Examiners' Report Paper A 2015 (Chemistry)

1. Introduction

The application pertains to the improved treatment of facial wrinkles. According to the client, the current practice of injecting botulinum toxins into the muscle efficiently reduces wrinkles. However, three disadvantages of the botulinum injection are identified: (1) the botulinum protein has to be injected into the muscle by a specialised medical doctor, (2) the treatment is unpleasant and can cause side effects like inflammation, (3) the half life is relatively short and the treatment needs to be repeated every three to six months. The present invention tries to overcome these issues.
The client suggests that the botulinum protein can be coupled to a polymer to form a conjugate, and the botulinum protein or the conjugate can be provided as a nanoemulsion. The experimental data in table 2 and 3 make it plausible that some conjugates and nanoemulsions can solve the first two issues, while a prolonged activity -compared to a botulinum injection- could not be achieved.

The client indicates that polyethylene glycol (PEG) is a preferred polymer and mentions that only conjugates wherein PEG has an average molecular weight of 2000 to 15000 Da are suitable for the treatment of wrinkles. In the description, the client specifies two other polymers, polyvinylpyrrolidone and hyaluronic acid. It is, however, evident from the experimental data in Tables 2 and 3 that their use causes unacceptable side effects or does not show the required activity.

The conjugates are applied on the face in the form of a cream.
A cream comprising un-conjugated botulinum protein and an aqueous solution comprising the botulinum-PEG conjugate of the present application for the cosmetic treatment of wrinkles is disclosed in document D1. It is further mentioned that the conjugate has an increased half-life compared to the un-conjugated botulinum when injected into the muscle. D1 speculates about self-administration of the conjugate and the usage of nanotechnology in the future. However, D1 is silent about a nanoemulsion, or a cream that comprises the conjugate.

In the letter, the client describes processes to generate nanoemulsions starting from an aqueous phase, which contains the botulinum protein or the conjugate and an oil phase, which optionally contains a surfactant. The client mentions that methods for producing nanoemulsions are known to the skilled person and that high shear forces must be generated to form nanoemulsions. From D2 it is known that high shear forces are generated by exposing a mixture of an oil phase and an aqueous phase to a pressure of more than 1000 bar. The client describes that he uses a particular process, wherein both phases are mixed and subjected to pressures of at least 1000 bar during a period of from 30 seconds to 10 minutes using a microfluidiser. The client indicates that the particle size has an impact on the efficacy of the treatment. It is evident from example 3 and table 1

that the particle size can be tailored by choosing the ratio of the aqueous phase and the oil phase as well as the ratio of surfactant and oil.

The document D2 deals with nanoemulsions based on proteins and refers to methods for producing such nanoemulsions. In the working example a nanoemulsion is formed by microfluidising an oil phase and an aqueous phase comprising botulinum protein. The nanoemulsion can be applied to the facial skin of a patient in form of a cream. D2 does not mention the conjugates of the present application.

The client's letter provides many embodiments, which can be used for dependent claims.

2. Independent claims

A first product claim could read as follows:
Nanoemulsion comprising a botulinum protein – polyethylene glycol (PEG) conjugate, wherein the PEG has an average molecular weight of from 2000 to 15000 Da.

25 marks are available for this claim. The average molecular weight is essential. Claims without this limitation lose 8 marks. Claims that only refer to medium-weight PEG lose 2 marks. Limitation to the preferred range of 5000 to 10000 Da leads to a deduction of 5 marks. Defining the droplet diameter of less than 1000 nm or defining the nanoemulsion as containing oil and/or water does not change the scope of the claim and no marks are deducted. 2 marks are deducted for reciting surfactants. Candidates who define the average droplet diameter as less than 500 nm or less than 100 nm, or who specify that all droplets have the same size lose up to 8 marks. Candidates who also claim botulinum conjugates with polypyrrolidone or hyaluronic acid lose up to 10 marks, since such conjugates are not suitable for the treatment of wrinkles. For claims that do not recite PEG at all, a maximum of 10 marks are awarded.
For limitations including the intended non-medical use, or restricting to a specific weight ratio of surfactant and oil 4 marks are deducted. In the present case, it is inappropriate to draft the claim as a product by process claim or to recite the two phases in combination with the weight ratio of surfactant to oil as 2:1 or more as in paragraph [0014] which refers to the production of nanoemulsions. Such claims are worth a maximum of 10 marks. Minor clarity issues result in a loss of 2 marks. Candidates who present a claim that is not novel receive no marks for such a claim.

A further product claim is expected and could read as follows:
Cream comprising the nanoemulsion of claim 1, or a botulinum protein – PEG-conjugate wherein the PEG has an average molecular weight of from 2000 to 15000 Da.
Alternatively, the claim could be drafted as a composition containing the cream comprising the nanoemulsion of claim 1, or a botulinum protein – PEG-conjugate wherein the PEG has an average molecular weight of from 2000 to 15000 Da.
Such a claim is worth 20 marks. Restricting the claim to one alternative results in a deduction of 5 marks.

Candidates who limit the claim by defining further components of the cream lose 4 marks per component. Candidates who do not restrict to the average molecular weight of from 2000 to 15000 Da lose 5 marks.
For further limitations marks are deducted as detailed for the nanoemulsion claim.
Candidates who draft two independent claims, one for each alternative, or who draft an independent claim for a cream comprising the botulinum protein – PEG-conjugate and a dependent claim for a cream comprising the nanoemulsion can also receive full marks.

Candidates who have both a nanoemulsion claim and a cream claim and who unnecessarily restrict to the same features in the nanoemulsion claim and the cream claim lose marks only once.

Candidates are also expected to draft the following kit claim:
Kit comprising the cream of claim 2 and an application pipette.

5 marks are available for this claim. Candidates who do not indicate the presence of the application pipette or who limit to an intended use lose 2 marks. Further limitation results in a loss of 2 marks. A maximum of 2 marks is available for drafting the kit as a use claim.

Also a claim to a cosmetic treatment is expected and could be drafted following the wording of claim 3 of D2:
Method for the cosmetic treatment of wrinkles, wherein the cream of claim 2 is applied to a person’s face.

10 marks are available for this claim. Candidates lose 5 marks when the claim contravenes Article 53(c) EPC or when a clear second medical use claim is presented. It is clear from applicant’s letter that the treatment of wrinkles is purely cosmetic and there is no hint to a treatment by therapy or surgery. Candidates who limit the claim to, e.g., an administration interval lose 3 marks per limitation.

Finally, a method claim could be drafted as follows:
Method for producing a nanoemulsion according to claim 1, comprising the following steps: (a) mixing of an oil phase and an aqueous phase comprising the botulinum-PEG conjugate, (b) exposure of the mixture to a pressure of more than 1000 bar.

Such a claim is worth 10 marks.

Candidates who present a claim reading a method for producing a nanoemulsion according to claim 1, comprising the following steps: (a) mixing of an oil phase and an aqueous phase comprising the botulinum-PEG conjugate, (b) exposure of the mixture to a pressure of more than 1000 bar for a period of from 30 seconds to 10 minutes using a microfluidiser receive up to 8 marks.
The combination of the technical features “mixing both phases”, “at least 1000 bar” and “from 30 seconds to 10 minutes” and using a microfluidiser is essential. For this

embodiment, candidates lose 2 marks for each essential feature that is not present in the claim. Limitation of the method by further features such as the ratio of the phases, the non-optional presence of a surfactant or recitation of a volume percentage of a phase leads to a deduction of 2 marks for each limitation. For method claims that are not unified with the product claims up to 5 marks are deducted.

Claims that do not express the general inventive concept of using a botulinum-PEG-conjugate for applying on the facial skin do not receive any marks. No marks are awarded for suggesting a divisional application.

No marks are available for additional first or second medical use claims. It is clear from applicant's letter that the treatment of wrinkles is purely cosmetic and there is no hint to a treatment by therapy or even surgery.

Some candidates present a claim reciting a conjugate of botulinum-PEG per se. This claim is not novel over D1 and does not attract any marks.

In many instances two or more independent claims to the nanoemulsion or the process of producing the nanoemulsion were drafted, for instance, a nanoemulsion comprising the botulinum protein-PEG conjugate and a nanoemulsion defined as a product-by process. A choice needs to be made when drafting the independent claims. In accordance with the previous years, marks are only awarded for the independent claim with the lowest number of marks.

3. Dependent claims

The paper mentions a number of preferred embodiments which could form the basis for dependent claims.
A good fall back position which is also supported by experimental data is the specification of the average droplet diameter of the nanoemulsion. 3 marks are available for specifying that the average droplet diameter is 100 +/- 10 nm.
1 mark is available for an average droplet diameter of less than 500 nm.
1 mark is available for a PEG with an average molecular weight of 5000 to 10000 Da.
2 marks are available for a cream that comprises further components, as for example shown in the example set of claims.
3 marks are available for the preferred method wherein the ratio of surfactant : oil is 2:1 or more.
2 marks are available for specifying that at least 90 vol% of the aqueous phase and 10 vol% or less of the oil phase is used.
1 mark is available for a cosmetic treatment wherein the cream is applied using a pipette.
Other useful dependent claims, forming relevant fall-back positions, are worth up to 2 marks.
A maximum of 15 marks is available for dependent claims.

When an independent claim recites optional or preferred features no marks are available for the optional features.

4. Description

15 marks are available for the description.
4 marks are available for summarising D1 and D2, 6 marks for defining the problem. Finally, up to 5 marks are awarded for deleting irrelevant matter, referring to the claims and transforming the letter into a real description.

Quite a number of answer papers have problems drafting a proper description. Often the discussion of the prior art is presented as a formal problem-solution approach. As a consequence, the basic idea of the invention is already included in the introduction and appears to be obvious. It is expected that the background art is indicated and the technical problem is discussed.

5. Model claims

1. Nanoemulsion comprising a botulinum protein – polyethylene glycol (PEG) conjugate, wherein the PEG has an average molecular weight of from 2000 to 15000 Da.

2. Nanoemulsion according to claim 1, wherein the PEG has an average molecular weight of from 5000 to 10000 Da.

3. Nanoemulsion according to claim 1 or 2, wherein the average droplet diameter is less than 500 nm.

4. Nanoemulsion according to any of claims 1 to 3, wherein the average droplet diameter is 100 +/- 10 nm.

5. Nanoemulsion according to any of claims 1 to 4, wherein the droplets have the same size.

6. Cream comprising the nanoemulsion of any of claims 1 to 5, or a botulinum protein – PEG-conjugate wherein the PEG has an average molecular weight of from 2000 to 15000 Da.

7. Cream according to claim 6 comprising one or more compounds selected from the group consisting of thickeners, colorants, perfumes, vitamin C, retinol, collagen or coenzyme Q.

8. Kit comprising the cream of claim 6 or 7, and an application pipette.

9. Method for the cosmetic treatment of wrinkles, wherein the cream of claim 6 or 7 is applied to a person’s face.

10. Method according to claim 9, wherein the cream is applied using a pipette.

11. Method for making a nanoemulsion according to any of claims 1 to 5, comprising the following steps:
    (a) mixing of an oil phase and an aqueous phase comprising the botulinum-PEG conjugate, and
    (b) exposing the mixture to a pressure of more than 1000 bar.

12. Method according to claim 11, wherein the surfactant is lecithin.

13. Method according to claim 11 or 12, wherein the ratio surfactant to oil is 2 to 1 or more.

14. Method according to any of claims 11 to 13, wherein the aqueous phase is at least 90 vol% and the oil phase is 10 vol% or less.

15. Method according to any of claims 11 to 14, wherein a microfluidiser is used.