

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor :	Gary D. Glick	Art Unit :	1612
Serial No. :	15/255,102	Examiner :	Benjamin J. Packard
Filed :	September 1, 2016	Conf. No. :	9812
Title :	METHODS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH AN ABNORMAL INFLAMMATORY RESPONSES		

DECLARATION OF GIANCARLO SANTUS UNDER 37 C.F.R. § 1.132

I, Giancarlo Santus, of Milan, Italy, hereby declare as follows:

[1] I have over 40 years of experience in pharmaceutical research and development worldwide. I am currently the General Director of Monteresearch, which is a company that specializes in formulation development and preparations of clinical trial samples. I graduated with honours in Pharmaceutical Chemistry and Technology in 1975 and earned a specialization in Pharmaceutical Analysis & Technology in 1984 from the University of Pavia. I have provided a summary of my profession experience below.

PROFESSIONAL EXPERIENCE

- ❖ 1977 - 1978 Senior Scientist S.p.A. and Post-doctoral Research fellow, Dept. of Pharmaceutical Technology, Faculty of Pharmacy, **State University of Pavia** (Italy)
- ❖ 1978 - 1979 Research Scientist for herbicide formulations in the Pesticide **Research Centre of Montedison**, (Milan, Italy)
- ❖ 1979 - 2001 **Recordati S.p.A.** (Milan, Italy)
 - 1985 – 1986 Sabbatical year as post-doctoral fellow; R. Guy and L. Benet, University of California San Francisco (CA, USA)
 - 1979-1990 Head of Pharmaceutical Technology Department

- 1990-2001 Director Pharmaceutical Technology R&D of Pharmaceutical Production (2000- 2001)
 - 1998 - 2001 Responsible SPP (Prevention and Protection Service, Law 626/94)
 - 2000 - 2001 Pharmaceutical Production Director
- ❖ 1987 - 1994 Member of Board of Directors **Pharmetrix**, which is a company specializing in drug delivery systems (Menlo Park, CA, USA).
- 1992 - 1994 Chief Scientific Officer
- ❖ 2001 – 2005 Vice President Product Development **Nicox, Sophia Antipolis (F)**, which is an international ophthalmic company, developing solutions to help maintain vision and improve ocular health based on its proprietary nitric oxide (NO)-donating research platform; responsible for the filing of 7 international INDs.
- ❖ 2005 - 2010 CO-Founder and CEO **CTG Pharma srl** (Milano), developed an innovative, proprietary technology based on H₂S-releasing hybrids that forms the basis of new chemical entities characterised by optimal efficacy/tolerability profile through scientific collaborations with first class research international centres.
- ❖ 2006- 2009 Member of Board of Directors of **Sulfidris**, a spin-off of Milan University, which is a company focused on development of new drugs (SULFIDRACs) for the treatment and prevention of cancer.
- ❖ 2010 – present General Director **Montereseach** (Milano), a company specialized in formulation development, clinical samples preparation, batch release, etc.

[2] I am a co-inventor on the above-referenced patent application. I understand that the independent claims under examination in this patent application are as follows:

Claim 240. A solid pharmaceutical composition, which comprises:

an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; one or more disintegrants; one or more diluents; and one or more binders; and
an external phase comprising one or more lubricants.

Claim 254. A solid pharmaceutical composition, which comprises:

an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; crospovidone; lactose monohydrate; and povidone; and
an external phase comprising magnesium stearate and talc.

Claim 271. An enema preparation comprising a separately contained first component and a separately contained second component, wherein:

(i) the first component comprises a solid pharmaceutical composition, which comprises:

an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; one or more disintegrants; one or more diluents; and one or more binders;
an external phase comprising one or more lubricants.; and

(ii) the second component comprises one or more liquids and optionally one or more other pharmaceutically acceptable excipients together forming a liquid carrier.

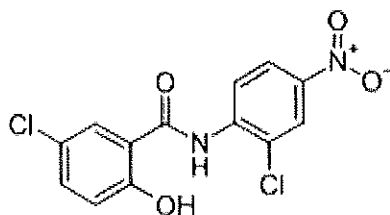
Claim 284. An enema formulation comprising water; methyl cellulose; povidone; methylparaben; propylparaben; sodium dihydrogen phosphate dehydrate; disodium phosphate dodecahydrate; crospovidone; lactose monohydrate; magnesium stearate; talc; and niclosamide, or a pharmaceutically acceptable salt thereof.

[3] I also understand that the Examiner has rejected claims 240-271 and 280-283 under 35 as being obvious over McCaffrey et al (US 5,663,155) in view of Weibel et al (US 2004/0091523). It is also my understanding that the Examiner has rejected Claims 272-279 and 284 as being obvious over McCaffrey and Weibel (*supra*) in further view of Armstrong (US

2014/0256661), Frizelle and Colls (Dis Colon Rectum, February 2005, v48 n2, 393-396) and Chen et al (CN 105063018).

[4] I am aware that this Declaration is being submitted to support rebuttal arguments against the aforementioned rejections.

[5] The Assignee of record on this patent application hired my current employer, Montereasearch, to formulate niclosamide (chemical structure shown below for convenience), so



that niclosamide could be administered rectally by enema in clinical trials. Administration of a niclosamide suspension as an enema was chosen after consideration of several rectal administration options, such as suppositories, rectal foams, rectal solutions, rectal gels, and rectal suspensions. The claimed niclosamide-containing formulations can form suspensions in liquid media that are suitable for administration by enema. Example 9 demonstrates that said suspensions, when administered rectally as an enema, have efficacy in a mouse model of ulcerative colitis.

[6] I led the development effort on this project and either performed or supervised all of the work that was done on this project. Example 8 in this patent application describes examples of such work. In particular, I developed a two-component formulation, which included (i) a solid, niclosamide-containing phase; and (ii) a liquid phase. I further demonstrated that the two phases could be reconstituted before the use to obtain an extemporaneous suspension that was suitable for administration by enema. At the outset of this project, I am unaware of any previous attempts to administer niclosamide rectally by enema. I was also unaware of any previous attempts to formulate niclosamide for this purpose. As will be discussed in more detail below, numerous, previously unknown challenges were encountered in arriving at the claimed formulations.

[7] The Solid Phase: The API and Excipients

The challenge associated with developing an effective solid phase is two-fold. The solid phase must fully break apart **as a result of** the force generated by a patient physically shaking **the** enema vehicle, but at the same time, be sufficiently flowable to allow for filling and emptying of its container, which may be a sachet. The claimed formulations accomplished this and overcame previously unrecognized problems.

The API

Flow properties of a solid typically cannot be predicted (or even estimated for that matter) *a priori* and can affect performance of a solid in a variety of applications, including as in the case of niclosamide, as a solid phase component of an enema preparation. Thus, it was not possible to determine or estimate *a priori* the performance of niclosamide alone or with excipients in an enema formulation.

As an initial matter, niclosamide is almost insoluble in water, and this excluded the possibility to develop simple aqueous solutions/formulations. Also, the solubility in other solvents physiologically compatible was evaluated, but niclosamide proved to be a very difficult compound to solubilize for purposes of developing an enema formulation.

In addition, niclosamide can be present in various solid forms, e.g., anhydrous, hydrated and solvated forms. Moreover, under certain conditions a transformation from one form to the other can occur. I developed assays using dynamic vapor sorption (DVS) to measure water uptake at different relative humidity conditions as well as Raman spectroscopy to differentiate anhydrous and hydrate forms. I performed extensive testing in order to arrive at the optimal solid form of niclosamide.

The flow property of solids varies from solid to solid – niclosamide itself was found to exhibit poor flow properties.

The Excipients

I was asked to prepare solid phases that contained two rather different dosage levels of niclosamide: 150mg and 450mg, and to package these (e.g., in a sachet). While minimizing the overall amount of solid material to be suspended was desired, I found it to be beneficial to include some level of excipient with the API (even at the higher solid volume 450 mg dose) to maintain workable and acceptable flow properties of the solid phase. I attributed this to the poor flow properties of niclosamide. This is discussed in more detail below.

Taking sachets as an example, they are typically filled using a special apparatus, and ease of filling depends upon the flow properties of the solid. It is easier to fill sachets with solids having acceptable flow properties. Initial solid phase samples contained a direct mixture of niclosamide 98.5% with 1% colloidal silicon dioxide and 0.5% magnesium stearate (known glidants/lubricants). This appeared to be quite optimal in view of the relatively high percentage of API to be suspended; however, the mixture exhibited very poor flow properties. I attempted to increase the percent of silicon dioxide and magnesium stearate, but these modifications did not improve the flow properties of the solid phase. In addition, increasing quantities of Avicel (known diluent) were added (up to 50 %) still without success. In addition to exhibiting extremely poor flow properties (the aforementioned compositions could not be used in the sachet-filling machine), the initial compositions also stuck to the walls of the plastic bottles when shaken with liquid phase, so the compositions were also unsuitable for delivery by enema. Additional conventional attempts to improve the flow properties ultimately also caused unwanted bulking of the material. At this stage, I informed the Assignee of record that it would not be possible to produce any of the formulations needed to conduct the clinical trials.

I then investigated a wet granulation approach, which produced technologically acceptable formulations. The stable formulations that were ultimately developed included an inner phase of API, diluents, disintegrants, to be granulated with a binder solution (e.g., povidone), and an external phase with lubricant and glidant. I also designed processes to minimize the agglomeration of API/diluent achieving proper flowability behavior. See, e.g., Example 8 in the specification.

[8] Liquid phase

An example of a liquid phase that performed effectively, and which was the liquid phase I ultimately developed, employed methylcellulose and povidone as suspending agents in presence of parabens (methyl p-hydroxybenzoate and propyl p-hydroxybenzoate) as preservatives and phosphates as buffers. The main challenge was to attain an acceptable balance of the following: (i) a composition viscosity that could suspend the granulate, (ii) maintaining the API in suspension for the duration of use and (iii) having a manageable reconstituted suspension from the point of view of the patient. Additionally, maximizing contact time with the target tissue was desired for efficacy. The main parameters under consideration were i) viscosity, ii) pH, iii) parabens activity. In particular, the antimicrobial activity of parabens, and its relationship to their ratios and

percentage, was the subject of a thorough investigation using the challenge test. Also, the recovery after reconstitution of the suspension needed to be evaluated to determine to amount of overfilling in order to guarantee to amount to be delivered by the patient.

[9] Packaging

I evaluated and selected various options to identify packaging that could house the reconstitutable suspension. The challenge was to find packaging able to contain the amount of solid phase needed to meet the dosing requirements. Ultimately, it was decided to put the solid phase in a sachet and the liquid phase in a bottle. The patient would only then need to combine the two phases and shake the suspension before use. We evaluated also gelatin capsules as an alternative container for solid phase, but this option was precluded especially for the 450 mg dose due to the relatively high total amount of the solid phase (909mg).

It was also necessary to dedicate time to the selection of the rectal cannula to be inserted on the bottle before patient use.

[10] Timing

Using the above-described development effort (which was not the first development effort), four to five months were required just to obtain GLP batches for rabbit pre-clinical study. An additional month was required to produce the technical batches. An additional 3-6 months were then required to obtain 2 liquid phase and 1 solid phase (150 mg strength) clinical batches and the final approval for the packaging of the patient kit.

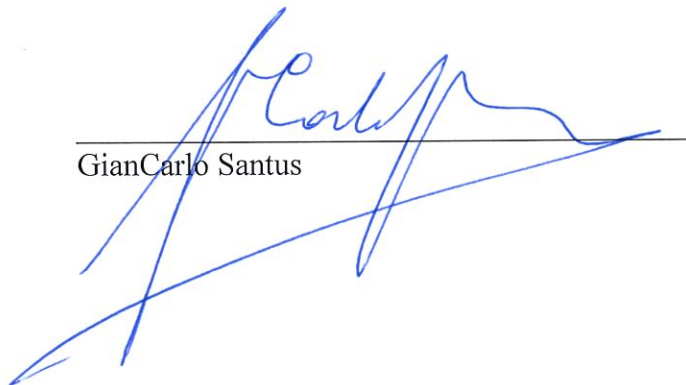
[11] The claimed formulations solved, to the best of my knowledge, previously unknown formulating/packaging problems associated with rectal delivery of niclosamide as a suspension by enema.

[12] I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title XVIII of the Unites States

Code and the willful false statements may jeopardize the validity of this application for patent or any patent issuing thereon.

Respectfully submitted,

Date: Sept. 17, 2018


GianCarlo Santus