Examiners' Report Paper A 2016 (Chemistry)

1. General considerations

The invention described in the client's letter is about biodegradable polyalkyl 2-cyanoacrylate (PACA) nanoparticles entrapping peptide biopharmaceuticals such as metabolic peptides, specifically insulin.

The client's letter clearly addresses the problem of administering insulin by the oral route in the treatment of diabetes ([001]).

This problem comprises two aspects, that of preserving insulin integrity and bioactivity during passage through the stomach, and that of improving intestinal absorption to achieve an effective therapeutic effect of lowering elevated blood glucose levels for a prolonged period after oral administration ([008], [017]). This is of relevance for the design of pharmaceutical dosage forms for oral administration for the treatment of diabetes.

2. Contribution and scope of the claims

The client's letter describes the preparation of insulin-loaded PACA nanoparticles ([027]).

In figure 1 of the client's letter, compositions B, E, J, L and N are shown to achieve various degrees of reduction of blood glucose levels after oral administration compared to the control, which are maintained over a prolonged period of time. It is stressed that the prolonged duration of this effect is indicative of enhanced insulin absorption in the small intestine, which is advantageous for maintaining physiological insulin levels ([030]), and hence for treatment of diabetes, such as type 2 diabetes ([034]).

Documents D1 and D2 both disclose insulin-loaded PACA nanoparticles.

D1 describes PACA nanoparticles prepared by polymerisation of isobutyl 2-cyanoacrylate which can entrap and transport insulin for intestinal absorption by oral administration for the treatment of type 2 diabetes. D1 implicitly suggests the suitability of other alkyl 2-cyanoacrylates by indicating that “the rate of biodegradation of polyalkyl cyanoacrylates (PACA) depends on the length of the alkyl chain”. In D1, the PACA nanoparticles are made by interfacial polymerisation.

The client’s letter mentions interfacial polymerisation ([020]), but it only describes a method for the preparation of PACA nanoparticles by anionic polymerisation ([021]-[026] and examples).

D2 describes insulin-loaded PACA nanoparticles made by anionic polymerisation of ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate.

While PACA nanoparticles prepared by polymerisation of alkyl 2-cyanoacrylates other than isobutyl 2-cyanoacrylate, ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate would be novel over D1 and D2, the client’s letter clearly indicates that short chain alkyl 2-cyanoacrylates, such as C_6 alkyl or lower, are preferred in view of the rates of polymer degradation ([018]). A claim to PACA nanoparticles not covering the polymers of alkyl 2-cyanoacrylates having C_6 alkyl or lower would be against the client’s explicit instructions.

In D2, the question of the release properties of PACA nanoparticles entrapping various bioactive peptides, including insulin, is addressed. It is disclosed that formation of covalent peptide-polymer bonds may cause large amounts of the peptide entrapped in the nanoparticles to remain unreleased, this being an undesirable effect impairing the bioactivity and therapeutic effectiveness of PACA nanoparticles.

For insulin, however, no covalent peptide-polymer interactions are reported, and it is explained that insulin does not interfere with the polymerisation reaction at pH 5. Strikingly different results are obtained when the polymerisation reaction is carried out at pH 1.9. In that case, the PACA nanoparticles are unstable and have an unacceptably low insulin loading ([007] of D2).

From D2, candidates should have realized that the insulin-loaded polyethyl 2-cyanoacrylate and poly-n-butyl 2-cyanoacrylate nanoparticles prepared at pH 5 anticipate the compositions A and B of example 1 of the client's letter. The unstable nanoparticles prepared at pH 1.9 anticipate the compositions I and K of example 3 of the client's letter.

The client's letter highlights the unexpected results observed for the encapsulation of insulin when the anionic polymerisation is carried out at pH 2 or less. Under these conditions, a non-covalent complex of insulin with PACA is formed during the polymerisation reaction, which is then entrapped within the PACA nanoparticles ([028], [029]). These nanoparticles have the surprising advantage of releasing insulin slowly over a prolonged period, and allowing enhanced intestinal absorption of insulin. This results in therapeutically effective insulin concentrations in the blood for longer periods ([030]).

However, surface stabilisation of the PACA nanoparticles using a pharmaceutically acceptable stabiliser, such as dextran, chitosan or pectin, is required in order to achieve sufficient insulin loading ([031], [032]).

It is emphasised in the client's letter that efficient nanoparticle stabilisation also depends on the alkyl chain length of the alkyl 2-cyanoacrylate monomers ([032]). In example 3 (table 3), it is shown that PACA nanoparticles prepared from 2-octyl 2-cyanoacrylate cannot be effectively stabilised by using a pharmaceutically acceptable stabiliser ([042]), and they exhibit an unacceptably low insulin loading.

Thus, it should have been clear to the candidates that the evidence provided by the client points at a new technical contribution related to the possibility of maintaining a pharmacologically effective reduction of blood glucose levels over a prolonged period of at least 12 hours after oral administration (figure 1, compositions J, L, N).

The client's letter does not identify the chemical nature of the non-covalent complex more accurately, and the candidates were not expected to try to define in their answers the non-covalent complex more precisely than the client's letter allows. It

was sufficient to realize that a non-covalent complex of insulin with PACA is disclosed neither in D1 nor in D2.

3. Independent claims

A total of **70 marks** are available for the independent claims.

The candidates were expected to propose independent claims directed to:

a) Biodegradable insulin-loaded PACA nanoparticles entrapping insulin in the form of a non-covalent complex with PACA and comprising a pharmaceutically acceptable stabiliser.

b) A method for preparing biodegradable insulin-loaded PACA nanoparticles by anionic polymerisation according to paragraph [021] of the client's letter carried out at pH of 2 or less in presence of a pharmaceutically acceptable stabiliser.

c) A pharmaceutical oral dosage form comprising the biodegradable insulin-loaded PACA nanoparticles.

d) Biodegradable insulin-loaded PACA nanoparticles, or a pharmaceutical oral dosage form comprising them, for use as a medicament, or more specifically, for use in a method of treatment of a metabolic disease such as diabetes.

The categories of claims a), b) and c) are clearly required by the client's instructions ([014]) in order to protect all aspects of his technology. D1 contains examples of claim wording which should have provided the candidates with an indication of the categories and types of claims which were expected. It is emphasised that candidates are encouraged to look for pointers provided throughout the paper, including the prior art, and not only in the client's letter.

3.1. Product claim (nanoparticles)

A maximum of **32 marks** can be awarded for an independent product claim. The claim can read:

Biodegradable polyalkyl 2-cyanoacrylate (PACA) nanoparticles comprising a (homo)polymer of a C_2-C_6 alkyl 2-cyanoacrylate, a pharmaceutically acceptable stabiliser (selected from dextran, chitosan or pectin), and insulin (or a synthetic analogue of insulin) entrapped therein, wherein insulin is in the form of a non-covalent complex with PACA, and wherein the nanoparticles have a hydrodynamic diameter of 10 nm to 300 nm as measured by dynamic light scattering.

An independent product claim defining the insulin-loaded PACA nanoparticles in product-by-process terms is also possible, since it is the method of manufacturing by anionic polymerisation at pH of 2 or less in presence of a pharmaceutically acceptable stabiliser that confers the inventive properties of the nanoparticles.

However, it is established case law that a product-by-process claim is only acceptable when it is impossible to define the claimed product other than in terms of a process of manufacture (Case Law of the Boards of Appeal of the EPO, 7th edition 2013, II.A.7.3). Candidates were expected to be familiar with these provisions. In the present paper, it is possible to define the PACA nanoparticles using only structural product features, namely “PACA nanoparticles entrapping insulin in the form of a non-covalent complex” ([030]). Thus, a product-by-process claim attracts at the most only 22 marks of the 32 marks available.

The set of claims has to meet the requirements of Rule 43(2) EPC. If the set of claims contains more than one independent product claims to the insulin-loaded PACA nanoparticles, only the worst claim receives marks.

A claim lacking novelty over D1 and/or D2 attracts no marks.

Insulin-loaded polyisobutyl 2-cyanoacrylate nanoparticles prepared by interfacial polymerisation, as disclosed in D1, as well as insulin-loaded polyethyl 2-cyanoacrylate and poly-n-butyl 2-cyanoacrylate nanoparticles made by anionic polymerisation at pH 5, as described in D2, both comprise insulin in free form ([028]). According to the client's letter, a non-covalent complex of insulin with PACA is only formed during anionic polymerisation at pH of 2 or less ([029]). Thus, the feature "non-covalent complex" is necessary to establish novelty over D1.

The unstable polyethyl 2-cyanoacrylate and poly-n-butyl 2-cyanoacrylate nanoparticles disclosed in D2 having irregular shape and low insulin loading obtained at pH 1.9 comprise a non-covalent complex of insulin with PACA. The formation of a non-covalent insulin-PACA complex, is inherent to the method of anionic polymerisation at pH 2 or lower ([028], [029], [031]), irrespective of whether or not the nanoparticles are stable. Thus, the feature "pharmaceutically acceptable stabiliser" is necessary to establish novelty over D2.

The feature "pharmaceutically acceptable stabiliser" alone establishes novelty over D2, but not over D1, which also discloses incorporating a pharmaceutically acceptable stabiliser into the nanoparticles ([006] of D1).

Any attempts to establish novelty over D1 and D2 only by excluding PACA nanoparticles prepared from isobutyl 2-cyanoacrylate, ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate, e.g. limiting to alkyl 2-cyanoacrylate monomers having C_6 alkyl or higher, do not help. Such an unduly restricted claim having merely formal novelty would only cover trivial alternatives and non-working embodiments, while simultaneously excluding the client's preferred PACA nanoparticles comprising ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate ([018]). No marks are awarded for such a claim.

Candidates were expected to claim novel subject-matter which also provides a credible solution to the technical problem which can be formulated on the basis of the evidence provided in the client's letter. This is emphasised by the client's wish to avoid any delay in examination, i.e. to avoid any objection of lack of inventive step by

the Examining Division. This sets the boundaries of the subject-matter which is to be claimed in order to attract full marks.

Though the client's letter refers in several passages to peptide biopharmaceuticals in general, more particularly metabolic peptides, it should have been clear to the candidates that the only enabling disclosure provided by the inventors relates to the preparation of insulin-loaded PACA nanoparticles.

The information in the client's letter does not make plausible that the technical effect underlying the invention, i.e. providing prolonged intestinal absorption of insulin for maintaining pharmacological action over at least 12 hours after oral administration, might be extrapolated to any other metabolic peptides. Rather, the contrary is true. The client's letter explains that formation of a non-covalent complex of insulin with PACA depending on pH is related to the physicochemical properties of insulin ([029]). The client's letter does not provide any basis for assuming any specific physicochemical properties for metabolic peptides other than insulin, and it provides no specific examples showing any other metabolic peptides but insulin.

Furthermore, D2 should have discouraged the candidates from making unfounded assumptions in this regard, as it clearly identifies a different physicochemical behaviour for secretin (one of the metabolic peptides mentioned in the client's letter) entrapped in PACA nanoparticles, namely the formation of covalent peptide-polymer bonds (independently from pH), which impairs peptide release, bioactivity and therapeutic effectiveness ([005] of D2). Only synthetic analogues of insulin can be assumed to behave like insulin, and the term "insulin" as used in the client's letter actually embraces them ([013]).

Thus, candidates were expected to regard the statements in the client's letter relating to other metabolic peptides apart from insulin as merely speculative. An unduly broad claim to PACA nanoparticles entrapping "metabolic peptides" based only on speculative, unsupported assumptions results in a loss of 15 marks.

PACA nanoparticles prepared by anionic polymerisation of alkyl 2-cyanoacrylate having C_8 alkyl or higher at pH 2 or less are clearly regarded in the client's letter as

non-working embodiments since efficient nanoparticle stabilisation is not feasible (table 3, [042]). Thus, the expected claims must be limited not to encompass C_8 alkyl or higher, e.g. by defining the range "C_2-C_6 alkyl" or "C_6 alkyl or lower" ([015], [018]). 10 marks are detracted for a claim comprising C_8 alkyl or higher.

Dextran is the pharmaceutically acceptable stabiliser used in the examples, yet the client's letter sets out clearly that at least chitosan and pectin are also used for this purpose with same good results as dextran ([032]). An undue restriction to dextran results in a loss of 10 marks.

The client's letter sets out clearly that only PACA nanoparticles having a hydrodynamic diameter of 300 nm or less as measured by dynamic light scattering are suitable for intestinal absorption ([016]), which is essential for solving the underlying technical problem of releasing insulin over a prolonged period after oral administration. Thus, candidates were expected to create the range "10 nm to 300 nm" from the values given in the client's letter. If this essential feature is missing, or if the broader range "10 nm to 500 nm" covering non-working embodiments is claimed, either directly or in product-by-process terms, 15 marks are detracted. However, it is also possible to claim a hydrodynamic diameter of "300 nm or less" without losing marks, since no particular significance is given in the client's letter to the value 10 nm. An undue restriction to a narrower range of "100 nm to 300 nm" results in a loss of 8 marks.

The independent product claim does not need to be limited by a parameter such as the insulin loading. Table 3 in the client's letter shows that PACA nanoparticles prepared from C_2-C_6 alkyl 2-cyanoacrylate and comprising a pharmaceutically acceptable stabiliser (compositions J, L and N) inherently exhibit, by virtue of the process of manufacturing, the required minimum insulin loading of at least 10% by weight defined in the client's letter as being sufficient for a significant pharmacological effect ([024]). There is no need to provide this minimum value in the wording of the claim. However, marks are not detracted for doing so.

3.2. Method claim

A maximum of **24 marks** can be awarded for an independent method claim. The claim can read:

A method for producing biodegradable polyalkyl 2-cyanoacrylate (PACA) nanoparticles comprising insulin entrapped therein, comprising the steps of:

a) dissolving a therapeutically effective amount of insulin in an acidic aqueous solution having a pH of 2 or less and comprising a pharmaceutically acceptable stabiliser (selected from dextran, chitosan or pectin);
b) mixing the aqueous solution with an oil and a nonionic surfactant and stirring to form a water-in-oil nanoemulsion;
c) dissolving a C_2-C_6 alkyl 2-cyanoacrylate monomer in an organic solvent;
d) slowly adding the organic solution of the monomer from step c) to the nanoemulsion from step b) under continuous stirring thereby spontaneously initiating polymerisation;
e) allowing polymerisation to progress and the organic solvent to evaporate, thereby producing PACA nanoparticles;
f) separating the nanoparticles from the nanoemulsion and purifying them.

The use of a pharmaceutically acceptable stabiliser in step a) is an essential feature. Failure to indicate this feature results in lack of novelty over the anionic polymerisation method of D2 carried out at pH 1.9. No marks are awarded in that case.

The feature “pH 2 or less” is essential for the formation of a non-covalent complex of insulin with PACA ([028]).

There is no basis in the client’s letter for generically claiming a “pH below the isoelectric point” for any possible metabolic peptides. The formation of a non-covalent complex with PACA is due to the physicochemical properties of insulin specifically, and clearly requires a pH of 2 or less ([029]). Further, claiming a “pH

below the isoelectric point" would result in lack of novelty over D2 which describes a pH of 5, lower than the isoelectric point of insulin. Such a claim attracts no marks.

Claiming the broader pH range of 1 to 6 ([026]), together with a pharmaceutically acceptable stabiliser, would cover merely trivial variations of the method of anionic polymerisation at pH 5 disclosed in D2, as demonstrated in the client's letter. This is penalised with a loss of 16 marks.

From the client's letter, it is also clear that the formation of a non-covalent complex of insulin with PACA is due to the "mechanism of anionic polymerisation" ([029]). There is no basis to speculate that a non-covalent complex could be also formed by interfacial polymerisation. Thus, the method claim should ideally include the steps a)-f) of paragraph [021] of the client's letter, or at least indicate that the polymerisation is carried out by "anionic polymerisation" (wherein the aqueous phase has a pH of 2 or less and comprises a pharmaceutically acceptable stabiliser). Failure to indicate this essential feature results in a loss of 12 marks.

It is not necessary to indicate the non-essential feature "0.5-1% by weight" of a pharmaceutically acceptable stabiliser which according to the client's letter is only a typical concentration ([025]). 5 marks are lost for this undue limitation.

If a reason for a loss of marks (a missing essential feature, an undue limitation or a lack of clarity) applies both to the independent product claim and to the independent method claim, marks are detracted only once, from the product claim (no double penalty).

3.3. Subsidiary product claim (pharmaceutical oral dosage form)

A maximum of **8 marks** can be awarded for an independent product claim directed to a pharmaceutical oral dosage form comprising the inventive insulin-loaded PACA nanoparticles. The claim can read:

(Pharmaceutical) oral dosage form, or (pharmaceutical) dosage form for oral administration, comprising the biodegradable insulin-loaded PACA nanoparticles as claimed in claim x (and pharmaceutically acceptable excipients).

3.4. Medical use claim

A maximum of **6 marks** can be awarded for an independent purpose-limited product claim according to Article 54(4) or 54(5) EPC directed to the inventive insulin-loaded PACA nanoparticles, or to a pharmaceutical oral dosage form comprising them, for use in a method of medical treatment. The claim can read:

Biodegradable insulin-loaded PACA nanoparticles as claimed in claim x, or a (pharmaceutical) oral dosage form comprising them as claimed in claim y, for use as a medicament, or specifically, for use in a method of treatment of a metabolic disease or disorder associated with elevated blood glucose levels by oral administration, or more specifically, for use in a method of treatment of diabetes by oral administration.

No marks are detracted if a more generic use (“as a medicament”), or a more specific disease (“diabetes”), are indicated in the claim. Both options are regarded as providing convenient medical use claims. If both claim types are present, the available 6 marks are split between them.

Full marks are also awarded for a claim to the insulin-loaded PACA nanoparticles, or to an oral dosage form comprising them, for use in a method of providing insulin to patients in need thereof, such as diabetes patients ([034]). Such a claim is regarded as being directed to an acceptable purposive limitation pursuant to Article 54(5) EPC.

The client’s letter emphasises the use of the biodegradable PACA nanoparticles of the invention for the treatment of metabolic diseases, in particular diabetes, by oral administration. If the essential feature “by oral administration” is not indicated, 2 marks are lost, since this is actually the specific medical use which the invention makes available.

4. Dependent claims

Up to **15 marks** are available for dependent claims providing solid fall-back positions. For example: alkyl 2-cyanoacrylate monomers for which best results are shown in example 3 including not only the preferred ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate but also n-hexyl 2-cyanoacrylate (3 marks); preferred nanoparticle size distribution of at least 90% between 100 nm and 300 nm (2 marks); insulin loading of 10% to 30% by weight (2 marks); specific pharmaceutically acceptable stabilisers (2 marks); amount of 0.5-1% by weight of stabiliser in the aqueous solution (1 mark); tablets or capsules (1 mark); coating on the oral dosage form (2 marks); treatment of type 2 diabetes (2 marks).

5. Description

Up to **15 marks** are available for a proper description of the invention, including a discussion of the prior art D1 (3 marks) and D2 (4 marks). Emphasis has to be given to D2 (previous results of the inventors) in order to identify and discuss the technical contribution described in the client's letter, namely the new and surprising properties of insulin-loaded PACA nanoparticles made by anionic polymerisation at pH of 2 or less in presence of a pharmaceutically acceptable stabiliser with regard to prolonged insulin release and enhanced intestinal absorption, resulting in the possibility of maintaining a significant pharmacological effect for longer periods after oral administration. 5 marks are awarded for a full discussion including all the aforementioned aspects with reference to the comparative results shown in figure 1 (compositions J, L, N). Finally, the relevant passages in the client's letter have to be adapted to include the limitations to insulin, pH of 2 or less, and the use of a C_2-C_6 alkyl 2-cyanoacrylate and a pharmaceutically acceptable stabiliser (3 marks).

EXAMINATION COMMITTEE I

Paper A (Chemistry) - 2016 - Marking Sheet

Category		Maximum possible
Independent claims	Product claim	32
	Method for preparing the nanoparticles	24
	Oral dosage and medical use	14
Dependent claims		15
Description		15
Total		100