water consumption

Process mass intensity (PMI)

Process Mass Intensity is the ratio of total input of materials, as detailed above and, in addition, including water.[80, 83] PMI focuses on reducing the costs of the raw materials input.

$$Process\ mass\ index\ (PMI\ kg.kg^{-1}) = \frac{Total\ mass\ in\ process\ (incl\ H_2O)}{Mass\ of\ product} \quad (8)$$

Process mass efficiency (PME)

Process mass efficiency is linked with process Mass Intensity, but the inverse definition.

$$Process\ mass\ efficiency\ (PME\ \%) = \frac{m_{product} x 100}{m_{input\ materials\ including\ water}} \quad (9)$$

Wastewater intensity (WWI)

Wastewater intensity is linked with Mass Intensity, but only considering process water flows.

$$Wastewater\ intensity\ (WWI\ kg.kg^{-1}) = \frac{m_{process\ water}}{m_{product}} \quad (10)$$

GC Metrics Related to Reagent consumption

Effective mass yield (EMY)

Effective Mass Yield is the ratio of the mass of product to raw materials and reagents.

$$Effective\ mass\ yield\ (EMY\ \%) = \frac{m_{products} x100}{m_{raw\ materials} + m_{reagents}} \quad (11)$$

Reaction mass intensity (RMI)

Reaction Mass Intensity is linked with effective mass intensity, but the inverse definition.

$$Reaction\ mass\ intensity\ (RMI\ kg.kg^{-1}) = \frac{m_{raw\ materials} + m_{reagents}}{m_{products}} \quad (12)$$

Other relevant GC metrics

Energy consumption

The energy consumption from the different synthesis process methodologies in this study is calculated based on heat-transfer principles.[84] In Eq. 11, *Q* [W] refers to the heat added (or being removed) from the object, *m* [kg] is the mass (weight), *Cp* [J/kg.C] is the specific heat capacity, and *t* [s] is the time required for cooling down (or heating up).

$$Q = \frac{m.C_p.\Delta T}{t} \quad (13)$$

Volume−Time−Output (VTO)

VTO is defined as the volume of all reactors (*Vr*) (in m^3) multiplied by the residence time (*rt*) per batch, divided by the whole amount of product per batch in kg. In this context, the chemical process is acceptable for VTO values below 1; otherwise the process still needs to be improved.

$$VTO = \frac{V_r[m^3].rt[h]}{products[kg]} \quad (14)$$

Circular Metric Studies for N-doped CDs Synthesis Scenarios

The research here follows the Material Circularity Indicator (MCI) methodology of the Ellen MacArthur Foundation (EMA) CE100 program.[85] Seeing that the processes proposed have a low yield, recycling is mandatory.

Therefore, as described by Escriba-Gelonch *et al.* [86], a peculiarity of chemical processes is that the recovered or recycled chemical species remain the same with equal performance as the virgin ones. Using this methodology, it is possible to probe the high challenges of low-yielded processes to be circular, since the amount of unreacted materials strictly demands the recycling/reuse by circular loops. In the context of CDs, the quantum yield was taken as the utility value, as luminescence is a major characteristic of CDs exploited in several of their performances; following a similar replacement approach as described in [86]. In the case of scenario 4, where no value is provided, the utility value was considered as 1.

RESULTS AND DISCUSSION

Comparison of the NCDs synthesis process methodologies

The processes are given (Table 3) differ in their amount of use of raw materials, solvents and/or water. They also differ in energy consumption, since they use different sources for heating (heat, radio waves, and ionized gases). For example, the NCDs process using hydrothermal methodology has a higher energy demand, which is mainly due to the higher residence time. That means productivity in terms of material produced per time is an issue. The thermal (Scenario 3) method produces the highest product mass of almost 40 g, while the microplasma method (Scenario 6) produces the least amount with only 7 mg. That spans nearly four orders of magnitude.

Finally, the selected scenarios also include the purification process (Figure 2-7). In this context, dialysis, freeze-drying, vacuum distillation and solvent extraction are used for NCDs purification, which again differs in material and energy consumption as well as in their processing time. The mass of the product, and thus productivity, varies for the different methods. The reaction time of our synthesized CDs by microplasma treatment is approximately an hour, while the dialysis time is much longer and roughly 72 hours. There is obviously a major mismatch in the essential time constants, and as now, the productivity would be determined by purification. For several CD applications and assuming optimisation of productivity, this might be still commercially sufficient, as we might produce 200 - 500 mg per week, e.g. theranostic nanoparticles in medicinal treatment. Yet, for others such as water purification, we may need to make gram amounts and beyond. Our main limitation sits on the dialysis side. To increase the purified mass yield, we suggest increasing the volume of dialysis bags as well as the number of dialysis batches. We expect to increase dialysis productivity by a factor of ten this way; leaving another factor of ten to match the plasma-

synthesis productivity. If that is the goal, probably another faster purification approach needs to be developed.

In addition to the above-mentioned process parameters, the circularity metrics, different from the green chemistry metrics, consider functionality, meaning the performance per mass of the product, which is the quantum yield in the context of this research.[87] Table 3 shows high differences in terms of the quantum yield of produced NCDs. Thermal methods described in Scenarios 2 and 3 results in the highest quantum yield of 22 and 40%, respectively.

Thus, concerning sustainability the use of materials and energy as opposed to productivity and its performance are to be considered; with a view on the full process, covering both the nanomaterials synthesis and purification.

Green metrics calculation

The green chemistry metrics were calculated following equations (1-12) for a functional unit of 1 kg product, see Table 4.

Table 4. Green metrics calculation by 1 kg of products for different synthesis processes of N-doped CDs

Metric	Equation	Unit	Sc.1	Sc.2	Sc.3	Sc.4	Sc.5	Sc.6	Ideal value
CY	-	%	30	42	42	30	2.2	0.5	100
RME	1	%	30	42	15	30	2.3	0.44	100
CE	2	%	37	n/a	26	34	n/a	n/a	100
AE	3	%	100	100	100	90	102	100	100
E-factor	4	$kg.kg^{-1}$	2.3	1.4	5.6	2.3	43	228	0
MP	5	%	30	15	15	30	2.3	0.44	100
MI	6	$kg.kg^{-1}$	3.3	6.7	6.6	3.3	44	229	1
PMI	8	$kg.kg^{-1}$	137	11	6.6	30	44	1657	1
PME	9	%	0.73	8.7	15.2	3.3	2.3	0.06	100
EMY	11	%	30	15	15	30	2.3	0.44	100
RMI	12	$kg.kg^{-1}$	3.3	6.7	6.6	3.3	44	229	1
SI	7	$kg.kg^{-1}$	0	0.10	0	0	0	0	0
WWI	10	$kg.kg^{-1}$	133	4.8	0.0	27	0.0	1429	0
E. Cons.	-	$kW.h.kg^{-1}$	14,688	n/a	84,688	2,286	150,000	1,429	0

Reaction mass efficiency (RME)

The results of this first metric related to raw materials revealed that scenarios not related to plasma showed values between 15 and 42, being the highest the thermal procedure described in scenario 2. Plasma-linked procedures showed much lower RME values (Scenarios 5 and 6) due to the low reaction yield. Here, the reuse of raw materials is mandatory as discussed below in order to keep the process economically feasible.

Carbon and atom economy (CE and AE)

The carbon economy of the available hydrothermal (Scenario 1), microwave (Scenario 4) and thermal (Scenario 3) synthesis were in the same range, performing the first the highest value: 37. These results suggest that the hydrothermal process described in scenario 1 is the best in converting carbon atoms from starting materials into the product. All results concerning atom economy (AE) showed also to be highly efficient.

Process mass intensity (**PMI**)

The process mass intensity of scenarios 1 and 6 showed values much above the others (Figure 8). Especially the PMI of scenario 6 (microplasma) was 1657, due to a large amount of water used, *i.e.* the high reactant dilution, and the low mass-yield of the product (0.007 g). The second highest PMI value is given for the hydrothermal process with 137, which is again due to a large amount of water used as well as the relatively low yield.

E-factor

The E-factors of scenarios 1 to 4 were low, with a minimum value of 1.4 for scenario 2, see Figure 8. The higher mass-yield of scenarios 1 to 4 decreases the E-factor because of the higher efficiency. The mass-yield and the use of materials are guiding parameters for the E-factor, which penalises scenarios 5 and 6 where the factor achieves non-advantageous high values, especially in scenario 6 where this value amounts 228.

Waste water and solvents intensity

Concerning parameters related to solvents (*SI*) and waste water (*WWI*) intensity, most scenarios do not use solvents, and therefore this parameter comes to 0. Only scenario 2 computes 0.10 kg/kg, due to the hexane needed for the extraction process after the reaction in order to recover the oleic acid used for the reaction. This situation is not the same with water, since most the scenarios use water, and especially scenario 6 uses a lot (1429 kg/kg).

Scenario 1 also needs a considerable amount of water (133kg/kg), which penalises in terms of green metrics. Scenarios 3 and 5 show good performance on this index, since they use neither water nor solvent, as stated before.

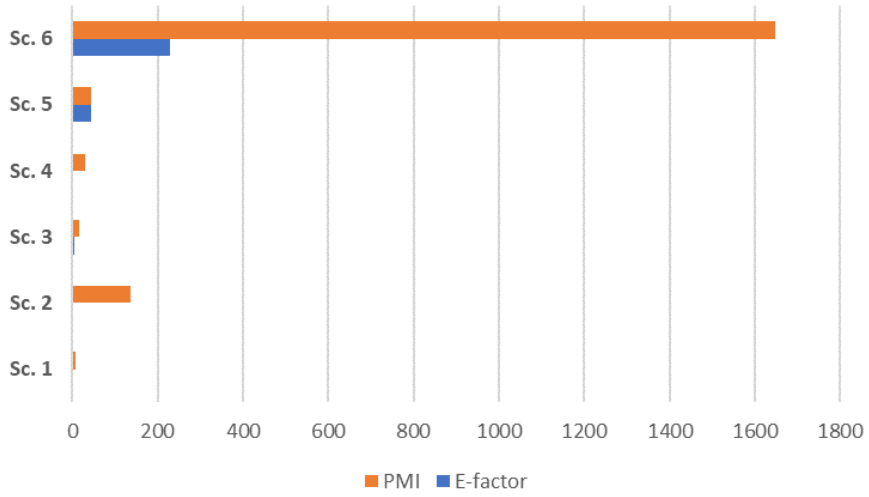

Fig. 8: Comparison of process mass intensity (PMI) and E factor of various NCDs synthesis process methods.

Operation temperature

Operating temperature is also an essential parameter that needs to be considered in large-scale production. Operating synthesis processes at high temperatures lead to an increase in energy consumption and pose a risk to the safety of a process. As a result, It might significantly increase the production cost and make the product less competitive in comparison to the other synthesis routes that can be operated at room temperatures. Working in a high-temperature environment also causes a hazard risk to operators of synthesis processes. For this reason, the low (room) temperature-based synthesis process is ideally considered as a green process. As a result, the operating temperature in scenarios 1, 2, and 3 are estimated around 180, 215, and 170^{0}C, respectively. Scenarios 5 performs an extremely high operating temperature, up to nearly 10,000 ^{0}C, due to the temperature of electrons flow in thermal plasma, while the operating temperature of scenario 4 and 6 is only 100 and 20 ^{0}C, respectively. It can be seen that non-thermal plasma synthesis of NCDs in scenario 6 is considered to be the greenest method in terms of operating temperature as it can be operated at room temperature (20^{0}C). Therefore, the total cost of production might decrease significantly.

Energy consumption

In terms of energy consumption, the scenarios linked with thermal procedures (1, 3 and 5) have obviously higher energy demands (Figure 9). Foremost among these is the thermal plasma method (Scenario 5). The latter, consuming 150,000 (kW.h/kg product), is in the range of two orders of magnitude higher than the demands of low-temperature microplasma method (Scenario 6). Nonetheless, the energy consumption is still high in other thermal procedures, being 84,668 and 14,688 (kW.h/kg product) for the thermal (Scenario 3) and hydrothermal (Scenario 1) methods, respectively. Interesting to mention that microwave and microplasma consume the least energy with 2,286 and 1,429 (kW.h/kg product) respectively, due to the lower working temperatures.

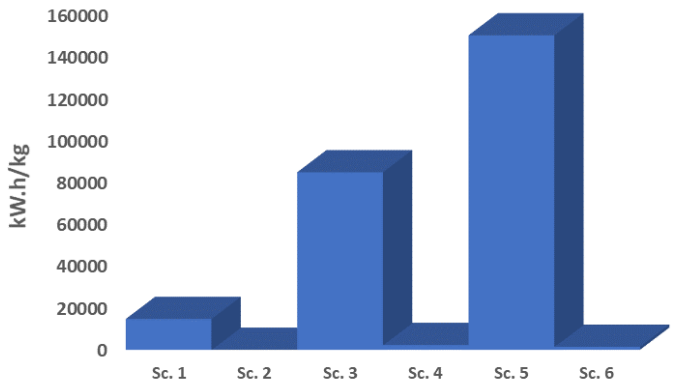

Fig. 9: Energy consumption of the NCDs synthesis process methods.

Cost analysis of precursors

To enable a proper uniform prices scale pattern, which eliminates all confounding factors derived from managing different suppliers with different criteria, taxes and interests, we assumed that all chemicals used are at the same class and purchased from Sigma-Aldrich. Therefore, we used the prices listed on the company's website for the calculation of chemical costs. A cost analysis for the production of 1 kg of NCDs was performed for each synthesis scenario taking the simple data records from Table 3. The results are shown in Figure 10, where high differences can be appreciated. First, scenario 1 appears to be the cheapest thanks to the inexpensive starting bee pollen, followed by scenario 5, where the fact of working with just one reactant (ethylene gas) is an advantage. Yet, scenarios 2 to 4 appear to be in the same range of costs. This is because of two reasons: first, all 3 methodologies are in the same range of mass-yield, which means that the amount of raw materials is also in the same order of magnitude. Second, despite being most of the reactants inexpensive, each methodology has one expensive reactant which is also in the same range of price, making comparable the

production costs in different scenarios. In this connection, scenario 2 uses hexane ($284.53/3L), scenario 3 uses monoethylene amine ($250.05/5.82kg), and scenario 4 uses TTDDA ($266.92/1.67kg). Scenario 6 results to be the most expensive not because of the costly materials, but because of the lowest mass-yield, which demands a much higher amount of starting materials per kilo of final compound ($12,509 per kg of product). The materials are inexpensive in this scenario (see table 3), and in the way that for the cost analysis recycling was not considered, the process becomes costly. Yet, one advantage of this process is the absence of side reactions, which enables the reuse of the starting materials in a circular context, as discussed below. Therefore, the real cost of the materials would be much lower if, in the end, all of the starting materials can be transformed to NCDs after successive reuse loops. Sc.6' in Figure 10 shows the hypothetical costs in a cumulative yield scenario of 30% mass-yield after successive recycling loops. As shown, incomparable mass-yield conditions with scenarios 2 to 4, the cost of scenario 6 would be even lower than scenarios 2 to 4. This is an example where circularity becomes a key point in a process design.

Apart from using the above-mentioned precursors, using waste materials to synthesize CDs is an approach to reduce the cost of starting materials. Solid waste materials from agriculture and industrial activities such as banana peels commonly go to landfill. Atchudan et al. (2021) used the peels of Dwarf banana fruits from the food market to synthesize CDs by hydrothermal method with a particle size of 5 nm.[88] Similarly, other waste materials (orange peels,[41] lemon peels,[42] rice residue,[43] coffee ground,[44] etc.) were also used to synthesize CDs at a low cost of starting materials.

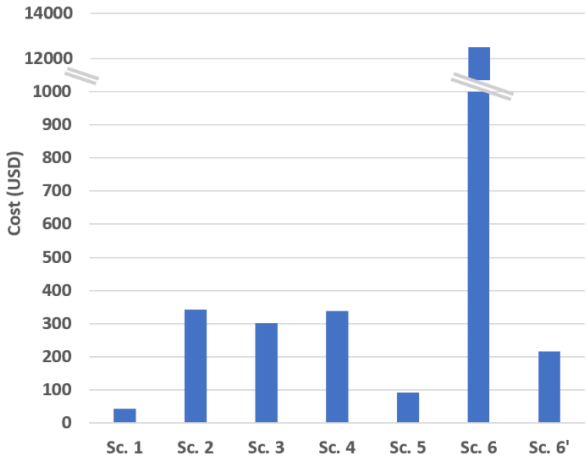

Fig. 10: Costs of starting materials for the production of 1 kg of NCDs in different synthesis scenarios. No recycling loops are considered except of Sc.6'.

Overall green metrics ratios

Figure 11 shows a comparative picture of all relative parameters (in %) for each scenario. The optimal value of them is 100, so the more open is the plot, the best. In the picture, scenarios 1, 3, and 4 show the overall best performance in green metrics. Apparently, the worst scenarios in this context are 5 and 6, where besides AE, all parameters are close to 0.

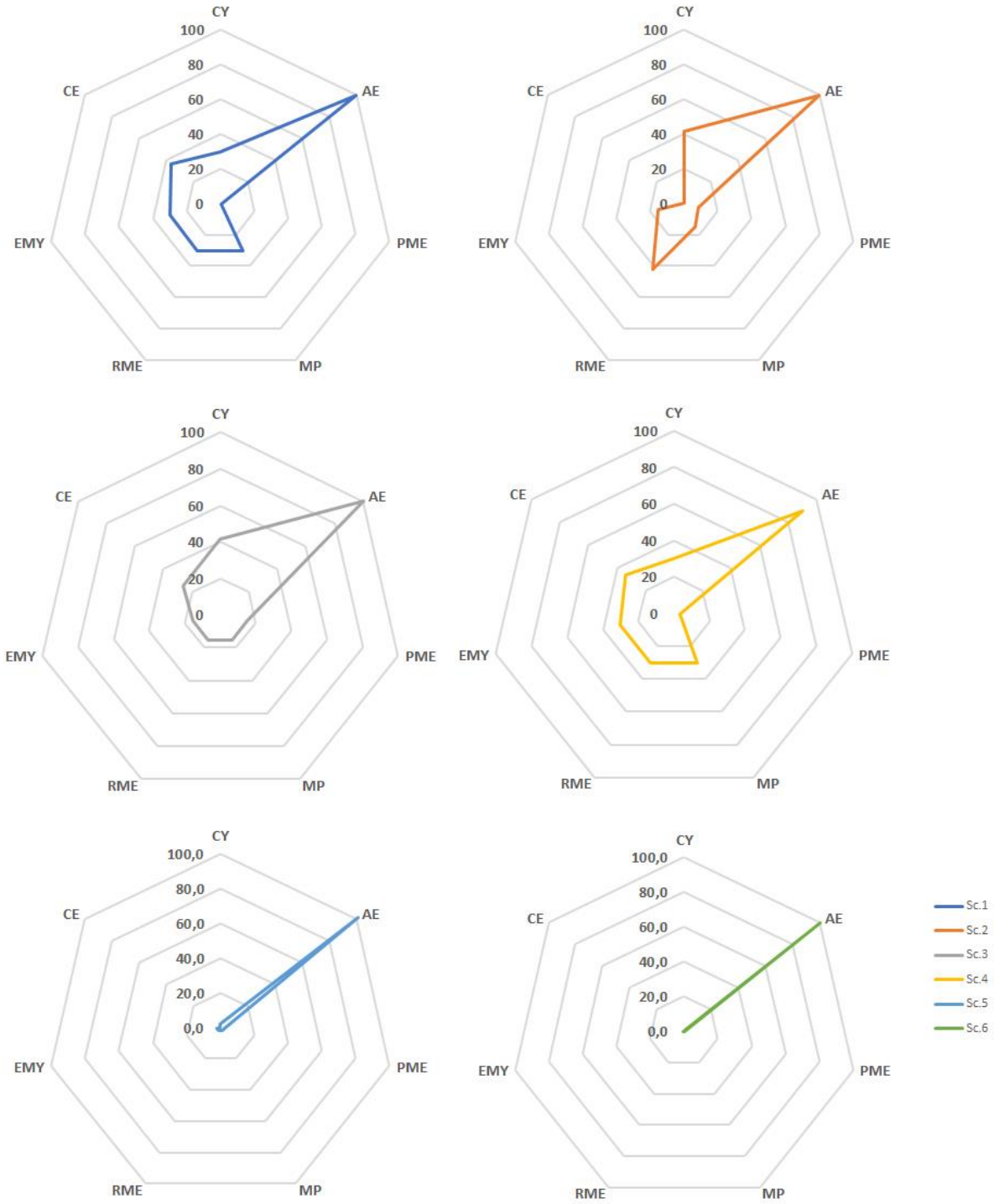

Fig. 11: Comparative plots of Green chemistry metrics for the different scenarios of NCDs synthesis.

Circular metrics

Being different from the green chemistry metrics, in CE reuse of the starting materials is considered and measured, using so-called circular transition indicators with the MCI as a central metric.[53] In this way, even the low mass-yield processes can achieve high MCI values through recycling/reuse strategies, which can deliver also interesting economical results as illustrated in the costs analysis of scenario 6. To meet this objective, a recycling/reuse design was performed and evaluated for each scenario, according to the process parameters obtained from the literature. In this context, Figure 12 shows a flowchart of the material loops for the purification and recycling operation proposed for scenario 2 as an example. Such engineering of the purification of nanomaterials is hardly discussed so far in the literature. Yet this analysis shows the importance of that for the sustainability and circularity of nanomaterial syntheses.

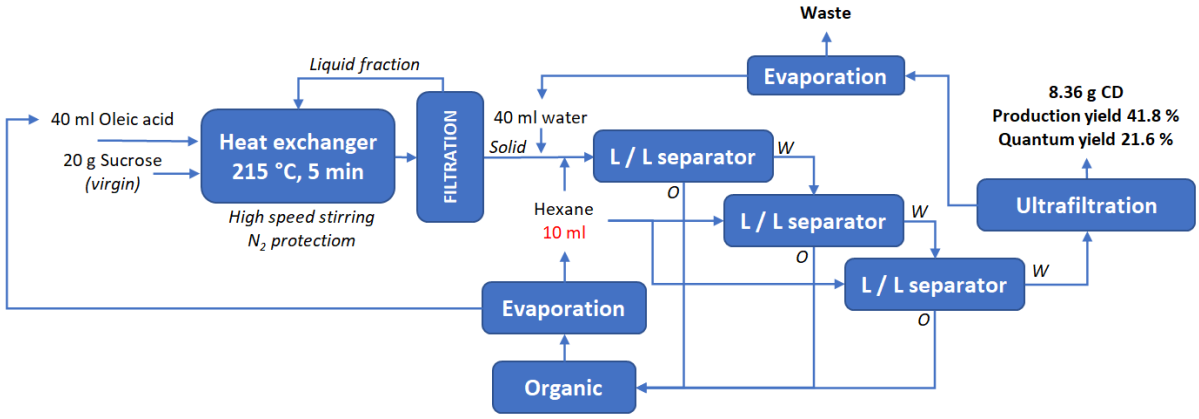

Fig. 12: Proposed flowchart of the circular scenario 2.

Table 5 shows the results of the circular metrics calculated for each scenario. The table is divided into sections A and B showing the circular metrics in the current linear fashion and those for the proposed looped scenarios (assuming recycling) respectively. Partial analysis of the key reactants was also performed when possible. In the first (section A), the virgin amounts are considered to be equal to *M*, and obviously $F_R=C_R=0$. Additionally, waste (*W*) has the same value of *Wo*, and appears to be at least one order of magnitude higher than the corresponding scenario in section B. Processes in section A (see table 5A) do consider neither composting nor reuse/recycling/recovery operations. Due to the low mass-yield of most of the processes, LFI appears to be above 0.8 in all scenarios, being the lowest for scenarios 2 and 4 because of the higher yield and the subsequent lower waste. Concerning MCI,

scenarios 1 and 6 have low values around 0.1, being the highest scenarios 2 and 4, yet with very poor MCI values around 0.250.

Section B calculates the circular metrics assuming reuse of the process materials (reactants and solvent), meaning to assume recycle-looped processes for each scenario. Where available (scenario 1), documented material loss is subtracted from the unreacted starting material, i.e. the initial starting material by mass minus the mass-yield. Where not available (other scenarios than 1), a complete recovery of the unreacted starting material is assumed. The same approach was taken for the solvent (please note that this is the dominating factor in combined reactant-solvent based metrics as the mass of the solvent is much higher). As expected, this can drastically decrease the use of virgin materials (V), waste production (W), and lost fractions (C_C). As shown in Table 5B, the loops would increase the *MCI* and therefore the circularity, as compared to section A. The recycling fraction of the process scenarios under study (F_R) would be above 60% in Table 5B, as well as the efficiency of the extraction process of the starting nanomaterials (E_F) in the range of 90%.

Scenario 1, as said, is different from the other scenarios, since it has 28% loss (C_C) requiring to refresh the process by 60% virgin materials in the next loop, allowing only for a recycling fraction (F_R) of 40%. This fact penalises also the rest of the results, because it increases the amount of waste (showing the highest W value) giving a linear flow index (*LFI*) of 0.55, meaning above 50%. This is the reason why the MCI value for the bee pollen is the lowest (0.509) of all scenarios. Nevertheless, the MCI of the whole process is much higher (0.971), because of the recycling of most of the water used in the process (operation at low concentration). Bee pollen is the cheapest reactant of all scenarios.

Table 5A Circular metrics calculation for the NCDs synthesis process methodologies, in their current linear fashion.

	Sc. 1		**Sc. 2**	**Sc. 3**	**Sc. 4**		**Sc. 5**	**Sc. 6**	
	Pollen	**Overall**	**Sucrose**	**Overall**	**Glu+TTDDA**	**Overall**	**Ethylene**	**Citric acid**	**Overall**
M (kg)	10	810.0	20	233	10	60	2.95	1	11.54
W (kg)	6.8	806.8	12.06	222	6.126	41.13	2.28	0.999	10.49
LFI	0.84	0.998	0.802	0.922	0.8063	0.843	0.887	0.999	0.955
MCI	**0.244**	**0.102**	**0.279**	**0.170**	**0.274**	**0.242**	**0.201**	**0.100**	**0.141**

Table 5B Circular metrics calculation for the NCDs synthesis process methodologies in an assumed circular fashion, using the looped processes proposed in this paper.

	Sc. 1		**Sc. 2**	**Sc. 3**	**Sc. 4**		**Sc. 5**	**Sc. 6**	
	Pollen	**Overall**	**Sucrose**	**Overall**	**Glu+TTDDA**	**Overall**	**Ethylene**	**Citric acid**	**Overall**
M (kg)	10	810	20	263	10	60	3	1	12
FR	0.40	0.97	0.60	0.79	0.60	0.67	0.77	0.90	0.90
V (kg)	6.0	23.0	8.0	55.0	4.0	20.0	0.67	0.10	1.1
CC	0.280	0.024	0.003	0.053	0.013	0.019	0.002	0.100	0.100
CR	0.400	0.972	0.600	0.791	0.600	0.667	0.773	0.896	0.905
EF	0.300	0.975	0.995	0.933	0.979	0.972	0.997	0.889	0.890
W (kg)	7.47	29.96	0.09	21.51	0.19	1.71	0.01	0.16	1.80
W0 (kg)	2.80	19.80	0.06	14.00	0.13	1.13	0.01	0.10	1.15
WF (kg)	9.33	20.31	0.06	15.01	0.13	1.16	0.01	0.11	1.30
LFI	0.55	0.03	0.20	0.14	0.21	0.18	0.12	0.13	0.12
F(X)	0.90	0.90	0.38	0.20	0.90	0.90	0.61	0.83	0.83
X	1.00	1.00	2.37	4.42	1.00	1.00	1.48	1.09	1.09
MCI	**0.509**	**0.971**	**0.923**	**0.971**	**0.812**	**0.838**	**0.930**	**0.896**	**0.899**

As utility values *X*, quantum yields (*QY*) are taken as this luminescent property is a key performance parameter of the NCDs and widely documented (see Table 3). This 'utility' *X* is normalized by the *F(X)* function as described by EMA-CE100.[85] Therefore, a high *QY* increases MCI as shown in scenarios 2, 3, and with lower impact, in scenario 5. The utility factor for scenario 3 shows the highest increase to 4.42 due to high *QY*. Therefore, scenario 3 has the highest MCI value. The opposite is given in scenario 4, which at the end appears to be the most linear process. No *QY* is available in the literature, keeping *X* to 1. Hence, even having good recycling parameters such as 60% of F_R and waste generation 1.71kg / 60kg of starting materials, scenario 4 is penalised by the absence of performance values, which decreases the MCI to 0.838.

Overall, the MCI values of the NCDs synthesis process methodologies with recycling added are all above 80% and a major part being 90% or higher, meaning close to circular; with the exception of the mentioned bioreactant (pollen)-based scenario 1, and scenario 4 due to the absence of performance values. Scenarios 1 and 3 score the same highest value 0.971, followed by scenario 5. The latter achieves this position due to the good performance in QY (13%) which delivers a utility factor of 1.48, the high recycling fraction (F_R = 0.77) and the low waste generation (0.01kg / 3kg of ethylene).

Safety concerns for NCDs synthesis

Nanomaterials pose hazards and risks concerning human health, and the environment.[88] Particularly, food science and engineering demand for safety control and risk assessment[90] and use as nanopesticides is one of our target applications.[20] The toxicity of conventional QDs depends on the size, concentration, charge, outer coating, bioactivity, and photolytic, oxidative, and mechanical stability.[91] It is generally high due to the content of cadmium or other heavy metals. Yet, hardly any health or environmental constraints have been reported for CDs.[92-95] CDs have good biocompatibility, and no significant toxic effect is observed at different doses. They cause neither any abnormality nor damage in organs, and specifically do not exhibit gene toxicity.[96] NCDs, as shown in this paper, can be synthesized from natural and harmless raw materials, such as sugars and pollen bees. Nevertheless, the use of highly toxic and flammable solvents in some cases such as ethylene (scenario 5) and ethylenediamine (scenario 6) is still a drawback concerning safety constraints.

In addition, cold plasma, herewith described as microplasma in scenario 6, has been described as an advantageous non-thermal treatment even suitable to be used to chemically modify food surfaces at room temperature (~20 °C) and atmospheric pressure (14.7 psi) in safety conditions.[97]

Good manufacturing indicators

To apply a circularity assessment means to assume that the CDs synthesis processes can be brought to industrial capacity, i.e. a scale-up from laboratory to pilot scale. This involves developments concerning the process and analytical chemistry, process engineering, and safety and regulatory requirements.[54]

In this context, Dach *et al.*[98] propose a methodology package in order to define the degree of good manufacturing of a process to compare different pathways to the same chemical compound. Eight evaluation criteria or Good Manufacturing Indices (GMI) are applied to three main stages: Chemical Development, Process Development, and Chemical Production.

- **Economic factors**
  - Criterion 1. Material Cost: A high cost of raw materials, availability, and required quantities penalizes good manufacture. The use of natural resources in most of the assessed scenarios may reduce costs. In the scenarios under study, the costs of raw-materials per kilo are in the range of $70 for scenarios 1 and 5, $300 for scenarios 2 to 4 and more than $12k for scenario 6, the latter due to the low mass-yield.

- **Process Efficiency Factors** (Criteria 2−5)
  - Criterion 2: Atom Economy (AE): Hardly any data exist for nanomaterial syntheses and their lack of atomic stoichiometry set limits to the application of a criterion based on AE. Generally, raw materials with major contents of carbon and nitrogen atoms should be favourable; as oxygen and hydrogen atoms reduce the 'AE'. In the scenarios herewith assessed, AE was higher than 90%.
  - Criterion 3: Yield: For the above-mentioned lack of stoichiometry, no yield can be defined; yet a mass-yield is the right surrogate. Thermal methods have a comparatively high mass-yield for NCDs and nanomaterials in general, being up to 50%. Plasma- and solvent-based methodologies have typically lower mass-yields, yet there is no theoretical reason why those could not be higher. Meaning more development is demanded here.
  - Criterion 4: Volume−Time−Output (VTO): Thermal methods are reasonably fast at good mass-yields; meaning they achieve good productivity or VTO. Plasma methods are fast, yet their mass yields need to be improved, as showed in Table 4 – Scenario 5.
  - Criterion 5: Environmental Factor (E-Factor)/Process Mass Intensity (PMI): The recycling strategies presented in this paper improve significantly the E-factor and PMI of NCD syntheses shown in Figure 8, which are very low typically when done in a linear fashion.
- **Process Reproducibility Factors** (Criteria 6−7).
  - Criterion 6: Quality Service Level (QSL): For the scenarios considered here, no data in terms of reproducibility and robustness are provided by the sources. This gap may be filled by future studies.
  - Criterion 7: Process Excellence Index (PEI): This paper highlights the importance of recycling and reuse; not only their efficiency is important, but also the cycle time of these operations. This index could not be calculated with the data provided by the sources.
- **Ecoscale definition**
  - Criterion 8: Modified EcoScale: This procedure, developed by van Aken *et al.*[99], provides a so-called EcoScore by cumulating penalty points in the case non-sustainable measures have been used. This procedure has been applied for each scenario as described in Table 6. According to Table 6, scenario 2 has the best score mainly because of the lower mass-yield penalty points. Scenario 6 looks also very

promising, having in most categories very low penalty values; yet the safety and yield of this process needs to be improved.

Table 6. Ecoscale calculation for the different NCDs synthesis scenarios. *(Sc. = Scenario)*

EcoScale Parameter	Sc. 1	Sc. 2	Sc. 3	Sc. 4	Sc. 5	Sc. 6
1. Yield	35	29	29	35	39	50
2. Price of reaction components	3	5	5	5	5	0
3. Safety *(hazard warning symbols)*	0	0	5	5	10	10
4. Technical setup	3	1	0	2	2	0
5. Temperature/time	3	2	2	2	0	1
6. Workup and purification	0	3	3	0	0	0
Total Penalty Points	44	40	44	49	56	61
EcoScale score	**56**	**60**	**56**	**51**	**45**	**39**

The GMI can be quantified with the methodology described by Dach *et al.* [98], based on research performed at Boehringer Ingelheim Pharma GmbH. Here, this methodology is applied for quantifying and comparing the good manufacturing performance of the 6 scenarios assessed in this paper. Table 7 summarizes the values obtained for each criterion and each scenario accordingly. This table is distributed in two sections: Section A shows the values obtained for each criterion per parameter, section B shows the good manufacturing scores obtained for each value in section A. The final GMI for each scenario is the sum of section B values. Process reproducibility factors (criterions 6 and 7) could not be applied because of the absence of data in the literature. Each criterion has a weight or relative importance in the assessment for the calculation of GMI, which can vary for different process optimization objectives and by company priorities. Here the relative importance is assigned to evaluate the capability of the scenario to be brought to industrial capacity. To meet this goal, Dach *et al.*[98] propose to take VTO as the most impactful criterion and use it as predominant as shown in Table 7.

Concerning the price (first criteria), scenarios 1 and 5 scored the highest followed by scenarios 2 to 4. The high costs per kg penalized scenario 6. Criterion 2 is not conclusive since the available values score in the same range. The quantification of atom economy in nanotechnology is difficult, and most of the data in this context are not provided. That is the reason because the weight of criterion 2 was only 5%. Scenario 6 is also very penalised in eco-efficiency (criterion 5) due to the low concentration used as well as the low mass-yield. Scenarios 3 and 4 are the procedures, which meet all criteria with the weights proposed in the literature, with a GMI of 97.2 and 95.9% respectively. These procedures correspond to the

thermal process (citric acid with MEA) and microwave (glucose with TTDDA). The worst scenario is scenario 6 (microplasma) with a value of 45.9%. This value is obtained because of the high price and the environmental factors scored due to the low concentration. The second worst scenario is scenario 1 (pollen bee) with a value of 56.5%, which is very penalised by the high VTO factor, which weighs 40% of the total amount. It is worth noting that thermal plasma (ethylene) scored an interesting GMI of 87.2%, despite being still penalized by the low yield.

Table 7. Good manufacturing index calculation for the different NCDs synthesis scenarios.

		Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5		Criterion 8	
	Scenario	Price (USD)	AE	Mass-yield (%)	VTO	E-factor	PMI	Eco-scale	
Section A	1	41.89	37	30.0	4.2857	2.33	136.67	56	
	2	341.29	n/a	41.8	0.0005	1.39	11.46	60	
	3	300.46	26	41.8	0.0010	5.56	6.56	56	
	4	337.37	34	30.0	0.0019	2.33	30.00	51	
	5	91.91	n/a	23.0	0.0622	43.25	44.25	45	
	6	12,509.70	n/a	0.4	0.0714	227.57	1657.14	39	
Weights (%)		15	5	5	40	10	15	10	FINAL GMI (%)
		Partial GMI values							
Section B	1	14.9	5.0	3.6	0.0	9.9	13.8	9.3	56.5
	2	14.6	n/a	5.0	40.0	9.9	14.9	10.0	94.4
	3	14.6	3.5	5.0	40.0	9.8	14.9	9.3	97.2
	4	14.6	4.6	3.6	40.0	9.9	14.7	8.5	95.9
	5	14.9	n/a	2.8	39.4	8.1	14.6	7.4	87.2
	6	0.0	n/a	0.1	39.3	0.0	0.0	6.5	45.9

CONCLUSIONS

This study uses single-criterion and multiple-criteria assessments for scenarios for judging the sustainability of six selected process synthesis methodologies for N-doped carbon dots (NCDs), including hydrothermal, thermal, microwave, thermal plasma, and microplasma. The single-criterion assessment has been performed through green chemistry metrics and circular transition indicators, and the multiple-criteria assessment by the Good Manufacturing Practice, developed by the Boehringer-Ingelheim Company, which includes the EcoScale index. This paper wants to make a hot-spot analysis and shows weaknesses in sustainability, and show the way out.

Scenario 3, the synthesis of NCDs using citric acid with monoethanolamine, shows the most promise when all assessments are considered. Scenario 3 is circular with the highest material circularity indicator (MCI) of 0.971, and has the second-best EcoScale index of 56%. In the latter, scenario 2, using oleic acid and sucrose for NCDs synthesis, scores best with 60%.

The assessment of the six synthesis process methodologies for N-doped carbon dots nanoparticles determines that scenarios 1, 3, and 4 score best in terms of green metrics, while scenarios 2, 3, and 5 do likewise with circular metrics. Finally, concerning good manufacturing criteria, scenarios 2, 3, and 4 show the best performance. In addition, NCDs produced from hydrothermal (scenario 1), microwave (scenario 4) and thermal method (scenario 2) need a purification process for good sustainability performance.

In view of all metrics considered, scenario 3 (citric acid with MEA) ranks best, followed by scenario 4 (microwave with glucose). Interesting to note that thermal plasma (scenario 5) shows good indices despite of the high-energy consumption. The latter is overcompensated by the fact that scenario 5 (as well as scenario 3) does use neither water nor solvent, which reduces the waste generation. Therefore, any improvement in energy consumption for the thermal plasma would let it jump up to even the best scenario. This gives also hope for future use of non-thermal plasma and its miniaturised version (scenario 6), which is also known as an energy-consuming technology, yet with considerable improvements over the years. It needs fewer operating processes than conventional methods, hence has profits from process simplicity. Yet this is not paid off so far in terms of green chemistry and circularity.

Finally, it is worth mentioning that *"utility"* constitutes a strong point to enhance circularity in the sense of the Ellen MacArthur definition. The plasma prepared nanomaterials are rich in functional groups such as $–NH_2$, –COOH, –CHO, *etc.* without the need for chemicals for surface modification. Those surface groups are key to the NCD functionality, *i.e.* their photoluminescent properties.[100]

ACKNOWLEDGEMENTS

The authors acknowledge support from the ERC Grant Surface-COnfined fast modulated Plasma for process and Energy intensification (SCOPE) from the European Commission with the Grant No. 810182.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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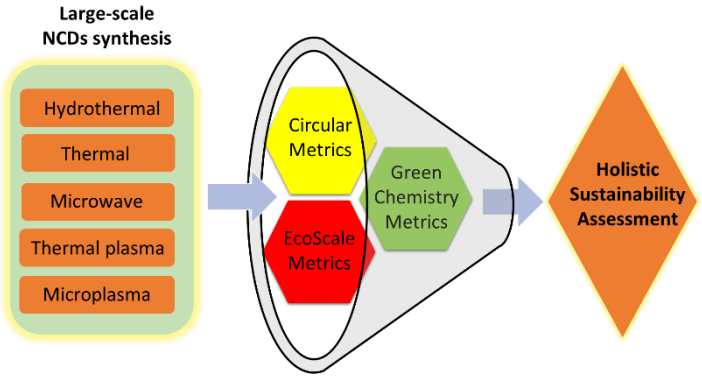

Green Chemistry, Circular, and Ecoscale metrics applied to N-doped carbon dots' synthesis pathways