METHOD FOR PREVENTING PLUGGING OF A CONTINUOUS-REACTION CHANNEL-SYSTEM AND MICRO-REACTOR FOR CARRYING OUT THE METHOD

Abstract: A method for preventing plugging of a continuous-reaction channel-system caused by a by-product of a continuous-reaction comprises the step of generating an ultrasonic wave travelling through said channel-system in a flow direction of feed flows of chemical substances participating in said continuous-reaction.
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— with amended claims (Art. 19(D))
**Description**

**Method for Preventing Plugging of a Continuous-Reaction Channel-System**

**And Micro-Reactor for Carrying out the Method**

The present invention refers to a method for preventing plugging of a continuous-reaction channel-system caused by a by-product of a continuous reaction, and a micro-reactor supporting the continuous-reaction channel-system for carrying out the method.

In micro-reactor continuous-reaction technology, a micro-reactor is continuously passed through by various chemical substances including a plurality of educts flowing into the micro-reactor and reacting therein to form a product flowing out of the micro-reactor. Such a micro-reactor is disclosed, for example, in EP 1 839 739 A1 of the same applicant. In some of these chemical reactions like metalation reactions where a hydrogen-metal or a halogen-metal exchange takes place, water present within the channel-system may react with one or more of the chemical substances, resulting in a precipitate plugging the channels. The local probability of such plugging to occur is not equal throughout the micro-reactor, but is highest at what are called hereafter plugging-susceptible areas which are confluence and mixing areas where the various educts come together, are mixed and react with each other.

Generally, the cause for plugging is solidifying NaOH, LiOH, KOH or RbOH which is formed in side reactions of the compounds comprising an alkaline metal and an organic moiety with the water impurities. Examples for those compounds are methyl lithium, ethyllithium, propyllithium, isopropyllithium, butyllithium, isobutyllithium, sec-butyl lithium, tert-butyllithium, pentyl lithium, isopentyllithium, sec-pentyllithium, tert-pentyllithium, sec-isopentyllithium, hexyllithium, isoheyxyllithium, sec-hexyllithium, cycohexyllithium, octyllithium, phenyllithium, o-tolylithium, m-tolylithium, p-tolylithium, trimethylsilylmethylolithium, phenylsodium, o-tolylsodium, m-tolylsodium, p-tolylsodium, butyllithium/potassium-tert-butoxide, butyllithium/sodium-tert-butoxide, etc., preferably isopropyllithium, sec-butyllithium, tert-butyllithium, sec-pentyllithium, tert-pentyllithium, sec-isopentyllithirnm,
sec-hexyl lithium, cyclohexyl lithium, octyl lithium and phenyl lithium, more preferably butyl lithium (n-, sec- or tert-) or hexyl lithium.

In case the metal in the metalation reaction is lithium, as an example, this reaction is called a lithiation reaction, for example the reaction of n-BuLi (butyllithium) with water, where according to the following equation LiOH precipitates as solid:

\[ C_4H_9Li + H_2O \rightarrow C_4H_{10} + LiOH \]  

As stated above, LiOH tends to be formed in the neighbourhood of the entrance of the micro-reactor. Generally, for plugging to occur, only traces of water impurities are sufficient. Although an exact limit of tolerable water content within the channel-system cannot be specified generally, because it depends on a number of parameters like the (type of) reactants, solvent, their flow-rates, and the chemical environment (pressure, temperature), a value of 10 ppm may be a realistic benchmark. Here, "tolerable" means that the reactor under such conditions is not subject to "severe" plugging.

It should be noted that because even a moderate plugging results in an increased pressure compared to using dry feeds, and consequently in a possible decrease in yield, only dry feeds / solvents are used, which is very cost-intensive because the drying procedures applied are very involved. For example, several ethers such as diethyl ether, methyl tertiary butyl ether (MTBE), tetrahydrofuran (THF) or solvents such as dimethyl sulfoxide (DMSO) are very hard - and therefore expensive - to completely separate from traces of water. In addition, drying is not in all cases without any problems. For example, the above reaction (1) is known to proceed very violently, and other substances like organic nitrates or azides may even be explosive. The reference to organic nitrates or azides is only to give a general example that some substances cannot be dried because the drying procedure is dangerous. Therefore, also from this perspective, a method is needed that goes without drying.

It is an object of the present invention, therefore, to provide a method for preventing plugging of a continuous-reaction channel-system that is inexpensive compared to available methods, applicable when non-dry feeds / solvents are used, without any dan-
ger, and economic. It is a further object of the present invention to provide a micro-reactor for carrying out the method.

These objects are achieved by the features of claim 1 and claim 7, respectively. Advantageous aspects are defined in the dependent claims.

According to the present invention, a method for preventing plugging of a continuous-reaction channel-system caused by a by-product of a continuous reaction comprises the step of generating an ultrasonic wave travelling through the channel-system in a flow direction of feed flows of chemical substances participating in said continuous-reaction, where "preventing plugging" according to the present invention includes "avoiding its coming into existence" as well as "removing plugging already present (partly or completely)". Therefore, the ultrasonic wave is guided by and along the channel-system to plugging-susceptible areas like an electromagnetic wave is guided in an optical fiber. Preferably, the ultrasonic wave is generated as close as possible to the plugging-susceptible areas, in order to reduce attenuation effects. Most preferably, the ultrasonic wave is generated outside but in close proximity of the micro-reactor. There is no restriction as for the detailed construction of a ultrasonic probe or device for generating the ultrasonic wave as long as it can be applied to transfer the ultrasonic wave into one or more of the feed flows to be transported thereby to the plugging-susceptible regions.

Usually, piezo-electric transducers are used for this purpose, that are adapted in design and power to their field of application. Just as one of numerous examples, there is disclosed in document US 2009169428 as a medical application a flow cell with a piezo-electric transducer, where ultrasonic energy is applied to a continuous flow of a suspension. In document EP 1 570 918 A2, there is disclosed the transmission of ultrasonic energy into pressurized fluids. In document US 5,830,127, there is disclosed a method for cleaning the interior channel of an elongated tubular instrument, like an endoscope, comprising the generation of ultrasonic waves in a liquid medium from within the interior channel. In document DE 10 2005 025 248 A1 there is disclosed a fluid guiding system in which, in order to prevent deposits in micro-channels of the system, an ultrasonic signal is coupled into the flowing fluid. It should be noted, however, that according to the present invention, plugging is prevented during normal operation of the micro-reactor, and one or more of the product feeds is used to transport the ultrasonic wave into the
micor-reactor for that purpose. Experiments have shown that for some reactions, the limit of tolerable water content, when the ultrasonic wave is applied, can be extended up to about 500 ppm. It should be noted that, although according to the above, the ultrasonic wave is travelling in the flow direction of the feed flows, the opposite direction is also possible and may be advantageous in case the location of plugging is near to the end of the micro-reactor, for example.

According to an aspect of the present invention, the ultrasonic wave is coupled into and transported by at least one of the plurality of reactant feeds flowing into the channel-system. That is, the reactants flowing into the channel-system constitute a medium carrying the ultrasonic wave. Therefore, the ultrasonic wave energy is not primarily transported to the plug-susceptible areas via the outer sheil of the micro-reactor, for example, although - as a matter of course - the outer sheil and its vibration-relevant physical properties can not be completely neglected in this respect. The material of the micro-reactor, for instance, determines the attenuation, and part of the ultrasonic wave energy may be transported from the coupling area via the outer shell to the plug-susceptible areas. This is, however, to be regarded as a side-effect. As a rough orientation, the frequency of the ultrasonic wave is preferably in the range of 16 kHz to 50 kHz or more, but should be adapted to the design and dimensions of the micro-reactor, the flow rates and the viscosities of the chemical substances, and the chemical reactions taking place, etc. Advantageously, the frequency and/or power is not held at a constant value but is swept, in order to reduce the risk of standing wave formation characterized by noda! points where, due to the absence of ultrasonic energy deposition, precipitates may agglomerate and plug the flowpath/chanel. The frequency may, furthermore, be modulated by a higher frequency which in turn may be swept.

To couple the ultrasonic wave into the micro-reactor in the above described way, the inventors used a custom manufactured Branson 400 W ultrasound system with a sonotrode of 5 mm length, adjusting the frequency to about 40 kHz. Of course, any other ultrasound apparatus can equally be employed, as long as it is suited for transmitting the ultrasonic wave to an on-going fluid, here the educts flowing into the micro-reactor.
According to an aspect of the present invention, the ultrasonic wave is coupled into the channel-system continuously, discontinuously or "on demand". In the first case, the required energy of the ultrasonic wave may be very low, because plugging is continuously stopped in the bud, and no control is needed that may otherwise be used to signal imminent plugging and counteract appropriately. The energy of the ultrasonic wave continuously coupled into the channel-system may be regularly or non-regularly varying or non-varying with time. In the second case, the ultrasonic wave is coupled into the channel-system according to a predetermined or fixed coupling-pattern, whereas in the third case, the coupling-pattern is not fixed but adapted to a current situation. The coupling-pattern may, for example, be determined by a characteristic pressure of one of the chemical substances and comparing the characteristic pressure with a target pressure range. The ultrasonic wave is then, for example, coupled into the channel-system only in case the characteristic pressure is outside the predetermined target pressure range. The predetermined target pressure has experimentally be determined to range between 0 and 10 bar above normal pressure in each of the feed lines, preferably in the range between 0 and 10 bar above normal pressure, and most preferably in the range between 0 and 3 bar, where normal pressure is the pressure of the system when in a water sensitive reaction only dry feeds are used. Normal pressure depends on the feed flow rate, the dimensions (diameters) and viscosities of the feeds etc. The coupling-pattern may also be specified by some rectangular function defining coupling times versus non-coupling times. The timing in this case may be, for example, correlated to the pulsation of a pump delivering the feeds or to the chemical reactions taking place. Alternatively, a continuous generation of the ultrasonic wave can be combined with a detection of the pressure in order to adapt the intensitiy of the continuous ultrasonic wave application to the plugging situation within the micro-reactor. To summarize, the power of the ultrasonic wave that is coupled into the channel-system may be any function of time, either pre-determined or situation-adapted.

According to the invention, a micro-reactor for carrying out the method comprises in flow-direction a plurality of feeding channels being provided each for one of the chemical substances (educts) and connected with each other at a confluence area, a mixing section adjacent to said confluence area, a retention section adjacent to said mixing section, and a discharge channel. The micro-reactor may be, for example, a micro-
reactor as disclosed in EP 1 839 739 A1 or any other micro-reactor having a similar channel-structure and preferably serving a similar purpose.

The above and further objects, features and advantages of the present invention become apparent by the following detailed description of a preferred embodiment with reference to drawing. In the drawing, there is:

Fig. 1 a schematic cross-section of a plate of a micro-reactor coupled to an ultrasonic wave generator according to a preferred embodiment of the present invention for carrying out the method as defined in claims 1 through 7; and

Fig. 2 a schematic perspective view of the arrangement of Fig. 1.

Fig. 1 schematically shows a cross-section of a plate 10 of a micro-reactor as described in more detail in EP 1 839 739 A1, for example, coupled to an ultrasonic wave generator 30. The plate 10 includes a meandering channel system 12 that is divided into a mixing zone 14 and a retention zone 16. Plate 10 comprises first and second feeds 18 and 20, respectively, for continuously introducing feed flows of chemical substances participating in a continuous-reaction taking place in the micro-reactor, and an outlet 22 where a reaction product is discharged. The ultrasonic wave generator 30 includes a sonotrode 32 that comes into contact with the feed flow flowing into the micro-reactor via the first feed 18, and transfers ultrasonic energy, generated by a to-and-fro movement of the sonotrode 32, to the feed flow. As clearly shown in Fig. 1, ultrasonic energy is coupled-in externally of the micro-reactor at an entrance side of the feed flow. Depending on the exact structure of the channel system 16, the location of contact of the sonotrode 32 and the feed flow can, however, also be located within the micro-reactor. Furthermore, although the ultrasonic wave generator 30 shown in Fig. 1 is a Branson™ generator, any other ultrasonic wave generator may be employed as long as it is adapted to transfer ultrasonic energy to one or more of the feed flows entering the micro-reactor. As stated above, the ultrasonic wave is guided through the channel system 12 using the feed flow as a medium.
Fig. 2 shows a stack of plates 10 building-up the micro-reactor coupled to the ultrasonic wave generator 30. A circle "A" specifies an inlet region where the chemical substances continuously flow into the channel system 12 via the first and second feeds 18, 20 to be mixed and chemically interconverted therein.

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Reference Numerals

10 micro-reactor plate
12 channel system
14 mixing zone
16 retention zone
18 first feed
20 second feed
22 outlet
30 ultrasonic wave generator
32 sonotrode
Claims

1. Method for preventing plugging of a continuous-reaction channel-system caused by a by-product of a continuous-reaction, said method comprising the step of generating an ultrasonic wave travelling through said channel-system in a flow direction of feed flows of chemical substances participating in said continuous-reaction.

2. Method according to claim 1, characterized in that said chemical substances comprise a plurality of reactants continuously flowing into said channel-system, and a product formed in said continuous-reaction by mixing and interconverting said plurality of reactants and continuously flowing out of said channel-system, wherein at least one of said plurality of reactants includes an compound comprising an alkali metal and an organic moiety reacting with water impurities in at least one of the feeds to form said by-product.

3. Method according to claim 2, characterized in that said alkali metal is selected from lithium, sodium, potassium, and rubidium.

4. Method according to claim 2 or 3, characterized in that said ultrasonic wave is coupled into and transported by at least one of said plurality of reactant feeds flowing into said channel-system.

5. Method according to one of claims 1 to 4, characterized in that said ultrasonic wave is coupled into said channel-system continuously, discontinuously or on demand.

6. Method according to one of claims 1 to 5, characterized in that said channel-system is part of a continuous-reaction micro-reactor.

7. Micro-reactor for carrying out the method according to claims 1 through 6, said micro-reactor comprising in said flow-direction:
- a plurality of feeding channels being provided each for one of said chemical substances and connected at a confluence area;
- a mixing section adjacent to said confluence area;
- a retention section adjacent to said mixing section; and
- a discharge channel.
1. Method for preventing plugging of a continuous-reaction channel-system of a micro-reactor caused by a by-product of a continuous-reaction, said method comprising the step of generating an ultrasonic wave travelling through said channel-system by being transported by a feed flow in a flowing direction thereof, wherein said ultrasonic wave is coupled into said continuous-reaction channel-system continuously or according to a predetermined coupling-pattern during normal operation.

2. Method according to claim 1, characterized in that said feed flow is a feed flow of chemical substances participating in said continuous reaction.

3. Method according to claim 2, characterized in that said chemical substances comprise a plurality of reactants continuously flowing into said channel-system, and a product formed in said continuous-reaction by mixing and interconverting said plurality of reactants and continuously flowing out of said channel-system, wherein at least one of said plurality of reactants includes an compound comprising an alkali metal and an organic moiety reacting with water impurities in at least one of the feeds to form said by-product.

4. Method according to claim 3, characterized in that said alkali metal is selected from lithium, sodium, potassium, and rubidium.

5. Method according to claim 3 or 4, characterized in that said ultrasonic wave is coupled into and transported by at least one of said plurality of reactant feeds flowing into said channel-system.

6. Method according to one of claims 1 to 5, characterized in that said ultrasonic wave is coupled into said channel-system continuously, discontinuously or on demand.
7. Method according to one of claims 1 to 6, characterized in that said channel-system is part of a continuous-reaction micro-reactor.

8. Method according to one of claims 1 to 7, characterized in that said coupling-pattern is determined by a characteristic pressure of said feed flow, wherein said ultrasonic wave is coupled into said continuous-reaction channel-system when said characteristic pressure is outside a target pressure range.

9. Micro-reactor for carrying out the method according to claims 1 through 8, said micro-reactor comprising in said flow-direction:

- a plurality of feeding channels being provided each for one of said chemical substances and connected at a confluence area;
- a mixing section adjacent to said confluence area;
- a retention section adjacent to said mixing section; and
- a discharge channel.
A. CLASSIFICATION OF SUBJECT MATTER

INV. B01J19/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

BO1J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical, search terms used)

EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search

30 June 2010

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Date of mailing of the international search report

06/07/2010

Authorized officer

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