

## Description

The invention relates to a method of manufacturing lactulose, in which an alkaline aqueous solution of lactulose and borax is prepared and heated at a temperature above 80 °C and the lactulose is separated from the resulting conversion products.

This method is known from, for example, Chemical Abstracts 86: 173392h. Since conversion requires an alkaline medium, sodium hydroxyde solution is additionally added. The yield of the method is comparatively high; the boric acid forms with the lactulose a complex which shifts the equilibrium away from the lactose. Furthermore, galactose, tagatose, other sugars, organic acids and dyes are formed from the lactose as conversion products.

It is an object of the invention to provide a method of manufacturing lactulose which is similarly economical, but which is ecologically more sound.

According to the invention this object is achieved in that the method mentioned hereinbefore can also be carried out when, apart from borax, substantially no alkalisng material is added to the solution.

An other method for the conversion of lactose into lactulose wherein use is made of borate is described in US 3,505,309. According to this method lactose is dissolved in dilute (0.005 mol/l) alkalimetal tetraborate solution, whereafter this solution is absorbed onto a strong-base anion exchange resin (quaternary ammonium groups fixed to a poly(styrene-divinylbenzene)matrix) in the borate form. Both solution and column are at a temperature of about 20 to 50 °C. During this column step lactulose is formed which is separated by elution from the column and recovered from the eluate.

However, this method as described in US 3,505,309 is not applicable at a large technical scale. This has been demonstrated clearly in example 2 of this publication. At 20-35 °C 25% of lactulose is formed with about 25% of lactose recovered. As can be seen from this experiment 50% of the lactose stays on the column as such or converted to other sugars like lactulose but also degradation products. Due to the strong base quaternary ammonium groups sugar borate complexes have a very strong interaction with the resin and can not be eluted just with water even at somewhat higher temperature. Besides, the higher the temperature the more degradation occurs. Therefore, for a feasible industrial process one can not use the resin to perform the conversion from lactose to lactulose since it would result in too much degradation products. Besides, at the other hand a good chromatographic separation of the various sugars seems impossible due to the too tight interaction with the quaternary ammonium groups.

In a somewhat related method disclosed in EP 39.127 lactose and boric acid in aqueous medium are reacted in the presence of a tertiary or quaternary amine as a catalyst. Preferred temperatures for this reaction range from about 38 °C to about 70 °C. Preferred pH values for this process range from about 9.0 to about 11.0. The use of tertiary amine instead of caustic unmistakably leads to the wanted ketoses, but the removal of the amines, especially the quaternary ones is difficult due to the strong complexes they form with boric acid. A lower pH would loosen the complex. Then, however, mineral acids would be needed. Triethylamine is regained by distillation. It is quite probable that degradation products are volatile, which might hamper the recirculation of the amine due to build-up of those impurities (e.g. organic acids). As can be seen from the results in Table 3 use of reclaimed reagents may lead to considerably lower conversion or more degradation. The results are not very reproducible.

Removal of the last traces of triethylamine has to be done with ion exchange, which means that this method is much more laborious. Besides when caustic is used as the catalyst for the isomerisation of al doses of ketoses bipolar membrane technology can be used to recover the used caustic. Loss of volatile amines to the environment may cause pollution as well.

According to the present invention, the sewage load with alkali salts - which after removing the alkali ions by ion exchangers are formed in the regeneration of the ion exchangers - is thus considerably reduced.

As a further step in this direction the method enables a recycling of the sodium ions according to two modified embodiments of the invention:

One embodiment consists in that the borax is manufactured in an aqueous solution of boric acid, preferably already simultaneously with the lactose, in that the sodium ions are transferred from the solution of the conversion products into the solution of the boric acid by electrodialysis.

In this manner a complete recycling of the sodium ions is possible.

For this purpose only two compartments separated by a cation exchanging membrane are necessary. One compartment is the cathode compartment and the boric acid solution, preferably boric acid-lactose solution, flows through it. The solution of the conversion products flows through the other compartment which is the anode compartment. Under the applied voltage the sodium ions move into the first compartment so that a borax solution is formed in the said compartment.

The other embodiment consists in that the sodium ions are removed from the solution of the conversion products substantially as completely as possible by means of a weakly acid ion exchanger and only thereafter by means of a more strongly acid ion exchanger, whereas the weakly acid ion exchanger is preferably at least partly regenerated with boric acid and the borax then formed is re-used, at least partly.

In other words: as long as the sodium ion concentration in the solution of the conversion products is so high that a weakly acid ion exchanger also binds the sodium ions, such an ion exchanger will be used. A strongly acid ion exchanger will then be used only for the complete separation of the sodium ions from the solution. As a result of the preferred regeneration of the weakly acid ion exchanger with boric acid, the sodium ions bound by same will remain in the production cycle. Only the rest is removed to the sewage. However, also in the case in which the weakly acid ion exchanger is not regenerated with boric acid, its use is of advantage. Anyhow it may be regenerated with a weaker acid which is better from an ecological point of view. Carbonic acid, for example, is ecologically sound.

As a further embodiment of the method according to the invention it is suggested that, for separating the lactulose, the solution of the reaction products after separating the sodium ions, prior to or after the separation of the borate ions, preferably after evaporating to 15 to 20% dry material is passed through a long container packed with a weakly basic ion exchanger as a chromatography column, preferably at 30 to 60 °C, water being used as an eluent.

This new use of an ion exchanger leads to an excellent separation of the lactulose, but also of the galactose from the mixture of the reaction products. A lactulose can be obtained having a degree of purity of over 99%, which up till now has been possible on an industrial scale only at incommensurably higher cost.

As the last step of the method and the modified embodiment of the invention it is finally suggested for the manufacture of lactulose powder to add, preferably spray, a concentrated lactulose solution having a purity of at least 90% lactulose, based on dry material, to a lactulose powder which is kept in motion, preferably stirred, so slowly and to distribute it therein so rapidly and finely that the lactulose solution always forms only a thin film on the surface of the powder particles from which the solid material grows on the powder particles.

It is known that it is not possible to crystallise lactulose simply by concentration from an aqueous solution.

Methanol or another organic solvent has so far been added for the manufacture of lactulose powder, in which solvent the lactulose has a smaller solubility and precipitates. The mechanically separated and dried powder then is always contaminated with a residue of the solvent.

The suggested new method on the contrary enables the manufacture of a free-flowing, only weakly hygroscopic lactulose powder of high purity.

Decisive for this method is the slow addition and immediate distribution and spreading of the lactulose syrup on the grains to form a thin film. Even only local accumulations of the syrup are to be avoided. Above all, already crystalline material must not dissolve again in the syrup. Suitable for this purpose are, for example, spray-driers, paddle driers and other hot-air driers having a stirring mechanism.

The above suggestions for the formation of a borax solution by electrodialysis, the removal of sodium ions from the solution of the conversion products by means of a weakly acid ion exchanger, the separation of the lactulose by means of a weakly basic ion exchanger as a chromatography column, and the manufacture of a lactulose powder are in combination advantageous within the scope of the present invention, but each of these measures may also be used separately to get certain advantages.

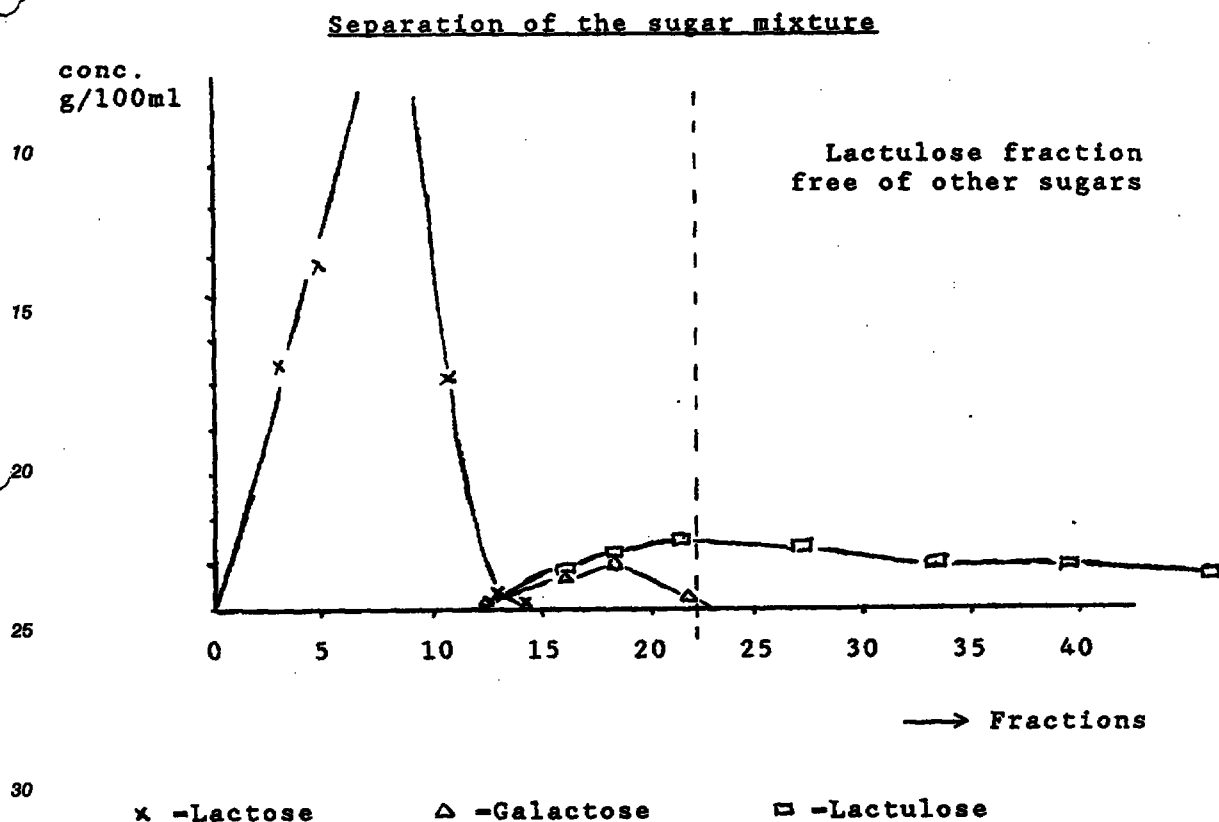
#### EXAMPLE

175 kg of lactose-monohydrate, 46.3 kg of borax and 800 kg of de-ionised water are heated at 95 °C and kept at this temperature for 3 hours. A mixture of reaction products is formed which comprises substantially 74.2 kg of lactulose, 75.3 kg of lactose, 8.0 kg of galactose and 0.8 kg of tagatose. The resulting sugar mixture solution is passed over a weakly acid ion exchanger and subsequently over a strongly acid ion exchanger, so that the sodium ions originating from the borax are removed. The solution is then evaporated to 15% dry material.

The solution having this concentration is passed over a chromatography column consisting of a weakly basic ion exchanger.

In fact the column consists of a hollow cylinder having a diameter of approximately 90 cm and a height of 2 m, filled with 1000 l of the weakly basic ion exchange resin. 1000 l of the solution are added at a temperature between 40 and 60 °C, to the column which was previously filled with water and subsequently replenished with water, at a flow rate of 1 to 2 bed volumes/hour.

The diagram hereinafter shows the achieved separation of the components of the solution. It appears that with only a small loss a nearly pure, lactulose fraction without other sugars can be obtained. The sharp separation of lactose and lactulose is particularly surprising.



The resulting lactulose solution is liberated from the boric acid in a boron-specific exchanger and is then evaporated to a content of 65% lactulose in, for example, a vacuum of 40 mbar. A marketable syrup is thus obtained.

However, the syrup may also be converted into a powder.

For that purpose, for example, a steamheated paddle drier is used (De Dietrich SP 200), total capacity 200 l and useful contents 130 l, stirrer speed 10 rpm. 20 kg of lactulose powder are put into the container and totally 100 kg of syrup heated at 60°C are drawn in at a flow rate of 2 l/hour. The whole is then dried for 30 minutes. 20 kg of the resulting powder remain as a sample for the next batch.

Instead of the addition of borax as described hereinbefore, the following method may be used:

175 kg of lactose-monohydrate, 30 kg of boric acid and 600 kg of de-ionised water are dissolved while stirring at approximately 45°C and are passed over the described weakly acid ion exchanger which is loaded with the sodium ions. Elution is carried out with de-ionised water. The resulting solution which has regenerated the ion exchanger at least partly with the boric acid and has taken up the sodium ions, is adjusted by means of sodium hydroxide solution at pH 8.3, i.e. the pH-value of the above described lactose-borax solution.

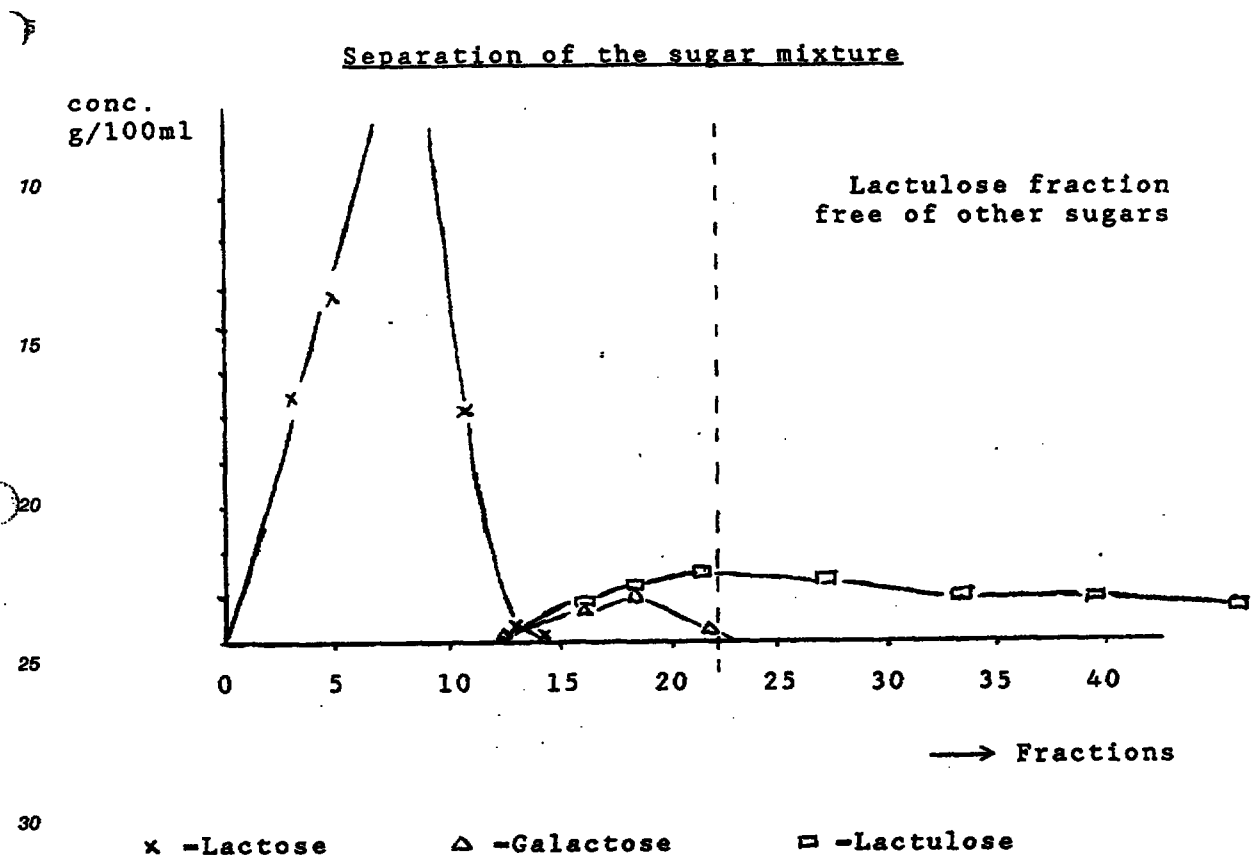
The conversion then occurs as with the said solution.

## Claims

1. A method of manufacturing lactulose, in which an alkaline aqueous solution of lactose and borax is prepared and is heated at a temperature above 80°C and the lactulose is separated from the resulting conversion products, characterised in that, apart from the borax, substantially no alkalisng material is added to the solution.
2. A method as claimed in Claim 1, characterised in that the borax is manufactured in an aqueous solution of boric acid, preferably already simultaneously with the lactose, in that the sodium ions are transferred



The diagram hereinafter shows the achieved separation of the components of the solution. It appears that with only a small loss a nearly pure, lactulose fraction without other sugars can be obtained. The sharp separation of lactose and lactulose is particularly surprising.



The resulting lactulose solution is liberated from the boric acid in a boron-specific exchanger and is then evaporated to a content of 65% lactulose in, for example, a vacuum of 40 mbar. A marketable syrup is thus obtained.

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Instead of the addition of borax as described hereinbefore, the following method may be used:

175 kg of lactose-monohydrate, 30 kg of boric acid and 600 kg of de-ionised water are dissolved while stirring at approximately 45°C and are passed over the described weakly acid ion exchanger which is loaded with the sodium ions. Elution is carried out with de-ionised water. The resulting solution which has regenerated the ion exchanger at least partly with the boric acid and has taken up the sodium ions, is adjusted by means of sodium hydroxide solution at pH 8.3, i.e. the pH-value of the above described lactose-borax solution.

The conversion then occurs as with the said solution.

## Claims

1. A method of manufacturing lactulose, in which an alkaline aqueous solution of lactose and borax is prepared and is heated at a temperature above 80°C and the lactulose is separated from the resulting conversion products, characterised in that, apart from the borax, substantially no alkalisng material is added to the solution.

2. A method as claimed in Claim 1, characterised in that the borax is manufactured in an aqueous solution of boric acid, preferably already simultaneously with the lactose, in that the sodium ions are transferred



from the solution of the conversion products into the solution of the boric acid by electrodialysis.

3. A method as claimed in Claim 1, characterised in that the sodium ions are removed from the solution of the conversion products substantially as readily as possible by means of a weakly acid ion exchanger and only thereafter by means of a more strongly acid ion exchanger.
4. A method as claimed in claim 3, characterised in that the weakly acid ion exchanger is regenerated at least partly with boric acid and that the borax formed during said regeneration is used at least partly in the method as claimed in Claim 1.
5. A method as claimed in any of the Claims 1-4, characterised in that for the separation of the lactulose the solution of the reaction products after separating the sodium ions, prior to the separation of the borate ions, preferably after evaporation to 15-20% dry material, is passed through a long chromatography column filled with a weakly basic ion exchanger, preferably at 30 to 60 °C, water being used as an eluent.
6. A method as claimed in any of the Claims 1 to 5, characterised in that for the manufacture of lactulose powder, a concentrated lactulose solution having a purity of at least 90% lactulose based on dry material is added, preferably sprayed, so slowly to a lactulose powder which is kept in motion, preferably stirred, and is distributed therein so rapidly and finely that the lactulose solution always forms only a thin film on the surface of the powder particles from which the solid material grows on the powder particles.

#### Patentansprüche

1. Verfahren zur Herstellung von Lactulose, bei welchem eine wässrige alkalische Lösung von Lactose und Borax hergestellt und bei einer Temperatur über 80 °C erhitzt wird und die Lactulose von den resultierenden Umwandlungsprodukten abgetrennt wird, dadurch gekennzeichnet, daß abgesehen vom Borax im wesentlichen kein alkalisierendes Material zur Lösung zugegeben wird.
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Borax in einer wässrigen Lösung von Borsäure, vorzugsweise bereits gleichzeitig mit der Lactose, hergestellt wird, daß die Natriumionen aus der Lösung der Umwandlungsprodukte in die Lösung der Borsäure durch Elektrodialyse transferiert werden.
3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Natriumionen aus der Lösung der Umwandlungsprodukte im wesentlichen so gut wie möglich mittels eines schwach sauren Ionenaustauschers entfernt werden und erst danach mittels eines stärker sauren Ionenaustauschers.
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß der schwach saure Ionenaustauscher zumindest teilweise mit Borsäure regeneriert wird und das während der Regeneration gebildete Borax zumindest teilweise im Verfahren nach Anspruch 1 verwendet wird.
5. Verfahren nach einem der Ansprüche 1-4, dadurch gekennzeichnet, daß zur Abtrennung der Lactulose die Lösung der Reaktionsprodukte, nach dem Abtrennen der Natriumionen, vor dem Abtrennen der Borationen, vorzugsweise nach dem Eindampfen auf 15-20% Trockenmaterial, durch eine lange Chromatographiesäule, gefüllt mit einem schwach basischen Ionenaustauscher, vorzugsweise bei 30 bis 60 °C hindurchgeleitet wird, wobei Wasser als Elutionsmittel verwendet wird.
6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß zur Herstellung von Lactulosepulver eine konzentrierte Lactuloselösung mit einer Reinheit von mindestens 90% Lactulose, bezogen auf das Trockenmaterial, zu einem in Bewegung gehaltenen, vorzugsweise gerührten Lactulosepulver so langsam zugegeben, vorzugsweise gesprüht, wird und darin so rasch und fein verteilt wird, daß die Lactuloselösung immer nur einen dünnen Film auf der Oberfläche der Pulverteilchen bildet, woraus das feste Material auf den Pulverteilchen wächst.

**Revendications**

1. Procédé de fabrication de lactulose, dans lequel une solution alcaline aqueuse de lactose et de borax est préparée et chauffée à une température supérieure à 80 ° C et le lactulose est séparé des produits de conversion obtenus, caractérisé en ce que, en dehors du borax, on n'ajoute à la solution à peu près aucune matière alcaline.
2. Procédé selon la revendication 1, caractérisé en ce que le borax est préparé dans une solution aqueuse d'acide borique, de préférence déjà simultanément avec le lactose, et les ions de sodium sont transférés de la solution des produits de conversion dans la solution d'acide borique par électrodialyse.
3. Procédé selon la revendication 1, caractérisé en ce que les ions de sodium sont éliminés de la solution des produits de conversion en substance aussi rapidement que possible à l'aide d'un échangeur d'ions faiblement acide et seulement ensuite à l'aide d'un échangeur d'ions plus fortement acide.
4. Procédé selon la revendication 3, caractérisé en ce que l'échangeur d'ions faiblement acide est régénéré au moins partiellement avec de l'acide borique et le borax formé au cours de la régénération est utilisé au moins partiellement dans le procédé selon la revendication 1.
5. Procédé selon l'une quelconque des revendications 1 à 4, caractérisé en ce que, pour séparer le lactulose, la solution des produits réactionnels, après séparation des ions de sodium, avant la séparation des ions de borax, de préférence après l'évaporation pour obtenir une matière sèche à 15-20 %, est envoyée à travers une longue colonne chromatographique remplie d'un échangeur d'ions faiblement basique, de préférence à 30 à 60 ° C, l'eau étant utilisée comme éluant.
6. Procédé selon l'une quelconque des revendications 1 à 5, caractérisé en ce que, pour la fabrication de poudre de lactulose, une solution de lactulose concentrée ayant une pureté d'au moins 90 % de lactulose sur base de la matière sèche est ajoutée, de préférence pulvérisée, assez lentement sur une poudre de lactulose maintenue en mouvement, de préférence agitée, et est distribuée assez rapidement et assez finement pour que la solution de lactulose ne forme toujours qu'un mince film à la surface des particules de poudre à partir desquelles la matière solide croît sur les particules de poudre.