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(54) Title: PROCESS FOR THE PREPARATION OF A MONOVALENT SUCCINATE SALT

(57) **Abstract**: The present invention pertains to a process for the preparation of a monovalent succinate salt comprising the steps of: a) fermenting a carbohydrate source to succinic acid by means of a micro-organism, b) adding a alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate, the alkaline earth metal being calcium or magnesium, as neutralising agent during the fermentation under formation of an aqueous medium comprising calcium succinate or magnesium succinate, c) reacting the alkaline earth metal succinate salt in an aqueous medium with a monovalent hydroxide, carbonate and/or hydrogencarbonate base to form an alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate and a monovalent succinate salt, d) separating the monovalent succinate salt from the alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate, e) recycling the alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate to step b.

PROCESS FOR THE PREPARATION OF A MONOVALENT SUCCINATE SALT

The present invention relates to a process for the preparation of monovalent succinate salts. The present invention also pertains to an integrated fermentation and salt exchange process for the manufacture of monovalent succinate salts.

Succinic acid, also known as butanedioic acid and ethanedicarboxylic acid, is a compound which is suitable for a variety of uses. It finds application in food, pharmaceuticals, cosmetics, and as a starting material for chemical applications. For example, it may be used as a starting material for the production of 1,4-butanediol, tetrahydrofuran, and gamma-butyrolactone.

Succinic acid may be prepared via fermentation of carbohydrates by micro-organisms. A common feature to all fermentation processes wherein acid is manufactured is the need to neutralize the acids excreted by the micro-organisms in the process. If the acids are not neutralized, the pH of the fermentation process will decrease. When the pH drops below a critical value, depending on the micro-organism used in the process, the micro-organism's metabolic process may be damaged, and the fermentation process brought to a halt. It is therefore common practice to add a base during the fermentation process to keep the pH of the fermentation mixture at a specified value.

US 5,168,055 describes a process for the production of a succinate wherein a carbohydrate-containing substrate is fermented with a succinate-producing microorganism and neutralized with calcium hydroxide or calcium oxide. The calcium succinate is isolated by filtration, and slurried in water. Concentrated sulphuric acid is added to convert the calcium succinate into succinic acid, under formation of insoluble calcium sulphate.

US 5,958,744 describes a process for the preparation of diammonium succinate where either an ammonium ion based material is used to neutralize the acid formed in the fermentor, or by substituting the ammonium cation for the cation of the succinate salt used in the fermenter. In the latter case the alkali metal bases sodium hydroxide and potassium hydroxide are preferred. The use of divalent bases such as calcium hydroxide is indicated to create solubility problems downstream. A dilute stream of aqueous disodium succinate is submitted to a concentration step and then to a reaction with ammonium and carbon dioxide.

WO 2008/143015 describes a process for the fermentative production of succinic acid via an ammonium succinate solution, wherein all by-products can be re-used in the production of succinic acid. The process comprises the following steps (1) to (5): (1) a crystallization/fermentation step for producing calcium succinate trihydrate by using a microorganism; (2) a transfer step for transferring/crystallizing calcium succinate trihydrate to calcium succinate monohydrate; (3) a crystal separation step for separating calcium succinate monohydrate; (4) a salt-substitution step for converting calcium succinate monohydrate separated in the preceding step to an ammonium succinate solution; and (5) a solid/liquid separation step for removing a calcium carbonate precipitate from the ammonium succinate solution.

US 2007/0015264 describes a method for producing succinic acid through addition of a magnesium compound as neutralizing agent. Subsequently, a salt exchange process is carried out wherein the magnesium acid compound is converted into an ammonium acid compound by reacting with ammonia or ammonium carbonate.

While the above references describe a number of compounds suitable as neutralizing agent, and a number of manners in which the resulting materials can be processed further, there is still need for a process for manufacturing succinic acid compounds by fermentation which allows working with highly concentrated solutions, which gives a high yield of the desired compound without producing substantial amounts of non-reusable components, and which provides the succinic acid in a form which enables easy and efficient further processing.

The present invention provides such a process. Accordingly, the present invention pertains to a process for the preparation of a monovalent succinate salt comprising the steps of:
a) fermenting a carbohydrate source to succinic acid by means of a micro-organism,
b) adding a alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate, the alkaline earth metal being calcium or magnesium, as neutralising agent during the fermentation under formation of an aqueous medium comprising calcium succinate or magnesium succinate,
c) reacting the alkaline earth metal succinate salt in an aqueous medium with a monovalent hydroxide, carbonate and/or hydrogencarbonate base to form an alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate and a monovalent succinate salt,

d) separating the monovalent succinate salt from the alkaline earth metal hydroxide, carbonate and/or hydrogen carbonate,

e) recycling the alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate to step b.

It has been found that there is a specific relationship between the nature of the alkaline earth metal in the succinate and the nature of the base. For both calcium as well as magnesium succinate, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate and potassium hydrogencarbonate. More specifically, where the alkaline earth metal succinate salt is calcium succinate the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate, potassium hydrogencarbonate, ammonium carbonate and ammonium hydrogencarbonate. It has been found that the use of these bases results in a very high yield being obtained, much higher than when, for example, ammonium hydroxide or triethyl amine is used. Where the alkaline earth metal succinate salt is magnesium succinate, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate and potassium hydrogencarbonate. Again, it has been found that the use of these specific compounds results in a very high yield being obtained, much higher than in the case of, for example, ammonium hydroxide, ammonium carbonate, or triethylamine. It is of particular interest to note that ammonium carbonate shows attractive results when used in combination with calcium succinate, but not when used in combination with magnesium succinate.

The high yields obtained in the salt exchange process according to the invention also result in the formation of high yields of magnesium or calcium carbonate, hydrogencarbonate and/or hydroxide, which can be recycled to the fermentation step. This makes for a low-waste, environmentally friendly process.

The succinate is finally obtained in the form of a monovalent salt. These monovalent salts are particularly suitable for further processing. Preferred monovalent salts are potassium and sodium succinate salts. Especially preferred is a sodium succinate salt.

The first step in the process according to the invention is fermenting a carbohydrate source to succinic acid by means of a micro-organism. The nature of the carbohydrate source used for the process according to the invention is not critical, even relatively raw carbohydrate sources can be used for the fermentation. Examples of suitable carbohydrate sources are sucrose, (liquefied) starch, and glucose syrup. Fermentation processes of this type are known in the art and require no further elucidation here.

During fermentation, an alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate, the alkaline earth metal being calcium or magnesium, is added as neutralising agent. This results in the formation of an aqueous medium comprising the corresponding alkaline earth metal succinate salt of calcium or magnesium. The amount of base added is determined by the amount of succinate produced and may be determined via pH control of the fermentation medium.

The present invention encompasses the use of calcium or the use of magnesium. Where calcium is used, calcium carbonate, calcium hydrogencarbonate and/or calcium hydroxide may be used. Calcium carbonate may be preferred because it results in a product with a low solubility. Where magnesium is used, magnesium carbonate, magnesium hydrogencarbonate and/or magnesium hydroxide may be used. Magnesium hydroxide may be preferred because it results in a product with a low solubility.

The next step is the salt exchange where the alkaline earth metal succinate salt is reacted with a monovalent base.

Optionally, the medium comprising the alkaline earth metal succinate is subjected to a step to remove the biomass from the medium before effecting the reaction with the monovalent hydroxide, carbonate and/or hydrogencarbonate base. Biomass removal may be effected, for example, by separation on size, e.g., through filtration, or by separation on density. Conventional methods include filtration, flotation, sedimentation, centrifugation, flocculation and combinations thereof. It is within the scope of the skilled person to determine an appropriate method. Other optional pre-treatment steps include washing, filtration, (re)crystallization and concentration, and combinations thereof.

The reaction of the alkaline earth metal succinate with the monovalent base takes place in an aqueous medium. The succinate is generally already present in an aqueous medium when it leaves the fermentation. Calcium succinate typically will be present in the fermentation medium in the solid state. Magnesium succinate typically will be present dissolved in the reaction medium.

Depending on the nature of the monovalent base, it may be added in solid form or dissolved or suspended in an aqueous medium. The amount of base is determined by stoichiometric and pH considerations. In general, the molar ratio between the base and the succinate is between 0.9:1 and 1.5:1, more in particular between 0.95:1 and 1.3:1. Under some conditions it may be preferred to use a surplus of base to obtain a high conversion. In that case, it may be preferred for the molar ratio between the base and the succinate to be between 5:1 and 3:1.

In a preferred embodiment according to the invention, the reaction is carried out in two steps wherein in the first step the alkaline earth metal succinate is reacted with a monovalent base to form a monovalent succinate, and in a second step some further base is added to ensure the removal of virtually all alkaline earth metal ions from the succinate. This is relevant for preparing a product with a low alkaline earth metal ion content. This may be necessary because of product specifications or certain further processing steps such as membrane electrodialysis. Additional purification steps like ion exchange may be necessary to reach the desired alkaline earth metal content.

As indicated above, where the alkaline earth metal succinate is calcium succinate, the base may be selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate, potassium hydrogencarbonate, ammonium carbonate and ammonium hydrogencarbonate. Which compound is preferred will depend on whether it is desirable to manufacture sodium succinate, potassium succinate, or ammonium succinate. The manufacture of sodium or ammonium succinate may be preferred, making the use of a sodium or ammonium compound preferred. Within the group of sodium compounds, sodium carbonate may be preferred because it may give a higher conversion. The use of hydroxides may sometimes be of interest for economical reasons.

Where the alkaline earth metal succinate is magnesium succinate, the base may be selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate and potassium hydrogencarbonate. The use of a sodium compound, resulting in the manufacture of sodium succinate may be preferred. When a high conversion is aimed for, the use of a hydroxide, in particular sodium hydroxide is preferred. On the other hand, for economical reasons the use of carbonate may sometimes be attractive.

The present invention allows processing of concentrated solutions or suspensions of alkaline earth metal succinate. In particular, solutions or suspensions may be used with a concentration in the range of 4 to 40 wt.%, more in particular in the range of 10 to 25 wt.%. For magnesium succinate, a concentration in the range of 4 to 25 wt.%, more specifically in the range of 10 to 25 wt.% may be mentioned in particular. For calcium succinate a concentration in the range of 4 to 40 wt.%, more specifically in the range of 10 to 25 wt.% may be mentioned in particular.

This results in monovalent succinate solutions of high concentration, for example in the range of 4 to 30 wt.% more in particular in the range of 8-30 wt.%.

It is preferred for the reaction between the alkaline earth metal succinate and the monovalent base to take place under intensive agitation. This can be done by means of conventional mixers and/or stirrers, for example in a stirred tank reactor.

It may be preferred for the reaction between the alkaline earth metal succinate and the base to take place at a temperature between 20 and 100°C, more preferably between 20 and 75°C.

In one embodiment, the process according to the invention is preferably carried out continuously. In other embodiments the process is carried out in batch or in fed batch.

The alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate and the monovalent succinate salt formed in the process according to the invention can be easily separated from each other. The alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate is in solid, particulate, form while the monovalent succinate salt is dissolved in the aqueous medium. The two components can therefore easily be separated by conventional processes, for example filtration or sedimentation.

Optionally, the alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate particles are washed with water after separation. In the case of a continuous process the particles are preferably continuously removed from the reaction medium. In the case of a batch process it may be preferred that the particles are removed from the reaction medium directly after formation or as soon as technically possible.

The alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate is recycled to the fermentation step.

If so desired, the aqueous medium containing the monovalent succinate salt may be subjected to one or more further purification/modification steps, such as activated carbon treatment, extraction, electrodialysis, etcetera. These purification steps are known in the art and need no further elucidation here. The product of the process according to the invention may very suitably be subjected to a modification step wherein, for instance, the succinate salt is converted into succinic acid. This results in a succinic acid of very high purity being formed. Said conversion may be conducted in manners known in the art, for example, by means of bipolar electrodialysis or addition of a strong mineral acid. The monovalent succinate salt may also be converted into other succinate salts or into succinate esters like dimethyl or dibutyl succinate.

In the above, the integrated fermentation and salt exchange process according to the invention has been described. While the salt exchange process is of particular interest in the context of this integrated process, situations may be envisaged where the process is carried out in a different context. Therefore, the present invention also pertains to a process for preparing a monovalent succinate salt from an alkaline earth metal succinate salt selected from calcium succinate and magnesium succinate, wherein the alkaline earth metal succinate salt is reacted in an aqueous medium with a monovalent hydroxide, carbonate and/or hydrogencarbonate base to form an alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate and a monovalent succinate salt.

In one embodiment, where the alkaline earth metal succinate salt is calcium succinate the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate, potassium hydrogencarbonate, ammonium carbonate and ammonium hydrogencarbonate. In another embodiment, where the alkaline earth metal succinate salt is magnesium succinate the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide, potassium carbonate and potassium hydrogencarbonate.

The present invention is further illustrated by the following Examples, without being limited thereto or thereby.

Example

Preparation of starting materials:

For preparation of magnesium succinate in an aqueous medium (solution), 80.0 grams of succinic acid were dissolved in 1000.0 grams of water. After heating to 50°C, a stoichiometric amount of solid magnesium oxide (27.3g) was added. To make sure all of the succinic acid would react, a small surplus (2.3g) of MgO was added. Finally, the mixture was filtered over a Büchner funnel, equipped with a filter paper. The filtrate, being a 9.4 %(w/w) solution of magnesium succinate, was collected.

Calcium succinate in an aqueous medium (suspension) was prepared in an analogous manner by letting succinic acid (80.0g + 4.2g surplus in 1000.1g water) react with solid calcium hydroxide (50.6g). After filtration and washing with approx. 800 ml of demineralised water, the residue (calcium succinate) was collected and dried in a dessication stove for 18 hours at 80°C. The calcium succinate was then suspended in water.

The slight surplus of reagents in both reactions was applied in order to obtain succinates with a minimal amount of impurities.

Experiments:

Magnesium succinate and calcium succinate were reacted with various bases to investigate the effectivity of the process according to the invention.

The following bases were used:

- sodium hydroxide [NaOH] (according to the invention)
- sodium carbonate [Na_2CO_3] (according to the invention)
- ammonium carbonate [$(NH_4)_2CO_3$] (according to the invention for calcium succinate, comparative for magnesium succinate)
- ammonium hydroxide [NH_4OH](comparative)
- trietylamine [$N(CH_2CH_3)_3$] (comparative)

The reactions were carried out in 500 ml beakers or Erlenmeyer flasks containing 100 ml of 10 wt% Mg-succinate or Ca-succinate in aqueous medium. Sodium carbonate and ammonium carbonate were added in solid form in stoichiometric amounts. Ammonia, NaOH and triethylamine were added in solute form, also in stoichiometric amounts. The reaction mixtures were stirred using a stirring bar and a magnetic stirrer.

Table 1

Exp.	**Reaction**	**m(Mg/Ca-Succ.) [g]**	**Base [g]**
1	MgSucc + NH_4OH	99.7	9.2
2	MgSucc + NaOH	100.0	10.8 (+ 89.4 H_2O)
3	MgSucc + Et_3N	100.0	13.5 (+ 86.7 H_2O)
4	MgSucc + Na_2CO_3	99.9	7.2
5	MgSucc + $(NH_4)_2CO_3$	99.6	6.5

Exp.	**Reaction**	**m(Mg/Ca-Succ.) [g]**	**Base [g]**
6	CaSucc + NH_4OH	10.0 + 89.8 H_2O	8.8
7	CaSucc + NaOH	10.0 + 90.1 H_2O	10.5
8	CaSucc + Et_3N	9.9 + 90.3 H_2O	12.9
9	CaSucc + Na_2CO_3	10.0 + 90.1 H_2O	6.8
10	CaSucc + $(NH_4)_2CO_3$	10.0 + 90.1 H_2O	6.1

The mixtures were allowed to react for 1 hour.

From each reaction mixture, samples of 25 ml were taken. These were centrifuged, after which Mg (or Ca) and succinate were determined analytically. The analytical data and the initial concentration of Mg2+ or succinate were used for calculation of the conversion of Mg-succinate or Ca-succinate to Na-, NH_4- or triethyl-amine-succinate. The results are given in Table 2.

Table 2

Experiment	**pH**	**Mg/Ca [ppm]**	**Succinate [wt%]**	**Conversion [%]**
1: MgSucc + NH_4OH (comparative)	9.6	8415	6.9	43.0
2: MgSucc + NaOH (invention)	12.4	12	4.0	99.8
3: MgSucc + Et_3N (comparative)	9.6	3480	3.9	56.6
4: MgSucc + Na_2CO_3 (invention)	10.5	880	7.7	94.1
5: MgSucc + $(NH_4)_2CO_3$ (comparative)	7.8	9487	7.5	37.4
6: CaSucc + NH_4OH (comparative)	11.1	3489	1.0	12.7
7: CaSucc + NaOH (invention)	13.0	281	6.5	95.4
8: CaSucc + Et_3N (comparative)	10.9	3297	1.0	13.3
9: CaSucc + Na_2CO_3 (invention)	10.5	19	7.0	99.3
10: CaSucc + $(NH_4)_2CO_3$ (invention)	8.0	829	7.0	98.7

As can be seen from Table 2, when sodium hydroxide is used, a conversion of well above 90% is obtained both for magnesium succinate and for calcium succinate. The same applies when sodium carbonate is used. For ammonium carbonate it should be noted that while for calcium succinate a conversion of 98.7% is obtained, the conversion for magnesium succinate is only 37.4%.

CLAIMS

1. A process for the preparation of a monovalent succinate salt comprising the steps of:

a) fermenting a carbohydrate source to succinic acid by means of a micro-organism,

b) adding a alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate, the alkaline earth metal being calcium or magnesium, as neutralising agent during the fermentation under formation of an aqueous medium comprising calcium succinate or magnesium succinate,

c) reacting the alkaline earth metal succinate salt in an aqueous medium with a monovalent hydroxide, carbonate and/or hydrogencarbonate base to form an alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate and a monovalent succinate salt,

d) separating the monovalent succinate salt from the alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate,

e) recycling the alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate to step b.

2. Process according to claim 1, wherein the monovalent hydroxide, carbonate and/or hydrogencarbonate base is a sodium and/or potassium base, preferably a sodium base.

3. Process according to claim 1 or 2, wherein the medium comprising the alkaline earth metal succinate is subjected to a step to remove the biomass from the medium before effecting the reaction with the hydroxide, carbonate or hydrogencarbonate base.

4. Process according to any one of the preceding claims, wherein the monovalent base is sodium hydroxide or sodium carbonate.

5. Process according to any one of the preceding claims, wherein the concentration of the alkaline earth metal succinate in the aqueous medium is between 4 and 40 wt%.

6. Process according to any one of the preceding claims wherein the alkaline earth metal carbonate, hydroxide and/or hydrogencarbonate is separated from the monovalent succinate salt by filtration.

7. Process for preparing a monovalent succinate salt from an alkaline earth metal succinate salt selected from calcium succinate and magnesium succinate, wherein the alkaline earth metal succinate salt is reacted in an aqueous medium with a monovalent hydroxide, carbonate and/or hydrogencarbonate base to form an alkaline earth metal hydroxide, carbonate and/or hydrogencarbonate and a monovalent succinate salt.

8. Process according to claim 7, wherein the monovalent hydroxide, carbonate and/or hydrogencarbonate base is a sodium and/or potassium base, preferably a sodium base.

9. Process according claim 7 or 8, wherein the monovalent base is sodium hydroxide or sodium carbonate.