

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

BIOFER S.P.A.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
VIFOR (INTERNATIONAL) AG.,	)	C.A. No. 1:22-CV-02180-AMD-SJB
	)	
Defendants.	)	
	)	
	)	
	)	
	)	

STIPULATED PROTECTIVE ORDER

The Court enters the following Protective Order governing the disclosure of “Confidential” and “Highly Confidential” Discovery Material by a Producing Party to a Receiving Party in this Action.

1. **Definitions.** As used in this Order:
 - a. Action refers to the above-captioned litigation.
 - b. Discovery Material includes all information exchanged between the parties, whether gathered through informal requests or communications between the parties or their counsel or gathered through formal discovery conducted pursuant to Rules 30 through 36, and Rule 45. Discovery Material includes information within documents, depositions, deposition exhibits, and other written, recorded, computerized, electronic or graphic matter, copies, and excerpts or summaries of documents disclosed as required under Rule 26(a).
 - c. A Producing Party is a party to this litigation, or a non-party either acting on a party’s behalf or responding to discovery pursuant to a Rule 45 subpoena, that produces Discovery Material in this Action.
 - d. A Receiving Party is a party to this litigation that receives Discovery Material from a Producing Party in this Action.
2. **Confidential and Highly Confidential Discovery Material.** This Protective Order applies to all Confidential or Highly Confidential Discovery Material produced or obtained in this case.

- a. For the purposes of this Protective Order, Confidential Discovery Material shall include:
 - i. Commercial information relating to any party's business including, but not limited to, tax data, financial information, financial or business plans or projections, proposed strategic transactions or other business combinations, internal audit practices, procedures, and outcomes, trade secrets or other commercially sensitive business or technical information, proprietary business and marketing plans and strategies, studies or analyses by internal or outside experts, competitive analyses, customer or prospective customer lists and information, profit/loss information, product or service pricing or billing agreements or guidelines, and/or confidential project-related information;
 - ii. Personnel data of the parties or their employees, including but not limited to employment application information; the identity of and information received from employment references; wage and income information; benefits information; employee evaluations; medical evaluation and treatment information and records; counseling or mental health records; educational records; and employment counseling, discipline, or performance improvement documentation;
 - iii. Information concerning settlement discussions and mediation, including demands or offers, arising from a dispute between a party and a non-party;
 - iv. Medical or mental health information;
 - v. Records restricted or prohibited from disclosure by statute; and
 - vi. Any information copied or extracted from the previously described materials, including all excerpts, summaries, or compilations of this information or testimony, and documentation of questioning, statements, conversations, or presentations that might reveal the information contained within the underlying confidential Discovery Material.
 - b. For purposes of this Protective Order, Highly Confidential Discovery Material shall include any Confidential Discovery Material which the Producing Party reasonably believes to be so competitively sensitive that it is entitled to extraordinary protections, including financial and marketing information, technical information (e.g., product specifications, formulations, manufacturing information, development work), and regulatory filings (e.g., New Drug Applications, Drug Master Files, FDA correspondence).
3. **Manner of Confidential or Highly Confidential Designation.** A Producing Party shall affix a "CONFIDENTIAL" designation to any Confidential Discovery Material produced in this Action and affix a "HIGHLY CONFIDENTIAL" designation to any Highly Confidential Discovery Material produced in this Action.

- a. As to documentary information (defined to include paper or electronic documents, but not transcripts of depositions or other pretrial or trial proceedings), the Producing Party must affix the legend “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” to each page that contains protected material.
- b. If only a portion or portions of the information on a document page qualifies for protection, the Producing Party must clearly identify the protected portion(s) (e.g., by using highlighting, underlining, or appropriate markings in the margins).
- c. If it is not feasible to label confidential Discovery Material as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” the Producing Party shall indicate via cover letter or otherwise at the time of production that the material being produced is CONFIDENTIAL or HIGHLY CONFIDENTIAL.

4. Timing of Confidential or Highly Confidential Designation.

- a. Except as otherwise stipulated or ordered, or where discovery is made available for inspection before it is formally disclosed, Discovery Material that qualifies for protection under this Order must be clearly so designated before the material is disclosed or produced.
- b. If the Producing Party responds to discovery by making Discovery Material available for inspection, the Producing Party need not affix Confidential or Highly Confidential designations until after the Receiving Party has selected the material it wants to receive. During the inspection and before the designation, all material made available for inspection is deemed “HIGHLY CONFIDENTIAL.” After the Receiving Party has identified the Discovery Material it wants produced, the Producing Party must determine which materials, or portions thereof, qualify for protection under this Order, and designate the materials as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” as required under this order.

5. Qualified Recipients.

- a. For the purposes of this Protective Order, the persons authorized to receive Confidential Discovery Material (hereinafter “Qualified Recipient”) are:
 - i. Up to two (2) designated in-house counsel for each of Plaintiff and Defendant (each of whom is: responsible for overseeing this litigation; is not involved in competitive decision making; and does not, and will not for a period of two (2) years from the final termination of this litigation, including appeals: (a) have any involvement related to patent prosecution, drafting, editing, filing, and/or making and/or participating in any decision relating to submissions to United States Patent and Trademark Office, or its counterpart organizations in any foreign jurisdiction regarding trivalent iron complexes or ferric carboxymaltose active pharmaceutical ingredient; or (b) have any involvement related to the preparation of submissions to the FDA, or their counterpart organizations in any foreign jurisdiction concerning trivalent iron complexes or ferric carboxymaltose active

pharmaceutical ingredient) as well as his or her secretarial, clerical and legal assistant staff, as designated in writing pursuant to the requirements of Sections 6.b.i. and 7 below.

- ii. Legal counsel representing the parties, and members of the paralegal, secretarial, or clerical staff who are employed by, retained by, or assisting such counsel; including vendors who are retained to copy documents or electronic files, provide technical, litigation support, or mock trial services, or provide messenger or other administrative support services;
 - iii. Any non-expert witness who is a former or current employee of the Producing Party during any deposition or other proceeding in this Action, provided that such person may only be shown copies of the Producing Party's Confidential Discovery Material;
 - iv. Consulting or testifying expert witnesses who will be providing professional opinions or assistance for this Action based upon a review of the CONFIDENTIAL information, and the staff and assistants employed by the consulting or testifying experts;
 - v. Any mediator or arbitrator retained by the parties to assist with resolving and/or settling the claims of this Action and members of the arbitrator's or mediator's staff and assistants;
 - vi. Court reporters for depositions taken in this Action, including persons operating video recording equipment and persons preparing transcripts of testimony;
 - vii. The Court and its staff, any court reporter or typist recording or transcribing hearings and testimony, and jurors; and
 - viii. Any auditor or regulator of a party entitled to review the confidential Discovery Material due to contractual rights or obligations, or federal or state laws, or court orders, but solely for such contractual or legal purposes;
 - ix. Any author or identified recipient of the Confidential Discovery Material, and provided that such persons may only be shown copies of the Confidential Discovery Material and may not retain any such material.
- b. For the purposes of this Protective Order, the persons authorized to receive Highly Confidential Discovery Material (hereinafter "Qualified Recipient") are:
- i. The designated individuals of group 5(a)(i) set forth above, only to the extent the Highly Confidential Discovery Material is attached to a brief or expert report filed or served in this Action.
 - ii. Each of groups 5(a)(ii) – (ix) under the same terms set forth above with

respect to Confidential Discovery Material.

6. **Dissemination by the Receiving Party.** Counsel for the Receiving Party shall:

- a. Require Qualified Recipients who are in-house counsel, non-expert witnesses, expert witnesses, mediators, arbitrators, or consultants and who receive information designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” to review and agree to the terms of this Protective Order and execute a copy of the Agreement attached hereto as Appendix A before receiving Confidential or Highly Confidential Discovery Material. In the context of a deposition or other proceeding in this Action only, if the Qualified Recipient is an employee or former employee of the Producing Party or an author or identified recipient of the Confidential or Highly Confidential Discovery Material, that Qualified Recipient need not first execute a copy of the Agreement attached as Appendix A.
- b. Prior to giving, showing, disclosing, making available or communicating “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” information to:
 - i. Any designated in-house counsel, first identify in writing (which can be by email) to the Producing Party each such in-house Counsel, and provide an executed copy of the Appendix A, signed by the In-House Counsel agreeing to be bound by the terms of this Order.
 - ii. Any proposed expert witnesses and consultants, first shall serve a written notice to the Producing Party that includes: (i) the person’s name and business address, (ii) the person’s present employer and title (along with a job description), (iii) the person’s up-to-date curriculum vitae or resume, (iv) a list of the cases in which the person has testified at deposition or trial and all companies with which the person has consulted or by which the person has been employed for the past five years, (v) any previous or current relationship (personal or professional) with any of the Parties. If the curriculum vitae of the expert or consultant provides the information required under this paragraph, then the information need not be separately provided. The Receiving Party shall include with such notice, an executed copy of the Appendix A, signed by the proposed expert or consultant agreeing to be bound by the terms of this Order.
- c. Instruct witnesses, consultants, and outside counsel who assist with case preparation or represent a witness that disclosure of the information designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” is prohibited as set forth herein.
- d. Maintain a list of any Confidential or Highly Confidential Discovery Material disclosed and to whom, along with the executed copies of the Appendix A Agreement.

The prohibition on disclosing information designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” exists and is enforceable by the Court even if the person receiving the

information fails or refuses to sign the Appendix A Agreement.

7. **Objections to Proposed Consultants, Experts and Designated In-House Counsel:** The Producing Party shall have ten (10) calendar days after receiving notification of designation within which to object to the proposed disclosure, as provided below, unless the end of the ten (10) calendar day period ends on a weekend or on a local, state, or federal holiday, which in that case the ten (10) calendar day period will end on the next regular business day; such disclosure shall not occur before the time for any objection by the Producing Party expires, and, if any such objection is made, before that objection is resolved, as provided below. Any such objection shall be made in writing to the counsel for the party seeking to make the disclosure. The parties shall meet and confer regarding the objection within five (5) business days from the date of the written objection. If the parties are unable to resolve the objection, and the party seeking to make the disclosure indicates that it still intends to disclose “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” Discovery Material to the person or persons in question, the Producing Party shall notify the Court within five (5) business days of the parties reaching an impasse. A failure to object or follow the Court’s procedures for raising the dispute within the requisite time limits shall be deemed a waiver of the objection, unless good cause for the failure is shown. Upon a timely objection and request to the Court, and during the periods set forth above and until any such motion is resolved by Order of the Court or agreement in writing between the party seeking to make the disclosure and the party objecting to the disclosure, no disclosure shall be made to the objected-to person or persons.
8. **Duty as to Designations.** Each Producing Party that designates information or items as CONFIDENTIAL or HIGHLY CONFIDENTIAL must exercise reasonable care to limit any such designation to specific material that qualifies under the appropriate standards, and designate only those parts of material, documents, items, or oral or written communications that qualify, so that other portions of the material, documents, items, or communications for which protection is not warranted are not swept unjustifiably within the ambit of this Order. Broadly described, indiscriminate, or routinized designations are prohibited.
9. **Limitations on Use.** Confidential or Highly Confidential Discovery Material shall be used by the Receiving Party only to prepare for and conduct proceedings herein and not for any business or other purpose whatsoever.
10. **Maintaining Confidentiality.** Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” shall be held in confidence by each Qualified Recipient to whom it is disclosed, shall be used only for purposes of this action, and shall not be disclosed to any person who is not a Qualified Recipient. Each party, each Qualified Recipient, and all counsel representing any party, shall use their best efforts to maintain all information designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” in such a manner as to prevent access, even at a hearing or trial, by individuals who are not Qualified Recipients. Nothing herein prevents disclosure beyond the terms of this Protective Order if the party claiming confidentiality consents in writing to such disclosure.

11. **Copies.** Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” shall not be copied or otherwise reproduced by the Receiving Party, except for transmission to Qualified Recipients, without the written permission of the Producing Party or, in the alternative, by order of the Court. However, nothing herein shall restrict a Qualified Recipient from loading Confidential or Highly Confidential documents into document review platforms or programs for the purposes of case or trial preparation or making working copies, abstracts, digests, and analyses of information designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” under the terms of this Protective Order.
12. **Docket Filings.** All documents of any nature including, but not limited to, briefs, motions, memoranda, transcripts, discovery responses, evidence, and the like that are filed with the Court for any purpose and that contain Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” shall be provisionally filed under seal with the filing party’s motion for leave to file under seal. A party seeking to file Discovery Material under seal must comply with the Court’s rules and electronic docketing procedures for filing such motions. Nothing in this agreement shall constrain the Court’s ability to restrict or permit public access to documents filed on the docket or alter the standards under which public access to documents is to be determined. *See Lugosch v. Pyramid Co. cf Onondaga*, 435 F.3d 110 (2d Cir. 2006).
13. **Challenges to Confidentiality Designations.** A Receiving Party that questions the Producing Party’s confidentiality designation will, as an initial step, contact the Producing Party and confer in good faith to resolve the dispute. If the parties are unable to resolve the dispute without court intervention, they shall write to the Court by electronically filing a letter not exceeding five pages in length, exclusive of attachments. A response not exceeding five pages in length, exclusive of attachments, must be served and filed within four days of receipt of the letter, unless a motion for additional time is granted. The party that produced the information designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” bears the burden of proving it was properly designated. The party challenging a “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” designation must obtain a court order before disseminating the information to anyone other than Qualified Recipients.
14. **Use at Court Hearings and Trial.** Subject to the Federal Rules of Evidence, Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” may be offered and received into evidence at trial or at any hearing or oral argument. A party agreeing to the entry of this order does not thereby waive the right to object to the admissibility of the material in any proceeding, including trial. Any party may move the Court for an order that Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” be reviewed in camera or under other conditions to prevent unnecessary disclosure.
15. **Return or Destruction of Documents.** Upon final termination of this Action, including all appeals, each party shall make reasonable efforts to destroy all Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL”. The destroying party shall notify the producing party when destruction under this provision is complete.

If a party is unable to destroy all Discovery Material designated as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL”, that material shall be returned to the Producing Party or the Producing Party’s counsel. This Protective Order shall survive the final termination of this action, and it shall be binding on the parties and their legal counsel in the future.

16. **Modification.** This Protective Order is entered without prejudice to the right of any party to ask the Court to order additional protective provisions, or to modify, relax or rescind any restrictions imposed by this Protective Order when convenience or necessity requires. Disclosure other than as provided for herein shall require the prior written consent of the Producing Party, or a supplemental Protective Order of the Court.
17. **Additional Parties to Litigation.** In the event additional parties are joined in this action, they shall not have access to Discovery Material as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” until the newly joined party, by its counsel, has executed and, at the request of any party, filed with the Court, its agreement to be fully bound by this Protective Order.
18. **Inadvertent Disclosure of Protected Discovery Material.**
 - a. A Producing Party that inadvertently fails to properly designate Discovery Material as “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” shall have 14 days from discovering the oversight to correct that failure. Such failure shall be corrected by providing written notice of the error to every Receiving Party.
 - b. Any Receiving Party notified that confidential Discovery Material was received without the appropriate confidentiality designation as authorized under this order shall make reasonable efforts to retrieve any such documents distributed to persons who are not Qualified Recipients under this order, and as to Qualified Recipients, shall exchange the undesignated or improperly designated documents with documents that include the correct “CONFIDENTIAL” or “HIGHLY CONFIDENTIAL” designation.

/s/ Sanket J. Bulsara, Oct. 31, 2022
SANKET J. BULSARA
United States Magistrate Judge

APPENDIX A

**IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK**

BIOFER S.P.A.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
VIFOR (INTERNATIONAL) AG.,	)	C.A. No. 1:22-CV-02180-AMD-SJB
	)	
Defendants.	)	
	)	
	)	
	)	
	)	
	)	

APPENDIX A AGREEMENT

ACKNOWLEDGEMENT AND AGREEMENT TO BE BOUND

I, _____ declare under penalty of perjury that I have read in its entirety and understand the Stipulated Protective Order that was issued by the United States District Court for the Eastern District of New York in the above-captioned case. I agree to comply with and to be bound by all the terms of this Stipulated Protective Order and I understand and acknowledge that failure to so comply could expose me to sanctions and punishment in the nature of contempt. I solemnly promise that I will not disclose in any manner any information or item that is subject to this Stipulated Protective Order to any person or entity except in strict compliance with the provisions of this Order. I further agree to submit to the jurisdiction of the United States District Court for the Eastern District of New York for the purpose of enforcing the terms of this Stipulated Protective Order, even if such enforcement proceedings occur after termination of this action.

Printed name: _____

Title: _____

Address: _____

Signature: _____

Date: _____

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

----- X
BIOFER S.P.A.,

Plaintiff,

-against-

VIFOR (INTERNATIONAL) AG,

Defendant.

JUDGMENT
22-CV-02180-AMD-SJB

----- X

A Stipulation and Order of Non-Infringement of the '320 Patent having been filed on August 27, 2024 and signed by the Honorable Ann M. Donnelly, United States District Judge on August 27, 2024, and the Parties hereby stipulating and agreeing, subject to the approval of the Court, as follows; it is

ORDERED AND ADJUDGED that:

1. The Parties stipulate and agree that under the Markman Order with respect to the term “pH between 7.0 and 9.0”, Plaintiff cannot prove that Defendant infringes the Asserted Claims, either directly, indirectly, literally or under the doctrine of equivalents.

2. The Parties therefore request that the Court enter final judgment for Defendant and against Plaintiff on Plaintiff’s claims for infringement of the Asserted Patent, and declare that Defendant does not infringe any of the Asserted Claims of the Asserted Patent based on the Markman Order with respect to the term “pH between 7.0 and 9.0”.

3. The Court has not made any findings on invalidity or unenforceability and there are no invalidity or unenforceability issues to appeal at this time.

4. The Parties stipulate that all other contentions regarding claim construction, infringement and non-infringement, invalidity and validity, as well as unenforceability and enforceability of the Asserted Patent are expressly reserved. Specifically, the Parties recognize

that Defendant contends that the Asserted Claims of the Asserted Patent are not infringed under any claim construction by the Court or proposed by the Parties, that the Asserted Claims are invalid and unenforceable, and that other defenses bar Plaintiff's claims. The Parties recognize that Plaintiff disputes each of these contentions. The Parties agree that if the case is remanded, Defendant's affirmative defenses and counterclaims will be reinstated, Defendant has the right to re-assert any and all of its contentions and grounds for non-infringement, invalidity and unenforceability, and Plaintiff has the right to challenge these contentions and grounds. The Parties further stipulate that if the case is remanded, the Court's May 30, 2024 oral Orders on the parties' respective motions to compel (as articulated in the May 30, 2024 status conference transcript), remain in effect.

5. Notwithstanding the foregoing, and for the avoidance of doubt, Plaintiff states specifically that it disagrees with the Markman Order including, inter alia, with respect to the Court's construction of the term "pH between 7.0 and 9.0", including with respect to any requirement that "the pH range must be maintained throughout the process", (see D.I. 139 at 12), and that it intends to challenge the Markman Order on the Court's construction of the term "pH between 7.0 and 9.0" on appeal. Nothing herein shall be deemed to be an admission, acceptance, or adoption by Plaintiff that Defendant does not infringe the Asserted Patent, other than as stipulated herein based on the Markman Order with respect to the term "pH between 7.0 and 9.0". Plaintiff expressly reserves its right to challenge all other claim constructions issued by the Court in its Markman Order on an appeal, except for the term "instant-by-instant", which the Court construed in accordance with the Parties' agreed upon construction.

6. The Parties expressly reserve all appellate rights including, but not limited to, the right to appeal the Court's claim constructions in the Court's Markman Order to the United States Court of Appeals for the Federal Circuit upon entry of final judgment.

7. In the event the U.S. Court of Appeals for the Federal Circuit reverses, vacates, modifies, or remands the Court's Markman Order with respect to the term "pH between 7.0 and 9.0", the Parties agree that (a) the final judgment of noninfringement set forth herein should not be affirmed, and (b) this Stipulation terminates, except for Paragraphs 4 and 5 of this Stipulation, which remain in effect.

8. The Parties agree that entry of judgment of non-infringement would be a final judgment that adjudicates all the claims for all the parties to this Action. Defendant agrees that its counterclaims shall be dismissed without prejudice. The Parties agree that the Court should enter final judgment of non-infringement in favor of Defendant consistent with this Stipulation with respect to all Asserted Claims in the First Amended Complaint (Dkt. 90).

Dated: Brooklyn, NY
August 30, 2024

Brenna B. Mahoney
Clerk of Court

By: /s/Jalitza Poveda
Deputy Clerk

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

-----X
BIOFER S.P.A.,

Plaintiff,

-against-

VIFOR (INTERNATIONAL) AG.,

Defendant.

-----X
BULSARA, United States Magistrate Judge:

ORDER
22-CV-2180-AMD-SJB

Plaintiff Biofer seeks clarification of the Court’s March 29, 2024 claim construction order. (Biofer Letter, Dkt. No. 149). The motion is denied. The request for clarification is nothing more than an attempt to have the Court resolve the parties’ inability to agree on a stipulation. Indeed, Biofer attaches the redline of a stipulation showing its proposed language against Vifor’s proposal. (Stip. and Order of Non-Infringement, attached as Ex. B to Biofer Letter, Dkt. No. 149-2). The parties are free to stipulate to any matter. Or not. But a stipulation is voluntary choice made by the parties, not one imposed by the Court.

As for clarification, none is necessary. Clarification is appropriate when there is some ambiguity, and for there to be an ambiguity there must be two, competing reasonable interpretations of the Court’s order. Disputes about a stipulation cannot create an ambiguity. Biofer “requests clarification as to whether or not the Court’s construction of ‘pH between 7.0 and 9.0’ requires that the pH must be maintained *throughout* the recited step.” (Biofer Letter at 2). But what is the ambiguity that Biofer is asking the Court to clarify? What is ambiguous about the Court’s March 2024 order? And importantly, if the Court were to reject this construction or reading of its

own order, it would be doing so in favor of what alternative? That the pH is not maintained throughout the recited step or oxidation process? If that is the case, that would be a late motion for reconsideration, which the parties state they are not seeking. (Biofer Letter at 1). (The fact that Vifor refuses to use the language from the Court's order in the stipulation is not evidence of an ambiguity; it is a refusal to stipulate.). Biofer is asking the Court to impose, declare, or reaffirm its March 2024 Order to achieve Biofer's intended end in the stipulation. Indeed, its letter admits as much. (Biofer Letter at 2) ("To the extent the Court clarifies that to be the intended meaning and import of the construction, then Plaintiff is prepared to enter the attached stipulation with *its* proposed language and proceed to an immediate appeal.") (emphasis added). The Court's order speaks for itself. There is no ambiguity and nothing to clarify, and therefore the motion for clarification is denied.

SO ORDERED.

/s/ Sanket J. Bulsara July 31, 2024
SANKET J. BULSARA
United States Magistrate Judge

Brooklyn, New York

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

-----X
BIOFER S.P.A.,

Plaintiff,

-against-

ORDER
22-CV-2180-AMD-SJB

VIFOR (INTERNATIONAL) AG.,

Defendant.

-----X
BULSARA, United States Magistrate Judge:

In this patent infringement action, Plaintiff Biofer S.p.A (“Biofer”) alleges Defendant Vifor (International) AG. (“Vifor”) infringed U.S. Patent No. 8,759,320 (the “’320 Patent”), which describes a process used in the creation of iron replacement therapy medicines. (Compl. dated Apr. 15, 2022 (“Compl.”), Dkt. No. 1 ¶¶ 4–10). The invention claimed in the ’320 Patent is the “process for the preparation of trivalent iron complexes with mono-, di- and polysaccharide sugars.” (’320 Patent at [54]).

The parties agree on the construction of all but two claim terms: (1) “pH between 7.0 and 9.0,” and (2) “said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups.” (Joint Disputed Claim Terms Chart, Dkt. No. 44 at 1). The Court conducted a *Markman* hearing on August 3, 2023. The Court concludes that the term “pH between 7.0 and 9.0” should be construed as “pH is maintained in the interval separating 7.0 and 9.0,” while the term “said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups” be construed as “said hypochlorite being added in a 1:1 molar ratio with respect to the aldehyde end groups, with the exception of a 2:1 molar ratio with respect to dextran.”

DISCUSSION

To be valid, “a patent must describe the exact scope of an invention and its manufacture to ‘secure to [the patentee] all to which he is entitled, [and] to apprise the public of what is still open to them.’” *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996) (alterations in original) (quoting *McClain v. Ortmyer*, 141 U.S. 419, 424 (1891)). To this end, patents must include both a “specification describing the invention ‘in such full, clear, concise terms as to enable any person skilled in the art . . . to make and use the same’” and “‘claims,’ which ‘particularly poin[t] out and distinctly clai[m] the subject matter which the applicant regards as his invention.’” *Id.* (alterations in original) (quoting 35 U.S.C. § 112). The claim “defines the scope of the patentee’s rights.” *Id.* at 372. And the scope of such a claim, or “the construction of a patent, including terms of art within its claim,” is “‘exclusively’ for ‘the court’ to determine.” *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 321 (2015) (quoting *Markman*, 517 U.S. at 372).

To “determin[e] the proper construction of a claim, ‘the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification, and if in evidence, the prosecution history.’” *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1152 (Fed. Cir. 1997) (quoting *Vitronics Corp. v. Conceptor, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Such “intrinsic evidence” is “the most significant source of the legally operative meaning of the claim language.” *Id.* (quoting *Vitronics Corp.*, 90 F.3d at 1582). “[T]he words of a claim are generally given their ordinary and customary meaning.” *Easyweb Innovations, LLC v. Twitter, Inc.*, No. 11-CV-4550, 2016 WL 1253674, at *5 (E.D.N.Y. Mar. 30, 2016) (Bianco, J.) (quotations omitted) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005)), *cfid*,

689 F. App'x 969, 971 (Fed. Cir. 2017). This “ordinary and customary meaning” is determined with reference to how “a person of ordinary skill in the art in question . . . as of the effective filing date of the patent application” would understand them “in the context of the entire patent.” *Id.* (quoting *Phillips*, 415 F.3d at 1313). Next, only if ambiguity remains, a court may look to extrinsic evidence—for example, expert testimony. *CVI/Beta Ventures, Inc.*, 112 F.3d at 1152–53.

Vifor makes the active ingredient for an injectable iron sugar product (Injectafer), and has patented this process for making such sugars. On June 24, 2014, the '320 patent, titled “Process for the Preparation of Trivalent Iron Complexes with Mono-, Di- and Polysaccharide Sugars,” was issued to inventors Stefania Sacchi, Mauro Montorsi, and Egidio Marchi. ('320 Patent at [54], [75]). Biofer was the assignee on the patent. (*Id.* at [73]). Biofer alleges that Vifor's process for making iron sugars infringes on the '320 Patent.

The '320 Patent describes a multi-step process for making trivalent iron (III) complexes with sugars. (*Id.* at col. 1, ll. 6–7). The resulting iron complexes are used in therapies to prevent and treat iron deficiency. (*Id.* at col. 1, ll. 12–18). Though the creation of trivalent iron complexes with sugars is not itself novel, (*id.* at col. 1, ll. 19–23), the invention aims to produce complexes with “good physical-chemical stability over time, low toxicity, use safety also by injection and a good bioavailability.” (*Id.* at col. 8, ll. 54–59).

The '320 patented process consists of four steps: (1) the activation of a sugar; (2) “complexation of the activated sugar with ferric hydroxide generated in solution;” (3) “purification of the [resulting] ferric hydroxide/sugar complex still not stabilized;” and (4) “stabilization of the [resulting] complex.” ('320 Patent at col. 8, ll. 62–66).

Both disputed claim terms arise from the first step—the creation of an “activated sugar” through oxidation—and are recited in claim 1 of the patent. (*Id.* at col. 16, ll. 44–56). This step is, in essence, a reaction whereby the end aldehyde group—a group of compounds made up of carbon atoms sharing a double bond with an oxygen atom, and sharing a single bond with another atom, found at the end of a chain of sugar molecules—is transformed into carboxylic acid through a loss of electrons. (Decl. of Jeffrey D. Winkler in Supp. of Pet. for Inter Partes Review (“Winkler IPR Decl.”), Dkt. No. 46-3 ¶¶ 27–28). Claim 1, in relevant part, states:

1. A process for the preparation of an activated sugar comprising the step of reacting a sugar having an aldehyde end group with bromine in a solution at a *pH between 7.0 and 9.0* with the specific oxidation of the end aldehyde, wherein
 - i) said sugar is selected from the group consisting of dextrans and dextrins and wherein
 - ii) said bromine is produced in situ through the addition of a hypochlorite and an alkaline or earth alkaline metal bromide to said solution, *said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups*, wherein said hypochlorite is added instant by instant, such that an excess of hypochlorite in solution is never present.

(’320 Patent at col. 16, ll. 44–56 (emphasis added)). In this case, the oxidation is performed by using the element bromine, which is to be produced “in situ,” *i.e.*, creating bromine by adding sodium hypochlorite (commonly known as chlorine bleach) to a solution of the sugar and water. (Winkler IPR Decl. ¶ 28). But the parties dispute how the ’320 Patent claims this step is performed to create the necessary result: (1) whether the pH range is 7.0–9.0 or includes an error range, and whether the solution must be “maintained” between 7.0 and 9.0 or includes any process in which, at any point, the pH dips into that range, however briefly; and (2) whether when the hypochlorite is added in “stoichiometric quantities,” it is added in a ratio of 1 mole of hypochlorite for every 1

mole of the end aldehyde, or can be added in “approximately” a 1:1 ratio, with the caveat that in the specific case of the dextran, hypochlorite would be added in an approximately 2:1 molar ratio. (Joint Disputed Claims Chart dated May 12, 2023, Dkt. No. 44; Tr. dated Aug. 3, 2023 (“Markman Tr.”), Dkt. No. 82 at 98:4–25).

I. “pH between 7.0 and 9.0”

For the first claim term—“pH between 7.0 and 9.0”—the parties’ dispute is two-fold: whether the term includes an error range and whether the claim only protects a reaction where the pH is “maintained” in this interval during the described process. Biofer contends that the claim should be construed to mean “pH range of between 6.8 and 9.2,” (Pl. Biofer’s Opening Claim Construction Br. dated June 12, 2023 (“Biofer Op. Br.”), Dkt. No. 45 at 21), while Vifor asserts it should be construed as: “pH is maintained in the interval separating 7.0 and 9.0.” (Def. Vifor’s Responsive Claim Construction Br. dated July 12, 2023 (“Vifor Resp. Br.”), Dkt No. 62 at 11). The Court adopts Vifor’s proposed construction.

i. “7.0 and 9.0”

The Court first addresses whether “pH between 7.0 and 9.0” means “pH between 6.8 and 7.2.” It does not. Precise claim terms without qualifying language—such as about, around, or approximately—mean what they say; that is, these precise values are to be taken as the plain meaning, absent evidence to the contrary. *See, e.g., Jeneric/Pentron, Inc. v. Dillon Co.*, 205 F.3d 1377, 1381 (Fed. Cir. 2000) (“Without broadening words that ordinarily receive some leeway, the precise weight ranges of claim 1 do not ‘avoid a strict numerical boundary to the specified parameter.’” (alteration, citation, and quotations omitted)); *Cobalt Boats, LLC v. Brunswick Corp.*, 773 Fed. App’x 611, 616 (Fed. Cir. 2019) (“Where a precise value is included in the claim

without a term such as ‘about,’ we interpret the claim language as imposing a strict numerical boundary, absent evidence that such a construction would be inconsistent with the intrinsic evidence.”). Here, the claim language contains precise values without qualifying language. Rather than claiming a pH “about, around, or approximately between 7.0 and 9.0” or “ 7.0 ± 0.2 and 9.0 ± 0.2 ,” the inventors claimed a precise pH range: between 7.0 and 9.0. (’320 Patent at col. 16, l. 46).

“Assigning [such] numerical precision to . . . ranges [] is particularly appropriate when other variables in the same claims explicitly use qualifying language.”

Jeneric/Pentron, Inc., 205 F.3d at 1381. The patent here contains several examples of qualifying language in the claimed invention and in the specifications. For instance, claim 5 states, “the hypochlorite added is in an aqueous solution containing *about* 12% by weight of active chlorine.” (’320 Patent, col. 16, ll. 65–67 (emphasis added)). And, the patent’s specifications for reactions other than oxidation use language and symbols indicating approximation, including “about” and “ $\pm$.” (*E.g.*, *id.* at col. 11, ll. 31–32 (“pH is brought to 11.0 ± 0.5 ”); *id.* at col. 12, l. 22 (same); *id.* at col. 11, l. 45 (“pH of 10.5 ± 5 ”); *id.* at col. 12, l. 34 (same); *id.* at col. 13, l. 7 (“pH of 10.5 ± 0.5 ”); *id.* at col. 13, l. 52 (same); *id.* at col. 13, l. 14 (“ 11.5 ± 0.5 ”); *id.* at col. 11, l. 38 (“ $85 \pm 2^\circ \text{C.}$ ”); *id.* at col. 11, l. 47 (“ $90 \pm 2^\circ \text{C.}$ ”), *id.* at col. 13, ll. 14–15 (“ $75^\circ \text{C.} \pm 2$ ”). But such qualification is absent with respect to the pH range in this claim.

The prosecution history also supports a precise reading and runs contrary to Biofer’s interpretation. “The prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.” *Actelion Pharms. Ltd. v. Mylan*

Pharms. Inc., 85 F.4th 1167, 1173 (Fed. Cir. 2023) (quotations omitted). A court “must . . . examine the prosecution history to determine whether the patentee has relinquished a potential claim construction in an amendment to the claim or in an argument to overcome or distinguish a reference.” *Bell Atl. Network Servs., Inc. v. Covad Commc’ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001).

In one of its amendments, Biofer claimed “[a] process for the preparation of an activated sugar comprising the step of reacting a sugar having an aldehyde end group with bromine in a solution at a pH between 7 and 9 . . .,” *i.e.*, without the decimal and zero digit. (Patent Amendment A filed Sept. 13, 2007, attached as Ex. 8 to Decl. of Sanya Sukduang in Supp. of Vifor’s Responsive Claim Construction Br. (“Sukduang Decl.”), Dkt. No. 63-8 at 3 (emphasis added)). The Examiner rejected that claim because prior art covered claims “at a pH of about 9.” (U.S. Patent and Trademark Office Action dated Nov. 17, 2011, attached as Ex. 9 to Sukduang Decl., Dkt No. 63-9 at 4). In response, Biofer amended and sought the current claim language, “pH between 7.0 and 9.0,” arguing that “the invention as now claimed . . . involves an inventive step over the prior art.” (Patent Amendment C dated Feb. 26, 2013, attached as Ex. 11 to Sukduang Decl., Dkt No. 68-10 at 8). Biofer’s use of precision to overcome prior art, which defined the upper pH bound with the qualifier “about,” is further evidence that the current claim language is precise, not an approximation. *See, e.g., MasterMine Software, Inc. v. Microsoft Corp.*, 874 F.3d 1307, 1311–12 (Fed. Cir. 2017) (finding statements from the prosecution of a related parent patent used to overcome prior art were relevant to defining the scope of the invention).

Biofer nonetheless contends that the pH values “were expressly defined by the patentee/inventor during prosecution to have an error range of ± 0.2 .” (Biofer Op. Br. at

21). Specifically, Dr. Myerson, one of Biofer's experts, declared that "a POSA¹ would understand the meaning and scope of the disputed claim language as encompassing a pH range from 6.8 to 9.2" because of the way Dr. Marchi, an inventor, performed experiments replicating the examples in the patent. (Decl. of Allan S. Myerson, Ph.D. in Supp. of Pl. Biofer's Op. Claim Construction Br. dated June 12, 2023 ("Myerson Decl."), Dkt. No. 48 ¶ 35). Dr. Marchi's declaration ("the Marchi Declaration") details several experiments he supervised, replicating examples from the '320 Patent. (Decl. of Egidio Marchi dated June 13, 2013 ("Marchi Decl."), attached as Ex. 12 to Sukduang Decl., Dkt. No. 63-12 at 18–26). In the Marchi Declaration, Dr. Marchi explains an experiment replicating Example 5 "at a pH of 8.0." (*Id.* ¶ 3). It states that "the pH is adjusted to a value of 8.0" and the "[s]odium hypochlorite . . . is slowly added over 2h maintaining the pH between 7.8 and 8.2." (*Id.*). He then explains Experiment 2, which replicated Example 5 "at a pH of 10.0." (*Id.* ¶ 4). It states, "the pH is adjusted to a value of 10.0" and "[s]odium hypochlorite . . . is slowly added over 2h maintaining the pH between 9.8 and 10.2." (*Id.*).

These experiments, Biofer suggests, means that the claimed pH values should be given an error range of ± 0.2 . The argument reads too much into the sounds of silence. The Marchi Declaration never states that he understood the claimed pH range to include an error range, of ± 0.2 or otherwise. As for the experiments, one of them, Experiment 2, takes place entirely outside of the claimed range of 7.0 and 9.0 (between 9.8 and

¹ A POSA is a "person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1313. "The terms used in patent claims are not constructed in the abstract, but in the context in which the term was presented and used by the patentee, as it would have been understood by a person of ordinary skill in the field of the invention on reading the patent documents." *Fenner Invs., Ltd. v. Cellico P'ship*, 778 F.3d 1320, 1322–23 (Fed. Cir. 2015).

10.2), providing little or no insight into the question here. (*See* Marchi Decl. ¶ 4). The other never goes to the range that Biofer seeks. That is, Experiment 1 never dips down to a pH of 6.8 or rises to 9.2 and reflects only that it was conducted between 7.8 and 8.2, not at the outer bounds of the claimed invention. (*Id.* ¶ 3). Again, this experiment provides no insight into the tolerance available for the outer bounds of the claim, which is the issue here. Ultimately, however, there is no reason to mine the Marchi Declaration for its unstated implications because the claimed invention language, as noted above, is clear. *See Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1319 (Fed. Cir. 2006) (“Where, as here, the written description clearly identifies what his invention is, an expression by a patentee during prosecution that he intends his claims to cover more than what his specification discloses is entitled to little weight.”). And that clear language contains no error range or qualification or other reference suggesting that a “pH between 7.0 and 9.0” should mean “between 6.8 and 7.2.” Had the inventors intended the claim to mean “6.8 and 9.2,” they could have easily done so. But they did not.

ii. “Between”

As noted, the invention claimed is “[a] process for the preparation of an activated sugar comprising the step of reacting a sugar having an aldehyde end group with bromine in a solution at a pH between 7.0 and 9.0 with the specific oxidation of the end aldehyde.” (’320 Patent at col. 16, ll. 44–47). The parties disagree as to whether the term “pH between 7.0 and 9.0” means “a pH maintained in the interval separating 7.0 and 9.0.” That is, they disagree whether the claim encompasses only a process which occurs *entirely* at a pH between 7.0 and 9.0, or if the claim covers a process where the

pH falls within that range at any time, even briefly.² The Court concludes that the term means “a pH maintained in the interval separating 7.0 and 9.0.”

After looking at the words of the claims themselves, “it is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning.” *Vitronics Corp.*, 90 F.3d at 1582. “The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.” *Id.* This Court “must interpret the claims in light of the specification yet avoid impermissibly importing limitations from the specification.” *Alloc, Inc. v. Int’l Trade Comm’n*, 342 F.3d 1361, 1370 (Fed. Cir. 2003) (citation omitted). But “[i]t is . . . entirely appropriate for a court, when conducting claim construction, to rely heavily on the written description for guidance as to the meaning of the claims.” *Phillips*, 415 F.3d at 1317. That is, “the written description can provide guidance as to the meaning of the claims, thereby dictating the manner in which the claims are to be construed.” *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001). In fact, not only is the specification highly relevant to the analysis, “[u]sually, it is dispositive,” and serves as “the single best guide to the meaning of a disputed term.” *Vitronics Corp.*, 90 F.3d at 1582. Accordingly, “[t]he construction that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.” *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

² Both sides contend that their construction encompasses the “plain and ordinary meaning” of the word “between.” (See Vifor Resp. Br. at 12; Pl. Biofer’s Reply Claim Construction Br. dated July 19, 2023 (“Biofer Reply Br.”), Dkt. No. 67 at 3–5).

The intrinsic evidence supports Vifor's construction.³ In the Description of the Invention, the '320 Patent states that if "an excess of hypochlorite [is] present . . . oxidation secondary reactions could occur." ('320 Patent, col. 7, ll. 14–17).⁴ As such, it goes on to warn: "it is important to *maintain the reaction pH* in the range between 5.0 and 12.0, preferably, between 7.0 and 9.0, since in this pH range the bromine consumption takes place at a high rate leading to the oxidation of the aldehyde end group." (*Id.* at col. 7, ll. 18–22 (emphasis added)). And in the Detailed Description of the Invention, the patent states: "Throughout the activation reaction of the sugar, the pH value is *controlled and maintained in the fixed range*, preferably between 7.0 and 9.0[.]" (*Id.* at col. 9, ll. 24–26 (emphasis added)).

Where "a patent 'repeatedly and consistently' characterizes a claim term in a particular way, it is proper to construe the claim term in accordance with that characterization." *GPNE Corp. v. Apple Inc.*, 830 F.3d 1365, 1370 (Fed. Cir. 2016). Biofer's assertion that the term "maintain" is used only occasionally and only in the specification, (Biofer Op. Br. at 24), not only downplays the importance of the specification, *supra* at 10, but also the pervasive use of the term. The reference is more than occasional, and *each* example which mentions the pH between 7.0 and 9.0 instructs that the pH is to be maintained during oxidation. ('320 Patent at col. 11, ll. 13–

³ "Intrinsic evidence includes the patent's claims, specification, and prosecution history." *Grace Instrument Indus., LLC v. Chandler Instruments Co.*, 57 F.4th 1001, 1008 (Fed. Cir. 2023); *see also supra* at 2–3.

⁴ If an excess of hypochlorite is present "in addition to bromine in the reaction environment, oxidation secondary reactions could occur, which would relate to other parts of the end sugar and to depolymerization phenomena." ('320 Patent at col. 7, ll. 15–18). "[D]epolymerization, if it's excessive, can be problematic or undesirable." (Markman Tr. at 9:14–15).

14 (Example 1) (“maintaining the pH value between 7.0 and 9.0”); *id.* at col. 12, ll. 59 (Example 3) (same); *id.* at col. 13, ll. 35–38 (Example 4) (same); *id.* at col. 14, ll. 13–16 (Example 5) (“The pH of the solution is brought to a value between 7.0 and 9.0 with a sodium hydroxide solution and over 2 hours, 48.66 g of 12% w/v active chlorine sodium hypochlorite are added, maintaining the pH within the fixed limits.”); *id.* at col. 14, ll. 66–67 (Example 6) (“[A]dded over two hours, maintaining the pH value between 7.0 and 9.0.”); *id.* at col. 15, ll. 46–47 (Example 7) (same)). Accordingly, the Court finds that the intrinsic evidence supports that the pH range must be maintained throughout the process. *See, e.g., GPNE Corp.*, 830 F.3d at 1370–71 (finding that a “node” is classified as a “pager,” where the specification “repeatedly and exclusively use[d] [the words “pager” and “pager units”] to refer to the devices in the patented system,” even where “nothing in the claim required that a ‘node’ must be a ‘pager’”); *Wisc. Alumni Rsch. Found. v. Apple Inc.*, 905 F.3d 1341, 1351 (Fed. Cir. 2018) (finding the meaning of “prediction” encompassed only dynamic—not static—predictions where the term was described as dynamic throughout the entire patent and no specifications described the prediction as static, and rejecting Apple’s argument that this construction “improperly imported a limitation from the preferred embodiment”).

Biofer contends that this construction improperly reads the word “maintain” into the claim, and that all the term means is that a sugar is reacted with bromine in a solution at a pH between 7.0 and 9.0. (Biofer Reply Br. at 1). To Biofer, this means there need not be “ongoing pH control for the entirety of the process,” (*id.* at 2), because “[b]etween says nothing about time,” and there is “no restriction intrinsically on duration that you spend within that range,” (Markman Tr. at 26:24–25, 27:4–5). Biofer argues that all “a pH between 7.0 and 9.0” means is that there is a range of pH values

between 7.0 and 9.0, (*id.* at 25:3–4), and there is no reason, at this point, to discuss “duration, time, [or] excursions,” because the claim is “plain on its face.” (*Id.* at 27:6–10).

Essentially, this boils down to Biofer arguing that construing the claim based on the language in the specification (*i.e.*, the experiments) is improper because claims of a patent are not limited to the examples in the specification. (Biofer Op. Br. at 24). Again, this downplays, if not mutes, the central role the specification plays in understanding the meaning of a disputed term. *Supra* at 10. None of the cases cited provides support for the rule or result Biofer seeks. Biofer points to *Ekchian v. Home Depot, Inc.*, in which the Court found that the preferred embodiment did not limit the claim where the party relied *only* on the embodiments to advance its claim interpretation. 104 F.3d 1299, 1303 (Fed. Cir. 1997) (“Lucas identifies nothing further to support its contention that the term ‘conductive’ is limited to the conductivity levels inherent in the disclosed examples. . . . We therefore conclude that the term is not so limited.”). Of course, here, Vifor’s interpretation of “maintain” is based on more than the specification. But *Ekchian* also does not stand for the proposition that the specifications cannot inform the Court of the limitations of the claim; in fact, it follows the general, understood approach: “examples disclosed in the preferred embodiment may aid in the proper interpretation of a claim term.” *Id.* It only warns that “the scope of the claim is *not necessarily* limited by such examples.” *Id.* (emphasis added). So, the case offers no comfort to Biofer, which is attempting to define the contested term solely on the basis of undisclosed embodiments.

Biofer also points to *Falana v. Kent State University* to show that the Court should not limit the scope because of the examples. 669 F.3d 1349, 1355 (Fed. Cir.

2012). In *Falana*, the Federal Circuit found that the district court did not err in failing to limit the claims “to an optically active compound ‘having a substantially temperature independent [HTP]’” where “the plain language of the claims nowhere suggests a limitation regarding temperature independent HTP, let alone a temperature [across a specific range].” *Id.* at 1354–55.

This case is not *Falana*: here, the claim language *itself* suggests a limitation. It instructs that “an excess of hypochlorite” should never be present in the solution. (’320 Patent at col. 16, ll. 50–56). The description of the invention merely explains the impact of failing to abide by that limitation. If there is an excess of hypochlorite, combined with bromine in the environment, oxidation secondary reactions could occur. (*Id.* at col. 7, ll. 14–18). To avoid this, it instructs “it is important to *maintain* the reaction pH in the range between 5.0 and 12.0, preferably, between 7.0 and 9.0.” (*Id.* at col. 7, ll. 18–20).

Because all the specifications that mention a pH between 7.0 and 9.0 mention that the pH must be maintained, the Court finds that Biofer’s proposed construction—covering any reaction that dipped into the range, even briefly—would “expand the scope of the claims far beyond any-thing described in the specification.” *Wisc. Alumni Rsch. Found.*, 905 F.3d at 1351–52 (quoting *Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc.*, 554 F.3d 1010, 1019 (Fed. Cir. 2009)) (finding that constructing the word “prediction” to include dynamic and static predictions where the specifications only illustrated dynamic predictions would improperly broaden the scope of the claim).

For the first time in its reply brief, Biofer argues that Vifor ignores the word “comprising” in the claim, which it argues “indicates that the claim is open-ended and allows for additional steps.” (Biofer Reply Br. at 2 (quoting *Solvay S.A. v. Honeywell Int’l Inc.*, 742 F.3d 998, 1005 (Fed. Cir. 2014))). Biofer claims that “the Federal Circuit

has repeatedly held that such open-ended ‘comprising’ claims involving reaction steps do not require the claimed conditions to be maintained for the entire duration, and permit part of those reactions to occur at unclaimed conditions.” (*Id.*). The Court does not read Biofer’s cited cases as supporting its belated argument.

In *Invitrogen Corp. v. Biocrest Manufacturing, L.P.*, the Federal Circuit found that “[t]he transition ‘comprising’ in a method claim indicates that the claim is open-ended and allows for additional steps.” 327 F.3d 1364, 1368 (Fed. Cir. 2003). There, the Court found that when the word “comprising” introduces recited steps—as it does here—that “the claim signals to patent practitioners that [the claim] allows activity . . . *before* the recited steps.” *Id.* (emphasis added). It goes on to say that “activity *outside* the claim, of course, is not limited by the temperature range recited in claim 1.” *Id.* (emphasis added). *Invitrogen* does not support Biofer’s position. Biofer is not arguing that there is an additional step outside of claim 1 that should not be limited by virtue of the limitations in the claim. Instead, Biofer is seeking to expand the claim to permit reactions outside of the pH claimed in claim 1. (Biofer Reply Br. at 1–2). Biofer’s position is that the process *within* the claim should not be limited by the claim language, where *Invitrogen* stands for the proposition that activity *outside* the claim should not be limited by the claim language, and that “claim language and its form do not restrict activities . . . that occur *before* the claimed method.” *Invitrogen*, 327 F.3d at 1368 (emphasis added).⁵

⁵ *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.* likewise stands for the proposition that when a claim uses the term “comprising,” “additional step[s] [are] permissible.” 320 F.3d 1339, 1350 (Fed. Cir. 2003). There, the district court erred in rejecting an additional period of incubation time beyond the required minimum time reflected in the claim, because “the utility of claim 1 is not premised on a

The Court finds that the intrinsic evidence supports Vifor's construction and that Biofer's counterarguments are without merit. Accordingly, the Court adopts Vifor's proposed construction.

II. "Said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups"

The second disputed term reads: "said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups." ('320 Patent at col. 16, ll. 52–54). Vifor argues that to add hypochlorite in "stoichiometric quantities" while ensuring that an "excess of hypochlorite in solution is never present," ('320 Patent at col. 16, ll. 55–56), hypochlorite cannot be added in more than a 1:1 molar ratio with respect to the end aldehyde. (Vifor Resp. Br. at 22). As such, Vifor's construction reads: "hypochlorite being added in 1:1 molar ratio with respect to the aldehyde end group of the sugar." (Vifor Resp. Br. at 1).

At the *Markman* hearing, Biofer conceded that it would be willing to construe the disputed term "stoichiometric quantities" as "hypochlorite being added in an approximately 1:1 molar ratio with respect to the aldehyde end group of the sugar," with the caveat that in the specific case of the dextran, hypochlorite would be added in an approximately 2:1 molar ratio. (Markman Tr. at 98:4–25). Vifor, at the hearing, said it could not agree to Biofer's *Markman* construction and continued to argue that "the 1 to 1 [molar] ratio of the hypochlorite with respect to the aldehyde end groups is the plain and ordinary meaning" of "stoichiometric quantities." (*Id.* at 101:1–3). With Biofer's concession, the Court now decides whether the term means "approximately a 1:1 molar

particular stopping point." *Id.* Biofer is not seeking to add additional steps, only seeking to broaden the scope of the claim outside the claimed pH range.

ratio” or a “1:1 molar ratio,” and whether there should be a carve out for the specific dextran case.

To the first point, the Court construes the term to mean “hypochlorite being added in a 1:1 molar ratio with respect to the aldehyde end group of the sugar.” The specification provides two reactions which teach that hypochlorite is in a 1:1 molar ratio with the end aldehyde of the sugar during oxidation. (Decl. of Jeffrey D. Winkler in Supp. of Vifor’s Resp. Br. (“Winkler Decl.”), Dkt. No. 63-3 ¶ 78). These reactions in the specifications do not indicate that the hypochlorite should be added in an “approximately” 1:1 molar ratio. And, as with the precision of the pH range, if the inventors wanted to define this as an “approximately” 1:1 molar ratio, they could have done so. *Supra* at 5–6.

Having conceded that it would accept a 1:1 molar ratio (carving out an exception for dextran), Biofer’s attempt to then add the word “approximately” finds no support in the patent. As with the pH range, there is no language or intrinsic evidence supporting a modification of the term (in this case, the ratio, as opposed to the range). Indeed, Dr. Chirik, one of Biofer’s experts, relies on what a POSA would understand: “based on the specification as well as the knowledge in the art how to calculate a stoichiometric quantity of hypochlorite using the average [dextrose equivalent] value of the dextrin or dextran, which allows for a reasonable range of variation and imprecision in the calculation.” (Decl. of Paul J. Chirik, Ph.D. in Supp. of Pl. Biofer’s Op. Claim Construction Br. dated June 12, 2023, Dkt. No. 47 ¶ 31)).

The Court finds that Vifor’s construction is more in line with the patent language. First, the reactions in the patent’s specifications teach a 1:1 molar ratio. *See, e.g., Dow Chem. Co. v. Sumitomo Chem. Co., Ltd.*, 257 F.3d 1364, 1373 (Fed. Cir. 2001) (“The

specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.”). Further, the prosecution history supports Vifor’s construction: Dr. Marchi, in his declaration, described 0.9 moles of hypochlorite to 1 mole of end aldehyde as “under-stoichiometric.” (Marchi Decl. ¶ 7). Through the experiments, Dr. Marchi showed that stoichiometric quantity meant a 1:1 molar ratio, not a 0.9:1 molar ratio. (Winkler Decl. ¶ 80). Accordingly, the Court finds Biofer’s addition of the word “approximately” lacks support and adopts Vifor’s 1:1 molar ratio.

However, the Court also finds that the intrinsic evidence supports Biofer’s 2:1 dextran exception. The detailed description of the invention section of the ’320 Patent states, in the context of what is to be added to activate the sugar, “hypochlorite in aqueous solution in a stoichiometric quantity with respect to the aldehyde end groups present in the sugar, if not branched; *in the specific case of the dextran*, a hypochlorite quantity corresponding with the *double of the moles is used*.” (’320 Patent at col. 10, ll. 22–26) (emphasis added). Vifor’s response to Biofer’s 2:1 caveat was two-fold: it argued that the examples Biofer relied on do not reference stoichiometric amount, and that in the case of the dextran, “a 2 to 1 ratio cannot be approximately a 1:1 ratio.” (Markman Tr. at 111:5–16). First, the doubled molar ratio comes from the detailed description of the invention, not just Examples 6 and 7. And, as noted above, the line in the detailed description explicitly uses the term “stoichiometric quantity” within the same sentence, only three lines above. (’320 Patent at col. 10, ll. 22–26). As for Vifor’s contention that Biofer is trying to include a 2:1 ratio within the bounds of an approximately 1:1 ratio, the argument is without merit. In fact, the proposed construction expressly notes that the ratio for the dextran is a caveat, different from the “approximately 1:1 molar ratio.”

Accordingly, the Court construes the disputed term “said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups” as “hypochlorite being added in a 1:1 molar ratio with respect to the aldehyde end group of the sugar and added in a 2:1 molar ratio in the specific case of the dextran.”

CONCLUSION

Except for this *Markman* decision, this case is otherwise stayed pursuant to the parties’ agreement. (See Order dated Mar. 15, 2024, Dkt. No. 138).

SO ORDERED.

/s/ Sanket J. Bulsara March 29, 2024
SANKET J. BULSARA
United States Magistrate Judge

Brooklyn, New York

EXHIBIT 1



US008759320B2

(12) **United States Patent**
Sacchi et al.

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(54) **PROCESS FOR THE PREPARATION OF TRIVALENT IRON COMPLEXES WITH MONO-, DI- AND POLYSACCHARIDE SUGARS**

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536/123.13; 536/124

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USPC 514/53, 59; 536/112, 121, 121.13, 124
See application file for complete search history.

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(57) **ABSTRACT**

Process for the preparation of trivalent iron complexes with mono-, di- and polysaccharide sugars, consisting of the activation of the sugar by oxidation with nascent bromine generated in situ by reaction between an alkaline or alkaline earth bromine and an alkaline hypochlorite, the complexation of the activated sugar in solution with a ferric salt dissolved in an aqueous solution, the purification of the resulting solution through ultrafiltration and finally the stabilization of the trivalent iron-sugar complex by heating at a temperature between 60° C. and 100° C. for a period between 1 and 4 hours at a pH between 9.0 and 11.0.

25 Claims, 1 Drawing Sheet

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FIG 1

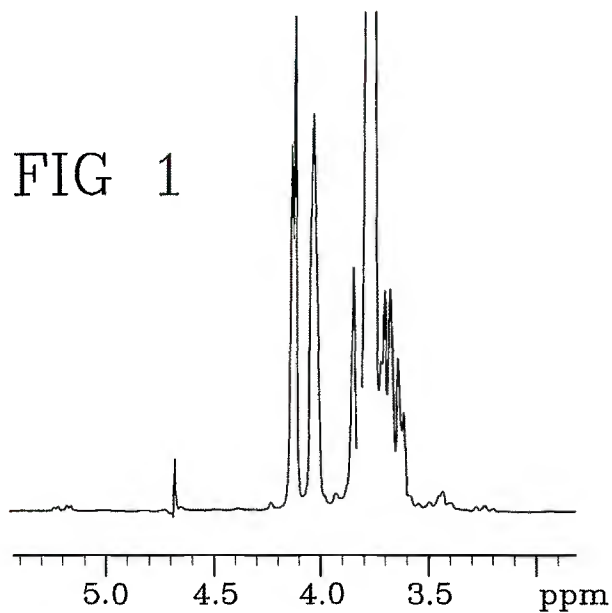
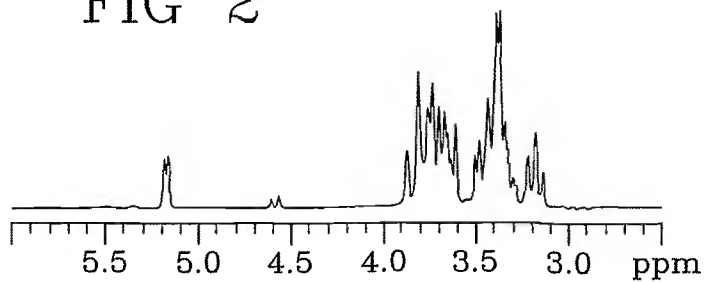


FIG 2



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**PROCESS FOR THE PREPARATION OF
TRIVALENT IRON COMPLEXES WITH
MONO-, DI- AND POLYSACCHARIDE
SUGARS**

The aim of the present invention relates to the synthesis of trivalent iron (III) complexes with mono-, di- and polysaccharide sugars. The products obtainable according to the method of the present patent can be: iron gluconate, iron polymaltose, iron dextran, iron saccharate stabilized with sucrose, or novel complexes such as the iron lactate or other.

These derivatives can be advantageously used in the therapy of different pathologies, such as

functional iron deficiency in patients suffering from a renal chronic failure;

bad absorption of the iron due to intestinal diseases; chronic blood loss also together with erythropoietin; constitutional anemia.

The synthesis of the trivalent iron complexes with sugars is known since many years even if, still today, the research in this field is active, as several methods used for the synthesis lead to not much stable complexes or said methods are difficult to apply.

It should be remembered that the iron complexes are produced above all for being orally, intramuscularly or intravenously administered to patients or animals, as suitable drugs for preventing or treating pathologies from iron deficiency.

For this reason, these iron derivatives must have some fundamental characteristics, such as: physical-chemical stability over time, safety in the administration, low toxicity, good bioavailability and easiness of production.

As for the toxicity and the bioavailability, it is known that the bivalent iron has an optimal oral bioavailability but has as well an intrinsic toxicity which is expressed at a gastrointestinal and hepatic level, above all due to the accumulation. For these reasons, the bivalent iron salts are not much used in therapy, even if the production cost is limited and can be orally administered, moreover the sideremy level reached with the therapy must always be accurately monitored. On the contrary, the trivalent iron is less toxic when is administered in products which effectively stabilize the iron through complexation of the same, as it occurs at a biological level for example by the ferritin, which complexes the iron but maintains a good capability of giving it to the biological systems assigned for transporting or using the same. The trivalent iron is a strong oxidant and so, if not trapped in systems capable of storing and giving it only when effectively required by the endocrine system, it can seriously damage some important organs, such as the liver and the kidneys.

From above, it is evicted that the complex must have an opportune stability which has to ensure, from one side, the required preservation of the product in vials and from the other side, the equally important capability of delivering the iron only to the proteinic systems intended to the depot storage or the transport of the iron itself. Therefore, the stability of the Fe^{+++} -sugar complex is one of the most important features, because from this depends not only the shelf life of the selected pharmaceutical form but also the bioavailability of the complexed iron. A poorly stable complex will cause great problems, not only about the administration but also the toxicity, as it will deliver the iron to all the biological systems capable of producing complexes with the iron, for example the hematic proteins, by subtracting it to the biological systems specifically assigned to the transport and the storage of the same.

It has been noted that the trivalent iron complex with the sugars is stable if some essential conditions are respected:

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- 1) physical-chemical homogeneity of the ferric hydroxide
- 2) Use of polysaccharides with a low content of low molecular weights
- 3) Sugars with the activated glucoside terminus.

1) The first condition is that the ferric hydroxide must be a homogeneous product, namely it must not be a mixture of polymorph forms which can complex the iron in a different way, each with a different stability. Furthermore, the ferric hydroxide must not be charged and therefore it must not be even partially salified with anions, a thing that can happen when one tries to isolate it from a solution of a salt thereof by basic treatment.

For example, the precipitation, in addition to $Fe(OH)_3$, of $Fe(OH)_2Cl$, or $NaFe(OH)_2CO$ and so on can occur, obtaining mixtures of hydroxides which make difficult the complex formation and decrease the stability thereof.

Erni I, et al. *Arzneim.-Forsch./Drug. Res.* 34, (II), No. 11 p. 1555-1558, 1984, state that the precipitated and isolated ferric hydroxide, even if in controlled and repetitive reaction conditions, always consists of different kinds of hydroxides.

All the above is confirmed by the fact that the ferric hydroxide, which is reacted with the sugar, is only partly solubilized and forms the complex by remaining partly as a bottom body or, as it often happens, precipitating the complex after a time. Therefore, in order to obtain an effective and repeatable reaction for the complex formation, it is necessary to carry out the iron hydration reaction in a solution, allowing the reaction itself to slowly re-equilibrate in the presence of sugar.

Moreover, everyone knows that the isolation and the purification of the ferric hydroxide are two steps that have a remarkable productive difficulty.

2) The second condition is that the sugar should be activated, namely the end group should not be in form of aldehyde or hemiacetal. In fact, this end group besides being unable to participate to the formation of the complex, can intervene by partly reducing the trivalent iron bringing it to the lower oxidation state of bivalent iron, which is largely bioavailable also by mouth, but just for this reason becomes particularly harmful for the organism, requiring a constant monitoring of the hematic levels.

Therefore, if the polyhydroxylate compound that one wishes to use for forming the complex with the iron contains some reducing end groups, such as an aldohexose sugar, since such groups can destabilize the complex, it is necessary that the aldehyde group, also in form of hemiacetal form, is transformed in a stable group which can contribute to the formation and stabilization of the complex with the Fe^{+++} . The more suitable transformations of the aldehyde end group are the reduction to an alcohol group or the oxidation to a carboxy group. This operation is called sugar "activation".

The conditions applied to various synthesis described in the patents do not foresee an alteration of the sugar, however the complex formation is carried out in a basic environment at high temperature, whereby in such conditions the end groups can likely undergo a modification similar to the one described by Cannizzaro for the aldehydes subjected to dismutation in a basic environment. However, in these conditions the sugar itself can undergo different degradation reactions.

In many other patents, sugar previously activated in a basic environment at high temperature is used. These conditions, even if less destroying than the preceding ones as the reaction takes place in absence of iron, lead however to a mixture wherein, together with a sugar in which the acetal group is partly oxidized to acid and partly reduced to 7 alcohol, modified and hydrolyzed sugars can be obtained, as it can be ascertained by the dark colour of the solution and the strong caramel smell.

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Other patents report a sugar activation through oxidation with bromine, bromites or chlorites which however represent reagents of a difficult handling, preparation and storage. Moreover, it is known that the use of such reagents, if not carried out in controlled pH conditions, reagent concentration and temperature, can lead to oxidation reactions driven with partial hydrolysis of the end sugar.

3) The third condition, in case of polysaccharide sugars, is that the sugar used should not contain very low molecular weight fractions, as these are able to complex a large quantity of iron but are unable to ensure the solubility of the complex. In fact, gelation phenomena of the solution or precipitation of a bottom body which effectively prevents the parenteral administration of the preparation can occur over time in preparations with a high content of very low molecular weights.

Generally, iron complexes with activated mono- or disaccharide sugars are stabilized by increasing the pH and introducing in the preparation large quantities of sugar. These complexes have a pH between 8.0 and 12.0 and therefore are administered only intravenously. Also sugars with too high molecular weights are harmful for the formation of the complex with the iron. Especially in case of dextran, the very high molecular weights can cause anaphylactic shock and increase the general toxicity of the complex, above all when administered by parenteral route.

It is therefore necessary to evaluate with a great attention the contents of high and low molecular weights, and for this reason there are some patents which claim sugars with particular molecular weights or ranges of molecular weight.

By analyzing the state of the art, it is possible to find several patents which report different synthesis systems wherein the three conditions above considered are completely or partly disregarded.

Many patents report, for example, the synthesis of iron/polysaccharides complexes starting from isolated ferric hydroxide, such as the U.S. Pat. No. 4,180,567 wherein dialyzed ferric hydroxide and non-activated dextran, dextrans or glucose are used as complexing agents, or the patent Fr 1,462,959, wherein ferric hydroxide and sorbitol are used as complexing agents. Also in the U.S. Pat. No. 4,749,695 ferric hydroxide is reacted with dextran at a high temperature, while in the patent GB 694,452 the isolated ferric hydroxide is reacted with cane sugar. The obtained product is precipitated and heated in a high temperature oven, and such synthesis leads to non-standardized and sometimes even toxic products.

On the contrary, there are several patents which, for obtaining the complexes in question, use trivalent iron salts in an aqueous solution, then the sugar is added by simultaneously rising the pH and the temperature. If the rising of the pH is gradually carried out, there can be a re-balance between all the variously hydrated intermediate compounds of the iron, namely, for example, starting from iron trichloride, by slowly increasing the pH a slow re-balance of FeCl_3 to FeCl_2OH then to $\text{FeCl}(\text{OH})_2$ to $\text{Fe}(\text{OH})_3$ or FeOOH is obtained, depending on the final pH. It should be kept in mind that also other balance intermediate forms are possible, such as $\text{NaFeCO}_3(\text{OH})_2$ if hydrogen carbonate or carbonate is used for increasing the pH. As above mentioned, the obtainment step of the ferric hydroxide, which being insoluble precipitates together with their balance forms, is determinant. A sharp increase of the pH leads to the obtainment of a ferric hydroxide which co-precipitates with all its balance components, since these latter are not able to re-balance themselves in favour of the end product, i.e. the ferric hydroxide.

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In many patents the sugar is not activated before its reaction with the ferric hydroxide, but it should be kept in mind that the aldohexose sugars, even if they have the aldehyde end group in form of hemiacetal, when subjected to a strong heating in a basic environment can undergo, besides a demolition action, also a dismutation reaction to the corresponding acid and alcohol. This dismutation is an activation of the sugar which, also unintended, makes the sugar suitable to the formation of a stable complex with the ferric hydroxide. The negative side of these synthesis methods is the end product, which is a mixture of products containing ferric hydroxide more or less complexed with sugars at least partly decomposed or modified in an uncontrolled way. In fact, it is apparent that also by carefully carrying out these steps for the formation of the complexes, considering the different hydrolysis, demolition and activation reactions of the sugar which can occur in a concomitant way, it is to be expected, of course, that the end product contains iron complexes with more or less modified different sugars species. Typical of these complexes is the caramel smell which comes with the end product in solution meaning that a partial demolition of the same has been attained.

For example, the patent BE 787662 lies within this class of patents, as it claims a method for the synthesis of complexes obtained by reacting ferric chloride hexahydrate in solution and a sugar included among a low molecular weight dextrin, maltose or glucose with a pH in the range from 11.0-14.0 and at a temperature of 90° C.: during the reaction, a mixture of ferric hydroxides precipitates and simultaneously the sugar is partly hydrolyzed and dismutated, namely it also undergoes a process which leads to its activation which however, taking place in the presence of trivalent iron, can lead to an important level of hydrolysis products.

Therefore, with this kind of process there is, from one side, the application of a simpler methodology, but on the other side, the process is varying both for the obtainment of ferric hydroxide, which remains partly not dissolved at the end of the reaction, and for the degradation/activation of the sugar. In U.S. Pat. No. 2,820,740, the applied methodology foresees a reaction between the dextran partly hydrolyzed and ferric chloride or ferric citrate in the presence of sodium carbonate at a temperature varying between 65 and 100° C. There remains some ferric hydroxide, which does not form the complex and which is finally filtered and eliminated. This residue shows that the reaction for obtaining the ferric hydroxide has been carried out in uncontrolled conditions and, as above mentioned, leads to a polymorph mixture of ferric hydroxide.

In the patent GB 1,019,513, a depolymerized sugar, dextran, is used, wherein the aldehyde end group has been eliminated by reduction with NaBH_4 . The sugar became activated and is able to give a stable complex, even if it is necessary to completely eliminate the boron because of its toxicity.

The ferric salt used is the ferric trichloride, to which a certain quantity of citric acid, which is an iron complexing agent, is added.

In the U.S. Pat. No. 2,885,393, depolymerized dextran is reacted and activated with a ferric chloride solution brought to a pH of 2.3 with sodium carbonate, by heating the whole at 65° C. for 30 minutes.

The U.S. Pat. No. 4,180,567 claims the activation of sugars either through reduction with NaBH_4 or through a basic treatment at pH 10.5-11.3 for 1 hours at 95° C.-100° C. Such sugars are reacted with ferric hydroxide dialyzed at high temperature, then the solution is concentrated and the bottom body is filtered.

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In the U.S. Pat. No. 4,599,405, a dextran with an average molecular weight equal to 5000 Daltons is reacted with ferric trichloride after the salt solution has been brought to pH 1.7 by slow addition of a Na_2CO_3 solution and subsequently NaOH is added up to pH 11.0 over 30 minutes. A suspension is formed, which is heated at 100°C . for about one hour. The solid which does not form the complex is eliminated by centrifugation and then the product is isolated by precipitation with solvents. Also with this method, there is the formation of a mixture of hydrated iron compounds which do not form completely soluble complexes with the sugars. It should be noted that the high temperature used in the formation of the complex, as also observed for other patents, can lead to the partial degradation/activation of the system which can be pointed out by the black colour of the obtained solution and by the caramel smell.

In the U.S. Pat. No. 6,291,440, a complex obtained between ferric hydroxide and hydrogenated dextran with a molecular weight between 700 and 1400 Daltons is claimed.

Dextran purification is carried out by membrane filtration, in order to eliminate both the high molecular weights which are responsible for the anaphylactic reactions and the very low molecular weights which are responsible for the instability of the preparations.

The patent DK 129353 claims a method for forming the complex between iron and a dextran with a maximum molecular weight up to 50000 Daltons, preferably between 1000 and 10000 Daltons. The dextran has the end groups oxidized to the corresponding acid, but the method for obtaining the same is not disclosed.

In the publication of the patent application WO 00/30657 a low weight dextran is claimed, obtained by hydrolysis at pH 1.5 and at 90°C . The dextran is fractionated by ultrafiltration with a cut off of 5000 Daltons and after depolymerization, is further ultrafiltered using a cut off between 350-800 Daltons, in order to eliminate the very low weights. On the obtained dextran, a reduction with NaBH_4 is carried out for reducing about the 15% of the end hemiacetal groups, and therefore the oxidation with NaClO of the remaining end groups is carried out. The formation reaction of the complex is carried out at a pH of 1.6 when the iron chloride has been partly neutralized with sodium carbonate. Also for this patent, is not clear why the sugar, in this case the dextran, is added when more than 60% of the ferric chloride has already been transformed in ferric hydroxide.

It is apparent that the presence, from the start, of the sugar not only promotes the complex formation during the transformation of the ferric chloride in ferric hydroxide, but it promotes the complete transformation of the iron salt in ferric hydroxide preventing the precipitation of the partly hydrated iron.

Finally, the patent EP 0150085 claims a dextran with a molecular weight between 2000 and 6000 Daltons oxidized with sodium chlorite which, according to the inventors, oxidizes in a specific way the aldehyde end group differently from what stated by the U.S. Pat. No. 4,370,476 wherein bromine is used for the oxidation and it is stated that also sodium hypobromite, sodium bromite, chlorine, iodine, sodium hypochlorite, sodium chlorite are likewise effective in the oxidation of the end groups of the dextran.

DESCRIPTION OF THE INVENTION

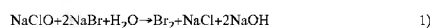
The aim of the present invention relates to a production process of trivalent iron complexes with polyhydroxylated compounds, such as the mono-, di- or polysaccharide sugars.

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The process includes different steps, the first of which consisting of the activation of the sugar. It is known since long that the sugars having an aldehyde end group, also in form of hemiacetal form, can be oxidized through different methods using bromine or other reagents, such as bromites, chlorites, hypochlorites, hypoiodites, or bromides and gaseous halogens, such as chlorine gas in a basic environment. All these reagents are either difficult to handle because of their dangerousness, see bromine and chlorine, or unstable, or they give rise to a specific oxidation reactions, by oxidizing aldehydes and primary alcohols.

In the patent GB 289280, only the oxidation of glucose and galactose is described, using bromides or iodides and chlorine in a strongly alkaline environment. The reaction is carried out at a temperature lower than 15°C . for avoiding the formed bromine from escaping from the environment. The chlorine is added all at once, this means that the environment itself becomes saturated with chlorine, or rather hypochlorite, and therefore both the bromine originating from the oxidation of the bromide, and the hypochlorite co-exist as sugar oxidants. This hinders a clean and complete reaction, as the hypochlorite is able to oxidize also the primary alcohol on the carbon in 6-position giving the glutaric acid and at the same time can hydrolyze the complex sugars, such as the polysaccharides. In the U.S. Pat. No. 6,498,269, the oxidation of even complex sugars in a strongly alkaline environment is reported, through treatment with halogen, generally gaseous chlorine, in the presence of a catalyst of the oxyammonium halide type, by obtaining a diacid as main product.

Surprisingly, we have found that if the use of bromine as an oxidizing agent is desired, its dangerousness and handling difficulty are overcome by producing such oxidizing agent in situ, slowly introducing sodium hypochlorite instead of gaseous chlorine in a strongly acid environment in the aqueous solution containing an alkaline or alkaline earth bromide and the sugar, at a pH between 5.0 and 11.0. The sugar activation is advantageously industrially carried out because of the easiness of handling of the reagents and the repeatability of the reaction itself, as the oxidizing agent is produced in situ by treating a small quantity of an alkaline or alkaline earth metal bromide with an alkaline or alkaline earth metal hypochlorite, preferably sodium hypochlorite at a pH in the range between 5.0 and 11.0, preferably between 7.0 and 9.0. In this way, the handling of reagents which require particular precautions, such as bromine, is avoided, and the activation reaction is further carried out in controlled conditions, in fact the bromide quantity used is between 0.5% and 5% by weight of the sugar to be activated, therefore the bromine quantity which is formed and is found in the reaction environment during the activation phase is really low with respect to the quantity of sugar to be activated. The bromine quantity needed for the sugar activation is produced instant by instant from the addition of the alkaline or alkaline earth hypochlorite, which is used in a stoichiometric quantity with respect to the number of end aldehydes according to the reactions:



Surprisingly, contrary to what happening by heating the sugar in an alkaline environment with the dismutation of the aldehyde group and the concomitant partial decomposition of the sugar, by our method an univocal and absolutely clean reaction is obtained, with the specific oxidation of the end aldehyde.

In fact, by using stoichiometric quantities of hypochlorite with respect to the aldehyde end groups and adding it slowly,

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such that all the added hypochlorite only serves for the bromide oxidation and an excess of hypochlorite in solution is never present, the specific oxidation of the aldehyde group is obtained, maintaining unchanged the remaining chemical structure of the sugar used. The oxidation reaction is controlled through the pH adjustment. In fact, as the acid formation leads to a remarkable lowering of the pH and the consumption of hypochlorite, it is sufficient to add the hypochlorite itself such that the pH is not lowered below 6.0 and the value of 10.0 is not exceeded. From the ^1H NMR spectrum which relates to the maltose oxidation, depicted in FIG. 1, it can be noted the univocity of the structure obtained after the activation reaction carried out according to the method of the present invention. Should, on the contrary, an excess of hypochlorite also be present, in addition to bromine in the reaction environment, oxidation secondary reactions could occur, which would relate to other parts of the end sugar and to depolymerization phenomena. Therefore, it is important to maintain the reaction pH in the range between 5.0 and 12.0, preferably, between 7.0 and 9.0, since in this pH range the bromine consumption takes place at a high rate leading to the oxidation of the aldehyde end group. With polysaccharide sugars, such as dextrans and dextrans, the activation reaction is carried out using, for the stoichiometric calculation, the average molecular weight or rather the value of dextrose equivalents, which shows the glucose equivalents corresponding with the aldehyde end groups. In this way, the reaction is carried out in strictly alkaline conditions and is of a simple repeatability. If a quantity of alkaline or alkaline earth hypochlorite different from the stoichiometric quantity is added, a partial sugar activation can be obtained, if a lower quantity of hypochlorite is used, with negative consequences on the stability of the end complex, otherwise, if a stoichiometric excess of hypochlorite is used, a further oxidation with a partial demolition of the end sugar can be obtained, in addition to the described activation. Furthermore, in this latter case, a depolymerization of the sugar itself with formation of oligomers and low molecular weights can be simultaneously obtained. In both cases, the end product is not homogeneous, being a mixture of sugars with a different chemical structure. The disadvantage of using a similar mixture of activated sugars is the obtainment of iron complexes with non homogeneous structure and stability.

In the ambit of the present invention, the preferred bromide is sodium bromide and the preferred hypochlorite is sodium hypochlorite.

The second step of the process relates to the complexation reaction of the sugar activated with a proper salt of water soluble trivalent iron; the preferred salt for the execution of the present invention is the iron trichloride hexahydrate in a concentrated aqueous solution. For the good result of the complexation reaction, it is necessary to initially mix the activated sugar with the trivalent iron salt before the increase of the pH, such that the sugar and the water can immediately stabilize the trivalent iron facilitating the complete hydration reaction of the iron. This is pointed out in that, during the formation step of the iron hydroxide by slow addition of a base of alkaline metal, the precipitation of the iron hydroxide itself never occurs, and the reaction always appears homogeneous. Only in the case of gluconic acid, when used in a concentrated solution at a pH between 3.0 and 4.0, there is the precipitation of the ferric hydroxide already complexed by the sugar, as in fact for obtaining the complete solubilization of the precipitate it is sufficient to increase the pH between 9.0 and 10.0. This fact is important since in no case a solid is precipitated or a bottom body is left, as in the case of processes wherein the sugar is added after an even partial

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increase of pH in order to obtain ferric hydroxide, or after complexation of the isolated ferric hydroxide. The addition of ferric salt to the early activated sugar solution does not lead to depolymerization phenomena of the sugar itself, even if the initial pH is very acid, because the solution temperature is maintained below 60°C . This step is critical, because the increase rate of the pH for the obtainment of the ferric hydroxide must be suitable for carrying out the iron hydration reaction and, at the same time, promoting the formation of an initial Fe-sugar complex, so as to allow the completion of the hydration reaction of the iron itself without hydroxide precipitation.

The third step of the process consists of the purification of the ferric hydroxide-sugar complex, even if such complex is still not been stabilized by heating. Surprisingly, we have found that once the pH of the starting solution containing the activated sugar and the iron has been increased in the range between 6.0 and 12.0, the ferric hydroxide-sugar complex, even if not yet stabilized, can be ultrafiltered through a membrane with a proper cut-off. This process allows to remove all the salts formed during the hydration reaction of the iron, by obtaining a compound which can also be stored for a long time, waiting to be subjected to following stabilization reactions.

Following to the purification, the trivalent iron-sugar complex is subjected to the stabilization step of the complex, wherein there is the modification of the ferric hydroxide in ferric oxy-hydroxide. This treatment takes place at a temperature between 60°C and 100°C for a period between 1 and 4 hours at a pH between 9.0 and 12.0. The stabilization treatment can also be carried out before the purification treatment through ultrafiltration, obtaining the same result. In particular, this occurs in the production of the trivalent iron complex with the activated glucose.

The complexes thus obtained and divided in glass vials or bottles can be successively sterilized by heating in autoclave at 125°C for 30 minutes without undergoing any stability modifications of the end complex. Finally, before the division in vials, the complexes between ferric hydroxide and sugar can be blended with other sugars in a desired proportion resulting, in some cases, in a further stabilization of the complex.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a depiction of the ^1H NMR spectrum relating to glucose oxidation.

FIG. 2 is a depiction of the ^{13}C NMR spectrum relating to glucose oxidation.

DETAILED DESCRIPTION OF THE INVENTION

The aim of the present invention consists of a process for the preparation of complexes of trivalent iron (Fe^{3+}) with mono-, di- and polysaccharide sugars, complexes characterized by a good physical-chemical stability over time, low toxicity, use safety also by injection and a good bioavailability.

Said process, characterized by execution easiness and safety, consists of four steps:

1. activation of mono-, di- or polysaccharide sugar;
2. complexation of the activated sugar with ferric hydroxide generated in solution;
3. purification of the ferric hydroxide/sugar complex still not stabilized;
4. stabilization of the ferric hydroxide/sugar complex.

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The process is completed with the possible mixing of the obtained complex with other sugars, a mixing which imparts a further stabilization to the complex, and with the packaging of the medicinal speciality through sterilizing filtration, subdivision of the solution in glass vials or bottles and final sterilization in autoclave at 125° C. for 30 minutes.

Preferred sugars in the execution of the present invention are: glucose, maltose, lactose, maltodextrins and dextrans.

The sugar activation is carried out by oxidation with nascent bromine by dissolving the sugar in purified water at a concentration between 10% and 50% by weight, adding an alkaline or alkaline earth bromide, preferably sodium bromide, in a quantity between 0.5% and 5% by weight based on the sugar weight, bringing the pH of the solution to a value between 5.0 and 11.0, preferably between 7.0 and 9.0, with sodium hydroxide and adding under stirring at a temperature between 10° C. and 60° C. in a period between 2 and 4 hours an aqueous solution containing a weighed stoichiometric quantity of an alkaline or alkaline earth metal hypochlorite, preferably sodium hypochlorite, with respect to the aldehyde end groups existing in the sugar. Preferred in the ambit of the invention are sodium hypochlorite aqueous solutions containing about 12% by weight of active chlorine. Throughout the activation reaction of the sugar, the pH value is controlled and maintained in the fixed range, preferably between 7.0 and 9.0, by adjusting the addition rate of the hypochlorite. At the end of the reaction, to the solution of activated sugar a concentrated aqueous solution of a ferric salt is added under stirring, at a temperature between 15° C. and 60° C., so as the trivalent iron/sugar weight ratio is in the range between 1:0.5 and 1:4. All the water soluble trivalent iron salts can be used, the greatly water soluble ferric chloride hexahydrate being preferred in the execution of the invention, whereby very concentrated aqueous solutions can be obtained, for example aqueous solutions containing 40% by weight of ferric chloride.

After the addition of the ferric salt solution, to the mixture under constant stirring an aqueous solution of sodium carbonate is added, preferably at 15% w/v, in a period between 1 and 6 hours with, so as to slowly increase the pH never exceeding the value between 2.3 and 2.7.

When this pH range has been reached, the stirring of the solution is continued for a time between 15 and 60 minutes and only subsequently, in a time between 1 and 2 hours, the pH of the solution is brought to values between 8.0 and 12.0 by addition of an aqueous solution of sodium hydroxide, preferably at concentrations between 15% and 30% w/w.

The solution of the trivalent iron-sugar complex thus obtained is subjected to purification with removal of the salts and all the products with a low molecular weight, by subjecting it to a membrane ultrafiltration with a cut-off between 3000 and 5000 Daltons for the mono- and disaccharide sugars, such as glucose, maltose, lactose, and with a cut-off between 400 and 50000 Daltons for the polysaccharide sugars, such as dextrans and dextrins.

The ferric hydroxide-sugar complex thus purified is stabilized by heating of the solution which contains the same at a temperature between 60° C. and 100° C., preferably between 75° C. and 95° C. for a time between 1 and 4 hours at a pH between 9.0 and 12.0. The purified and stabilized solution can be stored for a long time in a cooled environment and when one desires to use it for the preparation of medicinal specialities, it has to be heated at a temperature between 60° C. and 100° C., preferably between 75° C. and 95° C. for a time between 3 and 6 hours and therefore the end product can be isolated in different ways.

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For example, it can be isolated in form of a powder through spraying or freeze-drying, after having adjusted, if necessary, the pH of the solution at values between 4.5 and 7.0. Otherwise, it is possible to add the solution of the stabilized and purified complex with a further sugar quantity, also different from the one present in the complex, which further stabilizes the solution, which can be divided in glass vials or bottles which are then sterilized at 125° C. for 30 minutes, preferably at 121° C. for 20 minutes, or it can be freeze-dried, obtaining the end product in form of a powder.

In an advantageous embodiment, the process for the preparation of trivalent iron complexes with mono-, di- and polysaccharide sugars includes the activation of the sugar. The sugar is obtained by dissolving the sugar in purified water at a concentration between 10% and 50% by weight, adding an alkaline or alkaline earth bromide in a quantity between 0.5% and 5% by weight based on the sugar weight, bringing the pH of the solution to a value between 5.0 and 11.0 and adding under stirring in a time between 2 and 4 hours, at a temperature between 10° C. and 60° C., an alkaline or alkaline earth metal hypochlorite in aqueous solution in a stoichiometric quantity with respect to the aldehyde end groups present in the sugar, if not branched; in the specific case of the dextran, a hypochlorite quantity corresponding with the double of the moles is used.

Subsequently, the activated sugar complexation, is obtained by adding the solution of activated sugar under stirring, at a temperature between 15° C. and 60° C., with an aqueous solution of a ferric salt, such that the weight ratio of iron to sugar is between 1:0.5 and 1:4 (from 1:0.5 to 1:5), adding in a time between 1 a 6 hours, an aqueous solution of sodium carbonate in order to bring the pH to a value between 2.3 and 2.7, maintaining constant the pH in this range of values for a time between 15 and 60 minutes, and therefore bringing the pH to values between 8.0 and 12.0 by addition of a sodium hydroxide aqueous solution.

Subsequently, the complex between ferric hydroxide and sugar is purified by ultrafiltration of the solution. Finally, the complex is stabilized by heating of the ultrafiltered solution at a temperature between 60° C. and 100° C. for a time between 1 and 4 hours at a pH between 9.0 and 12.0. In the case of dextran, the heating takes place for a minimum of 5 hours. For example, the sugars are selected from glucose, maltose, lactose, maltodextrins and dextrans. The bromide is sodium bromide. The pH of the activation reaction of the sugar is between 7.0 and 9.0. The hypochlorite is sodium hypochlorite and the ferric salt is ferric chloride hexahydrate. The stabilization temperature of the complex is between 75° C. and 95° C. For example, the ultrafiltration is carried out with a membrane with a cut-off between 3000 and 5000 Daltons for the glucose, maltose and lactose, while for maltodextrins and dextrans with a cut-off 400 in order to remove the salts and with a cut-off between 30000 and 50000 Daltons in order to remove the low molecular weights.

For example, the stabilization treatment of the trivalent iron-gluconic acid complex is carried out before the purification treatment. The complexes which can be obtained are for example ferric gluconate, the complex between iron hydroxide and maltose, the complex between iron hydroxide and lactose, the complex between iron hydroxide and maltodextrins, the complex between iron hydroxide and dextran.

The enclosed FIG. 1 relates to activated glucose, while the enclosed FIG. 2 relates to glucose as such.

The following examples constitute a further illustration of the aim of the invention and are not to be intended as a limitation thereof.

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EXAMPLE 1

Preparation of ferric gluconate

50 grams of glucose are dissolved under stirring in 140 ml of purified water, and to the obtained solution 0.5 g. of sodium bromide are added by simultaneously bringing the pH of the solution to a value between 7.0 and 9.0 with a sodium hydroxide solution.

Over two hours, 164 g. of 12% active chlorine sodium hypochlorite solution are added, a quantity corresponding with a molar weight 1:1 with respect to the glucose, by maintaining the pH value between 7.0 and 9.0 and, at the end of the addition, the stirring is continued for other 30 minutes.

The control of the accomplished execution is carried out through HPLC or through polarimetric readings. The oxidation of glucose to gluconic acid is obtained, as it can be verified by the ^{13}C NMR spectrum depicted in FIG. 1.

The solution of gluconic acid is brought to a temperature between 16°C . and 20°C . and is added with 416 g. of a 40% ferric trichloride solution at 40% by weight (iron/sugar ratio=1:0.87 w/w). The stirring is continued for a complete homogenization of the solution and in about two hours a 15% w/v sodium carbonate solution is added, until bringing the pH at a value between 2.3 and 2.7.

Once such value has been reached, the solution is maintained under stirring for a time of 30 minutes by controlling that the pH remains between 2.3 and 2.7. Subsequently, with a solution of sodium hydroxide at 15% w/v, the pH is brought to 11.0 ± 0.5 over 1 hour, and during the increase of the pH between 3.0 and 4.0 the formation of a precipitate comprised of ferric hydroxide-gluconic acid complex occurs, which tends to solubilize while the pH increases until a complete solubilization at a pH above 9.0.

A brown-coloured solution is obtained, which has no solids in suspension and is brought to the temperature of $85 \pm 2^\circ\text{C}$. and maintained under this conditions for 2 hours. At the end of the stabilization reaction of the complex, the obtained solution is purified from the salts through an ultrafiltration system equipped with a membrane with a cut-off of 3000 Daltons.

The resulting solution purified from the salts, brought to a pH of 10.5 ± 5 , can be stored in a cooled environment and, before its pharmaceutical use, is again heated at a temperature of $90 \pm 2^\circ\text{C}$. for a period of 4 hours. The ferric gluconate is isolated by spraying, obtaining a yield higher than 85%, computed on the starting iron.

The physical-chemical features of the complex are the following:

average molecular weight (Mw)=43347 Daltons
numerical molecular weight (Mn)=30495 Daltons
polydispersibility=1.4
 Fe^{3+} content=48.6%

The molecular weights have been determined using the gel-permeation chromatography method, described on page 1065 by the United States Pharmacopoeia (USP) 28th Ed., which uses 2 columns in series TOSO HAAS column TSK-GEL G5000PW_{XL} 30 cmx7.8 cm ID+TOSO HAAS column TSK-GEL 2500PW_{XL} 30 cmx7.8 cm ID and dextrans with a known average molecular weight Mw as a standard, and with the following molecular weights at the top of the peak, expressed in Daltons: 4440, 9890, 21400, 43500, 66700, 123500, 196300, 276500.

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EXAMPLE 2

Preparation of ferric gluconate

The ferric gluconate complex can be obtained using the same methodology of the example 1, starting from commercial gluconic acid and ferric chloride.

24.5 grams of sodium gluconate are dissolved in 120 ml of purified water and to the obtained solution 205 g. of a 40% wt ferric chloride solution (iron/sugar ratio=1:0.87 w/w), keeping under stirring until a complete homogenisation of the reaction mixture is reached.

The solution temperature is brought between 16°C . and 20°C . and over 2 hours a 15% w/v sodium carbonate solution is added, to bring the pH of the solution at values between 2.3 and 2.7.

When such value has been reached, the solution is maintained under stirring for a period of 30 minutes, by controlling that the pH remains between 2.3 and 2.7.

Subsequently, with a 15% w/v sodium hydroxide solution, the pH is brought to 11.0 ± 0.5 over 1 hour, during this step with a pH between 3.0 and 4.0 there is the formation of a precipitate, formed by a ferric hydroxide-gluconic acid complex, which solubilizes while the pH is increased until a complete solubilization at a pH above 9.0.

A brown-coloured solution is obtained, which has no solids in suspension and is brought to the temperature of $85 \pm 2^\circ\text{C}$. and maintained under this conditions for 2 hours. At the end of the stabilization reaction of the complex, the obtained solution is purified from the salts through an ultrafiltration system equipped with a cut-off membrane of 3000 Daltons.

The resulting solution purified from the salts, brought to a pH of 10.5 ± 5 , can be stored in a refrigerated environment and, before its pharmaceutical use, is again heated at a temperature of 90°C . for a period of 4 hours. The ferric gluconate is isolated as such by freeze-drying, obtaining a yield above 85% computed on the starting iron. The physical-chemical features of the complex, with the molecular weights determined according to the methodology described in the example 1, are the following:

average molecular weight (Mw)=53745 Daltons
numerical molecular weight (Mn)=30976 Daltons
polydispersibility=1.7
 Fe^{3+} content=48.5%

EXAMPLE 3

Preparation of the ferric hydroxide/maltose Complex

60 grams of maltose are dissolved in 200 ml of purified water, to the solution thus obtained 0.6 g. of sodium bromide are added and the pH of the solution is brought to a value between 7.0 and 9.0 with a sodium hydroxide aqueous solution.

Over two hours, 98.5 g. of 12% active chlorine sodium hypochlorite are added, corresponding with the stoichiometric quantity with respect to the aldehyde end groups, by maintaining the pH value between 7.0 and 9.0. At the end of the addition, the stirring is continued for 30 minutes and the control of the accomplished activation is carried out through HPLC by detecting the residual maltose and activated maltose ratio.

To the activated maltose solution, brought at a temperature between 16°C . and 20°C ., 257 g. of a 40% wt (iron/sugar ratio=1:1.7 w/w) are added continuing the stirring until a complete homogenization of the reaction mixture-. There-

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fore, to the obtained solution a 15% w/v sodium carbonate solution is added over 3 hours, so as to slowly bring the pH at a value between 2.3 and 2.7.

When this value has been reached, the solution is maintained under stirring and in these conditions over 15 minutes, by checking that the pH value remains between 2.3 and 2.7, and therefore the pH value is brought to 10.5±0.5 over 1 hour, adding a 15% w/v. sodium hydroxide solution. The precipitation of iron hydroxide never occurs, neither in form of a complex. The obtained solution is purified from the salts through an ultrafiltration system equipped with a membrane with a cut-off of 3000 Daltons.

The resulting solution purified from the salts is brought to a pH of 11.5±0.5 and heated at a temperature of 75° C.±2 for a period of 2 hours, then the complex is isolated by freeze-drying.

The physical-chemical features of the complex, with the molecular weights determined according to the methodology described in the example 1, are the following:

average molecular weight (Mw)=53655 Daltons
numerical molecular weight (Mn)=35988 Daltons
polydispersibility=1.5
Fe³⁺ content=41.4%

EXAMPLE 4

Preparation of the ferric hydroxide-lactose Complex

50 grams of lactose are dissolved in 250 ml of purified water and to the obtained solution 0.5 g. of sodium bromide are added bringing the pH to a value between 7.0 and 9.0 with a sodium hydroxide solution. Over two hours, 98.5 g. of 12% active chlorine sodium hypochlorite are added, corresponding with the stoichiometric quantity with respect to the aldehyde end groups, maintaining the pH value between 7.0 and 9.0. At the end of the addition, the stirring is continued for 30 minutes and the control of the accomplished activation is carried out through HPLC by detecting the residual lactose and activated lactose ratio.

To the activated lactose solution, brought at a temperature between 16° C. and 20° C., 300 g. of a 40% wt iron chloride solution (iron/sugar ratio=1:1.7 w/w) are added continuing the stirring until a complete homogenization of the reaction mixture. Therefore, to the obtained solution a 15% w/v sodium carbonate solution is added over 3 hours, so as to slowly bring the pH at a value between 2.3 and 2.7.

When this value has been reached, the solution is maintained under stirring and in these conditions over 15 minutes, by checking that the pH value remains between 2.3 and 2.7, and therefore the pH value is brought to 10.5±0.5 over 1 hour, adding a 15% w/v sodium hydroxide solution. The precipitation of iron hydroxide never occurs, neither in form of a complex.

The obtained solution is purified from the salts through an ultrafiltration system equipped with a membrane with a cut-off of 3000 Daltons.

The resulting solution purified from the salts is brought to a pH of 11.0±0.5 and heated at a temperature of 75±2° C. for a period of 2 hours and then after cooling and correction of the pH value at 7, the active substance is isolated by spraying.

The physical-chemical features of the complex, with the molecular weights determined according to the methodology described in the example 1, are the following:

average molecular weight (Mw)=65571 Daltons
numerical molecular weight (Mn)=40669 Daltons

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polydispersibility=1.6
Fe³⁺ content=49.6%

EXAMPLE 5

Preparation of the ferric hydroxide-polymaltose Complex

70 grams of maltodextrins, characterized by a value of dextrose equivalents equal to 19, are dissolved in 200 ml of purified water and to the obtained solution 1.4 g. of sodium bromide are added.

The pH of the solution is brought to a value between 7.0 and 9.0 with a sodium hydroxide solution and over 2 hours, 48.66 g of 12% w/v active chlorine sodium hypochlorite are added, maintaining the pH within the fixed limits. At the end of the addition, the stirring is continued for 30 minutes and the accomplished activation is controlled through a HPLC-GPC technique.

To the activated maltodextrin solution, brought at a temperature between 16° C. and 20° C., 300 g. of a 40% w/v iron chloride solution (iron/sugar ratio=1:1.7 w/w) are added and the stirring is continued until a complete homogenization of the reaction mixture.

Over a period of 5 hours, an aqueous 15% w/v sodium carbonate solution, required for bringing the pH at a value between 2.3 and 2.7 is added under stirring, and when this value has been reached the solution is maintained in these conditions over 15 minutes, by checking that the pH value remains between 2.3 and 2.7.

With a 15% w/v sodium hydroxide solution, the pH is brought to the value of 9.0±0.5 over 1 hour. The precipitation of iron hydroxide never occurs, neither in form of a complex.

The obtained solution is purified from the salts through an ultrafiltration system equipped with a membrane with a cut-off of 30000 Daltons.

The resulting solution is heated at the temperature of 92±2° C. for a time of 3 hours and at a pH of 10.8±0.2.

The cooled solution is brought to pH 6.0±0.5 and then the product is isolated at the dry state through spraying.

The physical-chemical features of the complex are the following:

average molecular weight (Mw)=167319 Daltons
numerical molecular weight (Mn)=69319 Daltons
polydispersibility=2.4
Fe³⁺ content=34.8%

The molecular weights have been determined using the gel-permeation chromatography method which uses a column TOSO HAAS, column model TSK-GEL G5000PW_{XL} 30 cm×7.8 cm ID and, as a standard, dextrans with the following average molecular weights Mw expressed in Daltons: 48600, 80900, 147600, 273000, 409800, 667800.

EXAMPLE 6

Preparation of ferric hydroxide-dextran Complex

17.5 grams of dextran, with an average molecular weight between 2000 and 7800, are dissolved in 65 ml of purified water and to the obtained solution 0.34 g. of sodium bromide are added. The solution is heated at 50° C. and the pH is brought at a value between 7.0 and 9.0 with a sodium hydroxide solution.

4.14 g. of 12% w/v active chlorine sodium hypochlorite (2 mMoles), corresponding with the double of the dextran moles with an average molecular weight of 5000 Da are added over two hours, maintaining the pH value between 7.0 and 9.0.

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To the activated dextran solution, brought to the temperature of 40° C. or 30° C., 75 g of a 40% w/v iron chloride solution (iron/sugar ratio=1:2 w/w) are added, continuing the stirring until a complete homogenization of the reaction mixture.

A 15% w/v sodium carbonate aqueous solution, required for bringing the pH at a value between 2.3 and 2.7 is added over two hours, and when such value has been reached, the reaction mixture is maintained under these conditions for 30 minutes, controlling that the pH remains constant.

With a 15% w/v sodium hydroxide aqueous solution, the pH value is brought to 11.5±0.2 over 1 hour and the obtained solution is heated at 95±2° C. for three hours and thirty minutes, therefore, after cooling, is purified from the salts through an ultrafiltration system equipped with a membrane with a cut-off of 400 Daltons, in order to remove the salts contained.

Once desalted, the solution is maintained at a pH 11.0±0.2, heated at the temperature of 95±2° C. for a period of at least 5 hours and therefore cooled at room temperature. The pH of the solution is brought to the value of 6.0±0.2 and after addition of phenol, stored in sterile containers.

The active substance can also be isolated by spraying.

The reaction yield is above 85% with respect to the starting iron.

The physical-chemical features of the complex, with the molecular weights determined according to the methodology described in the example 5, are the following:

average molecular weight (Mw)=226392 Daltons
numerical molecular weight (Mn)=125590 Daltons
polydispersibility=1.8
Fe³⁺ content=36.7%

EXAMPLE 7

Preparation of ferric hydroxide-dextran Complex

17.5 grams of dextran, with an average molecular weight between 2950 and 7800, are dissolved in 65 ml of purified water and to the obtained solution 0.34 g. of sodium bromide are added. The solution is heated at 50° C. and the pH is brought at a value between 7.0 and 9.0 with a sodium hydroxide solution.

4.14 g. of 12% w/v active chlorine sodium hypochlorite, corresponding with the double of the dextran moles with an average molecular weight of 5000 Da are added over two hours, maintaining the pH value between 7.0 and 9.0.

To the activated dextran solution, brought to the temperature of 50° C., 42.4 g. of a 40% w/v iron chloride solution (iron/sugar ratio=1:3 w/w) are added, continuing the stirring until a complete homogenization of the reaction mixture.

A 15% w/v sodium carbonate aqueous solution, required for bringing the pH at a value between 2.3 and 2.7 is added over a period between two and five hours, and when such value has been reached, the reaction mixture is maintained under these conditions for 30 minutes, controlling that the pH remains constant.

With a 15% w/v sodium hydroxide aqueous solution, the pH value is brought to 11.5±0.2 over 1 hour and the obtained solution is purified from the salts through an ultrafiltration system equipped with a membrane with a cut-off of 400 Daltons: in this case, only the existing salts are removed, not the unreacted excess of dextran. If the removal of all the uncomplexed dextran is desired, then it is necessary to use a membrane with a cut-off of 50000 Daltons.

Once desalted, the solution is maintained at a pH 11.5±0.2, heated at the temperature of 95±2° C. for a period of at least

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5 hours and therefore cooled at room temperature. The pH of the solution is brought to the value of 6.0±0.2 and therefore the active substance is isolated through spraying. The reaction yield is above 85% with respect to the starting iron.

If one desires to maintain the active substance in a solution, phenol is added and the storage is carried out at 20° C. in sterile containers.

The physical-chemical features of the complex, with the molecular weights determined according to the methodology described in the example 5, are the following:

average molecular weight (Mw)=205127 Daltons
numerical molecular weight (Mn)=151276 Daltons
polydispersibility=1.4

EXAMPLE 8

Preparation of the ferric gluconate Stabilized with sucrose

To the ferric gluconate solution stabilized and purified from the salts, obtained according to the procedures described in the examples 1 and 2, 806 g. of sucrose are added under stirring, a quantity with which the iron/sucrose ratio equal to 1:15.6 is reached.

The solution thus obtained is freeze-dried, giving the ferric gluconate stabilized with sucrose.

EXAMPLE 9

Preparation of the ferric hydroxide/maltose Complex Stabilized with sucrose

To the solution containing the ferric hydroxide/activated maltose complex, after purification and stabilization carried out according to the procedure described in the Example 3, 458 g. of sucrose are added under stirring, a quantity with which an iron/sucrose ratio equal to 1:15 is reached. The solution thus obtained is freeze-dried, giving the stabilized complex of ferric hydroxide-maltose in a solid form.

The invention claimed is:

1. A process for the preparation of an activated sugar comprising the step of reacting a sugar having an aldehyde end group with bromine in a solution at a pH between 7.0 and 9.0 with the specific oxidation of the end aldehyde, wherein

i) said sugar is selected from the group consisting of dextrans and dextrins and wherein

ii) said bromine is produced in situ through the addition of a hypochlorite and an alkaline or earth alkaline metal bromide to said solution, said hypochlorite being added in stoichiometric quantities with respect to the aldehyde end groups, wherein said hypochlorite is added instant by instant, such that an excess of hypochlorite in solution is never present.

2. The process according to claim 1, wherein the hypochlorite is an alkaline or alkaline earth hypochlorite.

3. The process according to claim 2, wherein the hypochlorite is sodium hypochlorite and the bromide is sodium bromide.

4. The process according to claim 1, wherein the quantity of bromine is between 0.5 and 5% by weight, based on the total weight of sugar to be activated.

5. The process according to claim 1, wherein the hypochlorite added is in an aqueous solution containing about 12% by weight of active chlorine.

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6. Process according to claim 1, wherein the solution is an aqueous solution including the sugar to be activated in a quantity between 10 and 50% by weight, based on the weight of the solution.

7. The process according to claim 1, where, in a following step, Fe(III) salt is added to react with said activated sugar to form a Fe(III)-activated sugar complex.

8. Process according to claim 7, wherein said salt is iron trichloride hexahydrate.

9. The process according to claim 7, wherein the iron (III) salt is added to the solution containing the activated sugar in a weight ratio of iron to sugar between 1:0.5 and 1:5.

10. The process according to claims 7, wherein after the addition of the iron salt to the solution containing the activated sugar, the pH of the solution is controlled at a value between 2 and 3.

11. The process according to claim 7, wherein the pH of the solution is controlled by adding a sodium hydrogencarbonate solution in a time between 1 and 6 hours.

12. The process according to claim 11, wherein the pH of the solution is subsequently brought to a value between 8 and 12 to give a solution containing the Fe (III)-activated sugar complex.

13. The process according to claim 12, wherein the Fe (III)-activated sugar complex is subjected to purification.

14. The process according to claim 13, wherein the purification is carried out by ultrafiltration.

15. The process according to claim 14, wherein the ultrafiltration is carried out with a membrane having a cut-off between 400 and 50000 Daltons for the polysaccharide sugars.

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16. The process according to claim 15, wherein said complex is stabilized by heating of the solution containing the same at a temperature between 60° C. and 100° C., for a period between 1 and 4 hours at a pH between 9.0 and 12.0.

17. The process according to claim 16 wherein the stabilized complex is further stabilized through the mixing with a further sugar or further sugars.

18. The process according to claim 17 wherein the further sugar is different from the sugar present in the complex.

19. Process according to claim 7, wherein said complex is selected from: iron maltodextrin, iron dextran.

20. The process according to claim 9, wherein the iron (III) salt is added to the solution containing the activated sugar in a weight ratio of iron to sugar from 1:0.5 to 1:4.

21. The process according to claims 10, wherein after the addition of the iron salt to the solution containing the activated sugar, the pH of the solution is controlled at a value from 2.3 to 2.7.

22. The process according to claim 11, wherein the solution contains 15% w/v sodium hydrogencarbonate.

23. The process according to claim 12, wherein the pH of the solution is subsequently brought to the value between 8 and 12 through the addition of a sodium hydroxide solution.

24. The process according to claim 16, wherein said complex is stabilized by heating of the solution containing the same at a temperature between 75° C and 95° C.

25. The process according to claim 1 wherein said dextrin is a maltodextrin.

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