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Tablets Containing Nimesulide Obtained by Supercritical Impregnation: an LCA Study

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Non-steroidal anti-inflammatory drugs are commonly prescribed for different diseases. A common problem for this wide class of drugs is their low bioavailability, strictly linked to their poor water solubility and, therefore, to their low dissolution rate. In the last years, many studies on novel Drug Delivery Systems (DDS) were performed to improve those drugs dissolution rate. An innovative approach consists in the adsorption of the active principle on a porous substrate. Polysaccharide aerogels are biodegradable and biocompatible; moreover, they are characterized by open pore structures and high surface areas. For these characteristics, they are particularly suitable to be loaded with an active ingredient. In this work, the environmental impacts of starch aerogel loaded with nimesulide, a widely employed nonsteroidal anti-inflammatory drug, using supercritical carbon dioxide impregnation were calculated, following a Life Cycle Assessment (LCA) approach. All the emissions to air, water and soil were reported to a 1.5 g starch aerogel tablet containing the therapeutic dose of nimesulide (100 mg). The life cycle assessment analysis was conducted using SimaPro 8.5.2 software, whereas the Ecoinvent 3.4 database and primary data were used for the life cycle inventory, according to the reference standard for LCA (i.e., ISO 14040-14044). A cradle-to-factory gate approach was followed; therefore, the system boundaries were set from the agricultural stages to the supercritical impregnation. The ReCiPe method was used to evaluate the effect of the tablet production on the midpoint and damage impact categories.

1. Introduction

Drug delivery systems (DDS) are platforms designed to enhance the drugs pharmacological and therapeutic properties or to increase the poorly water-soluble drugs dissolution rate (Prosapio et al., 2017). Nimesulide is a poorly water soluble non-steroidal anti-inflammatory drug (NSAID) broadly used in the cure of acute ache associated with different diseases (Pouchain et al., 2015). In the case of low bioavailability, encapsulation methods based on size-reduction techniques have been frequently proposed, with the aim of obtaining DDS constituted by microspheres or microcapsules (Allémann et al., 1998). Alternatively, the active principle ingredient (API) can be dispersed on a porous structure, which can be a film (Concilio et al., 2015), a membrane (Baldino et al., 2016a) or an aerogel (Baldino et al., 2016b). Among them, because of their low density, large open pores, and large internal surface area, aerogels are promising candidates as matrices and carriers for active substances (Smirnova et al., 2004). They are generally obtained from hydrogel precursors using either supercritical drying (Cardea et al., 2013) or freeze drying (Jin et al., 2004). The best properties in terms of porosity and surface areas are ascribable to silica aerogels (Smirnova et al., 2003); nevertheless, they are biocompatible but not biodegradable. Differently from inorganic aerogels, polysaccharide-based aerogels accomplish the biodegradability that silica aerogel lacks and, therefore, can be used as carriers in the pharmaceutical field (García-González et al., 2011). In a previous work, the effect of process parameters (such as solvent exchanging time and starch concentration) on the morphology of starch aerogels produced from different sources was evaluated (De Marco et al., 2015a).
In the last years, starch, being one of the most abundant and low–cost polysaccharides, has been used as carrier for controlled delivery of drugs (De Marco et al., 2018) and vitamins (De Marco & Reverchon, 2017). Indeed, the API can be charged onto the porous carrier through supercritical carbon dioxide ($scCO_2$)

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impregnation (Mehling et al., 2009). The process is based in the solubilization of the API in the $scCO_2$ at the chosen operating conditions followed by its adsorption onto the porous substrate. Even though supercritical fluids' based processes are considered as "eco-friendly" because of the low amounts of organic solvents used (Prosapio et al., 2016), it is important to evaluate the environmental emissions associated to a specific production. A quantitative way to determine the environmental impact of a process or a product is the performing of the Life Cycle Assessment (LCA) analysis. An LCA analysis may consider the entire process, according to a cradle-to grave approach (Reap et al., 2008) or a part of it (De Marco & Iannone, 2017). Indeed, in the last years, many papers based on LCA analyses were published in different research fields, such as energy (González-García et al., 2014), food (De Marco et al., 2015b), pharmaceuticals (Wernet et al., 2010). Unfortunately, LCA studies regarding specific or very innovative productions turn out to be very difficult to be carried out, because of lack of databases.
Therefore, the aim of this study is the LCA analysis of the production (using $scCO_2$ impregnation) of a 1.5 g starch aerogel (SA) tablet containing the daily therapeutic dose of nimesulide (NIM). In the LCA analysis, the considered steps are aerogel production from starch, and supercritical impregnation of NIM in the aerogel. Data regarding the industrial stages of the process were collected from an Italian processor.

2. Process description

In Table 1, the details of the process under analysis and the main activities are reported.

Table 1: Process details and assumptions

Process	Characteristics and details
Energy supply to facility	Italian energy mix medium voltage
Gelation step	T=75°C; t=24 h; energy and water supply
Retrogradation step	T=4°C; t=72 h; energy supply for cooling
Alcogel formation	T=25°C; t=96 h; ethanol and water supply; energy supply
Aerogel formation	
Pressurization	t=0.08 h; carbon dioxide supply; energy supply
Operating conditions' stabilization	T=45°C; P=20 MPa; t=0.25 h; carbon dioxide supply; energy supply
Drying	T=45°C; P=20 MPa; t=5 h; carbon dioxide supply; energy supply
Depressurization	T=25°C; P=0.1 MPa; t=0.33 h
Supercritical impregnation	
Stabilization	t=0.33 h; carbon dioxide supply; energy supply
Impregnation	T=60°C; P=15 MPa; t=24 h; carbon dioxide supply; energy supply
Depressurization	T=25°C; P=0.1 MPa; t=1 h

2.1 Aerogel preparation

The aerogel preparation consisted in three steps: hydrogel, alcogel and aerogel formation. The *hydrogel* can be obtained solubilizing starch in distilled water at a concentration of 15% w/w, stirring the solution for 24 h at 75°C, and pouring the structure into cylindrical moulds. Then the samples are placed in a refrigerator at 4°C for three days. The *alcogel* is, then, obtained replacing the water filling the pores of the hydrogel by batch equilibration using two ethanol baths at increasing concentration (40% and 100% (v/v)) at room temperature. The equilibration time for each bath is 24 h (De Marco et al., 2018). The *aerogel* is obtained through a supercritical drying at 20 MPa, 45°C for 4 h.

2.2 Supercritical impregnation

Impregnation experiments were performed using a static method (Zhang et al., 2005), according to which a known amount of aerogel (about 100 g) was wrapped in filter paper placed on the bottom of the vessel to avoid its contact with NIM. In order to allow contact with $scCO_2$, a weighed amount of NIM was placed in a container opened on the top mounted axially on the impeller. The autoclave was, then, closed, heated to the fixed temperature and slowly filled with CO_2. After the working pressure (15 MPa) was reached, the system was stored for 24 h, which assured the dissolution of the API in $scCO_2$ and the attainment of the adsorption equilibrium. Indeed, the impregnation time depends by the vessel volume (Gurikov & Smirnova, 2018) and by the drug solubility in the supercritical carbon dioxide in correspondence of the chosen pressure and temperature. The amount of carbon dioxide in the vessel was determined from the density value calculated using the Bender equation (Bender, 1970). Then, CO_2 was vented out at constant flow rate (about 1 MPa/min) and recycled, after condensation. When temperature and pressure in the vessel were equal to the ambient,

the aerogel was removed from the autoclave and weighted. The weight increase of the aerogel indicated the amount of loaded drug.

3. LCA methodology

Data regarding the life cycle of the entire process (aerogel preparation + impregnation) can be correlated through the LCA analysis. The main steps of the analysis are described in the following part of this section.

3.1 Goal definition, functional unit and system boundaries

The goal definition is one of the most important phases of the LCA methodology, because the whole study will be influenced by the choices made in this step. The goal of this study is the evaluation of the environmental impacts related to the attainment of a starch aerogel tablet loaded with NIM. Both the aerogel production and the NIM impregnation are obtained through $scCO_2$ based techniques.
Another important step of an LCA analysis is the definition of the functional unit (FU), which is the reference to which inputs and outputs of the process have to be related. In this work, the FU was defined as a 1.5 g aerogel tablet containing the therapeutic dose of NIM (100 mg).
Through mass and energy balances of each operation, a gate-to-gate analysis was performed; therefore, the system boundaries are set from starch powder transportation to impregnated aerogel attainment.

Table 2: Life cycle inventory of the main inputs and outputs for starch aerogel production, and nimesulide impregnation on starch aerogel with respect to 1.5 g tablet.

Production phase	Input/Output	Unit	
Gelatinization step	Starch	g	8.59E-01
	Water	g	4.86E+00
	Electricity	kJ	2.60E+01
Retrogradation step	Hydrogel	g	5.73E+00
	Electricity for cooling	kJ	3.11E+00
Alcogel 40%	Hydrogel	g	5.73E+00
	Ethanol	g	4.53E+00
	Water	g	8.59E+00
	Output		
	Ethanol	g	3.54E+00
	Water	g	1.16E+01
Alcogel 100%	Alcogel 40%	g	3.73E+00
	Ethanol	g	1.13E+01
	Output		
	Ethanol	g	9.63E+00
	Water	g	2.86E+00
Drying	Alcogel 100%	g	2.54E+00
	Carbon dioxide	g	9.10E+01
	Methane	g	4.66E-01
	Electricity	kJ	1.56E+03
	Electricity for cooling	kJ	3.43E+01
	Output		
	Carbon dioxide	g	9.10E+01
	Ethanol	g	1.23E+00
Impregnation	Aerogel	g	1.31E+00
	Carbon dioxide	g	6.31E-01
	Nimesulide	g	1.88E-01
	Methane	g	4.50E+00
	Electricity	kJ	1.31E+01
	Electricity for cooling	kJ	5.26E-01
	Output		
	Impregnated aerogel	g	1.50E+00
	Carbon dioxide	g	6.31E-01

3.2 Data collection and life cycle inventory

The life cycle inventory (LCI) is one of the most time-consuming steps of a LCA analysis and consists in the search, collection, and interpretation of data regarding each step of the process. All inputs and outputs regarding resources, water, electricity and fuels have to be collected and quantified with respect to the chosen functional unit. Data regarding the starch aerogel production and its impregnation with NIM were collected directly from the production site, thanks to a Southern Italy processor, which uses supercritical carbon dioxide based processes in the attainment of aerogel and in the impregnation process. Background inventory data were taken from the Ecoinvent 3.4 database. All the data were organized in tables constituting the inventory through mass and energy balances made on each step of the production process. The resulting inventory for the inputs and outputs of the different main steps is shown in Table 2.

3.3 Impact assessment

The elaboration of the inventory data was performed through the LCA software SimaPro 8.5.2 (PRé Consultants, 2018) in agreement with the ISO 14040-14044 that is the reference standard for LCA. ReCiPe method (Goedkoop et al., 2009) was used to aggregate the inventory results in terms of midpoint categories and, then, in terms of damages to human health (HH), ecosystem diversity (ED) and resource availability (RA). The midpoint categories with the acronyms and the units used in the ReCiPe method are: climate change (CC, kg CO_2 eq), ozone depletion (OD, kg CFC-11 eq), terrestrial acidification (TA, kg SO_2 eq), freshwater eutrophication (FE, kg P eq), marine eutrophication (ME, kg N eq), human toxicity (HT, kg 1,4DCB eq), photochemical oxidant formation (POF, kg NMVOC), particulate matter formation (PMF, kg PM_{10} eq), terrestrial ecotoxicity (TET, kg 1,4DCB eq), freshwater ecotoxicity (FET, kg 1,4DCB eq), marine ecotoxicity (MET, kg 1,4DCB eq), ionising radiation (IR, kBq U235 eq), agricultural land occupation (ALO, m^2 x yr), urban land occupation (ULO, m^2 x yr), natural land transformation (NLT, m^2), water depletion (WD, m^3), mineral resource depletion (MRD, kg Fe eq), fossil fuel depletion (FD, kg oil eq).

4. Results and discussion

4.1 Environmental analysis of aerogel + NIM formation

The environmental analysis of the production of starch aerogel loaded with NIM was performed in terms of ReCiPe midpoint categories. The analysis was performed considering the production of a 1.5 g tablet containing the 100 mg therapeutic dose of the drug; the results of the impact assessment due to the gate-to-gate production are reported in Table 3. The relative contributions of the different stages of the gate-to-gate process are visually reported in Figure 1.

Table 3: ReCiPe impacts at midpoint level.

Category	Impact
CC	2.98E-01
OD	2.69E-08
TA	1.41E-03
FE	1.06E-04
ME	7.73E-05
HT	9.65E-02
POF	1.12E-02
PMF	4.61E-04
TET	6.74E-05
FET	1.02E-02
MET	9.06E-03
IR	3.97E-02
ALO	2.31E-02
ULO	2.73E-03
NLT	3.57E-05
WD	4.43E-03
MRD	1.27E-02
FD	8.61E-02

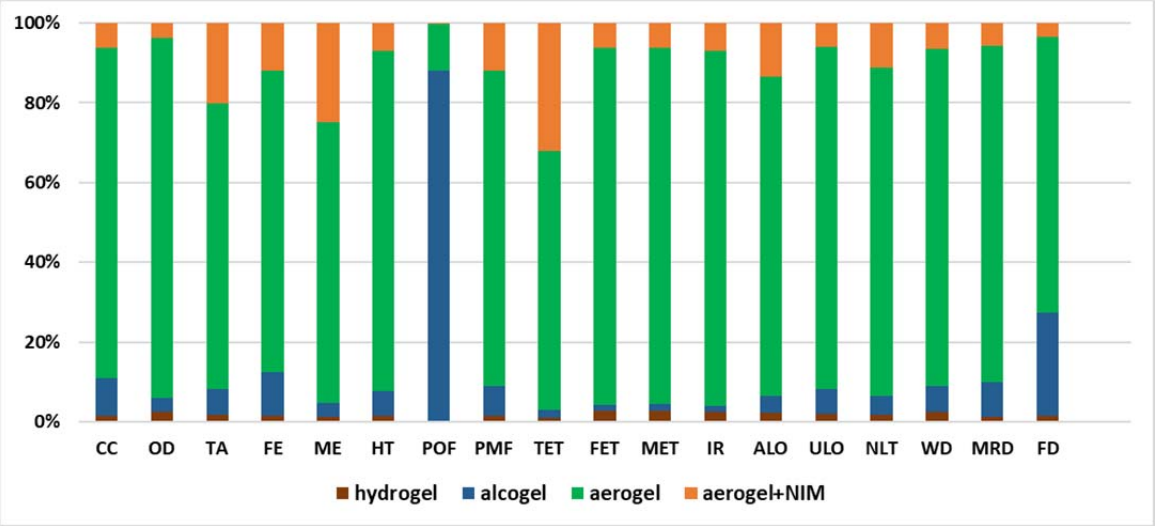

Figure 1. Relative contributions of the different stages with respect to the overall impact.

From Figure 1, it is clear that hydrogel formation step has a negligible contribution on all the ReCiPe categories.
The alcogel production has a high contribution (86.3%) on photochemical oxidant formation, because of the high quantity of ethanol used in solvent exchanges to transform the hydrogel in alcogel. The supercritical drying (aerogel formation) is the major contributor (>50%) to all the midpoint categories, with an exception for POF and FD. The supercritical impregnation of NIM onto the aerogel has an appreciable contribution (at least 5 %) in terms of TA, FE, ME, HT, PMF, TET, ALO, and NLT. In both the supercritical based processes, the emissions are due to the high consumption of electrical energy, mainly related to the condensation and recycling of carbon dioxide.
The results obtained in terms of midpoint categories were, then, grouped and normalized considering the three damage categories and are shown in Figure 2.

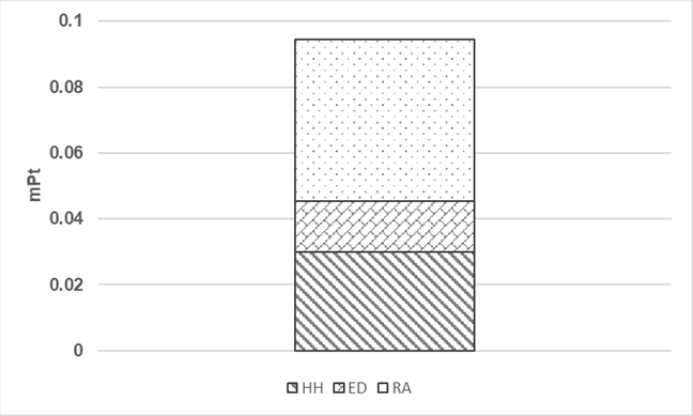

Figure 2: Environmental impact according to the normalised ReCiPe damage categories (millipoint, mPt).

5. Conclusions

In this study, we performed a LCA analysis regarding the production of starch aerogel loaded with nimesulide, a model drug.
The LCA analysis provided quantitative information of the environmental performance of the process, showing that the major contributors to the environmental impact are alcogel formation (on the POF) midpoint category and both the supercritical carbon dioxide based processes (mainly the drying to obtain the aerogel).

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