* **IN THE HIGH COURT OF DELHI AT NEW DELHI**

% Judgment delivered on: 24/11/2025

\+ **C.A.(COMM.IPD-PAT) 76/2022**

AMYLIN PHARMACEUTICALS, LLC AND ANR. ....Appellants

versus

ASSISTANT CONTROLLER OF PATENTS AND DESIGNS .....Respondent

Advocates who appeared in this case

For the Appellants : Mr. Saransh Vijay with Mr. Daksh Oberoi, Advocates.

For the Respondent : Ms. Rukhmini Bobde, CGSC with Mr. Amlaan Kumar, Mr. Vinayak Aren and Mr. Jatin Dhamija, Advocates.

CORAM:
HON'BLE MR. JUSTICE TEJAS KARIA

JUDGMENT

TEJAS KARIA, J

1. This is an Appeal under Section 117A of the Patents Act, 1970 ("**Act**") arising out of order dated 10.07.2018 ("**Impugned Order**"), issued by Assistant Controller of Patents and Designs ("**Respondent / Controller**") under Section 15 of the Act rejecting the grant of patent in the matter of the Patent Application No. 1498/DELNP/2011 titled as "*SUSTAINED*

RELEASE FORMULATIONS USING NON-AQUEOUS CARRIERS" ("**Subject Application**").

FACTUAL MATRIX

2. The Appellants, *Amylin Pharmaceuticals, LLC* and *Astrazeneca Pharmaceuticals LP* are corporations of United States of America. The Appellants filed the national phase application with Claims 1 to 32 before the Patent Office, Delhi on 01.05.2011 based on the PCT Application No. PCT/US2009/056058 claiming priority from the US Patent Application No. 61/094,381 dated 04.09.2008.

3. Upon receipt of the First Examination Report dated 29.03.2017 ("**FER**"), the Appellants filed a detailed response to the same on 27.09.2017 along with amended set of claims. Subsequent to the filing of the response to the FER, the Appellants received a hearing notice dated 16.10.2017. The Counsels for the Appellants attended the hearing as scheduled by the learned Controller on 13.11.2017 ("**Hearing**") and filed post-hearing written submissions dated 28.11.2017 ("**Post-Hearing Written Submissions**") along with amended set of claims.

4. Subsequent to the filing of the Post-Hearing Written Submissions along with the amended set of claims, the learned Controller rejected the grant of the Subject Application *vide* order dated 10.07.2018.

SUBMISSIONS ON BEHALF OF THE APPELLANTS

5. The learned Counsel for the Appellants submitted that in the Impugned Order, the Respondent had not considered and failed to appreciate the detailed submissions in respect of objections raised in the Hearing under Sections 2(l)(ja) and 3(d) of the Act, in the Post-Hearing Written Submissions and the amended set of claims as filed along with the Post-

Hearing Written Submissions. Therefore, the Respondent is not justified in holding that the amended Claims 1 to 19 does not fulfill the requirements of Section 2(l)(ja) of the Act i.e., lacks inventive step and also falls under Section 3(d) of the Act.

6. The learned Counsel for the Appellants further submitted that the Respondent failed to understand the fact that the present invention involves inventive step under Section 2(l)(ja) of the Act in view of cited prior art documents, US 2004/0224030 ("**D1**"), US 2008/0146490 ("**D2**"), JAIN R A et al: "*Controlled release of drugs from injectable in situ formed biodegradable PLGA microspheres: effect of various formulation variables*", European Journal of Pharmaceutics And Biopharmaceutics, Vol. 50, No. 2, 01.09.2000, ("**D3**") and WO 2005/102293 ("**D4**"). The Respondent held that it would have been obvious to an ordinary person skilled in the art ("**PSITA**") at the time the invention was made to utilize pre-mixed formulations comprising active pharmaceutical ingredient exenatide and stability agent sugar as taught by document D2 in microsphere delivery systems taught by document D1. The Respondent also holds that particularly, document D1 does not disclose a pre-mixed formulation having dispersed therein about 5% (w/w) exenatide as active pharmaceutical ingredient and about 2% (w/w) sucrose. However, document D2 discloses a pre-mixed formulation having dispersed therein about 5% (w/w) exenatide as active pharmaceutical ingredient and sucrose. Therefore, it would have been obvious to a PSITA at the time of the invention to combine the pre-mixed formulation of document D2 with the invention of document D1 to arrive at the claimed invention without undue experimentation for the

purpose of developing a more stable injectable formulation that has a higher rate of patient compliance due to the pre-mixed nature of the formulation.

7. The learned Counsel for the Appellants submitted that the present invention provides a one-component injectable microsphere formulation which does not require the practitioner to mix the formulation with a pharmaceutically acceptable carrier prior to injection. Additionally, the present invention offers advantages over two-component formulations by providing a long shelf-life of the composition in the carrier, sustained release of the active pharmaceutical ingredient, a less complex carrier, a more easily manufactured carrier, a less complex injection-delivery apparatus, and ease of use by patients.

8. The learned Counsel for the Appellants submitted that D1 does not teach or suggest a non-aqueous carrier comprising one or more triglycerides of C_6 to C_{12} fatty acids. The learned Counsel for the Appellants relied upon Paragraph No. [0062] of D1.

9. The learned Counsel for the Appellants submitted that the Respondent has erred in understanding that the "*injectable oleaginous suspensions*" as set out in Paragraph No. [0068] of Dl, are not equivalent to the instantly claimed non-aqueous carrier. The claims specify that the non-aqueous earner entails triglycerides of C_6 to C_{12} fatty acids. However, after the statement "*injectable oleaginous suspensions*", the specification continues and states that "any bland fixed oil" can be employed as a suspending medium, including synthetic mono or diglycerides. Therefore, Dl is silent regarding any non-aqueous carrier comprising triglycerides, much less the carbon range as set out in Claim 1.

10. The learned Counsel for the Appellants further submitted that the Respondent failed to take into consideration that Dl recites fatty acids such as oleic acid which can be used in the preparation of injectables. Since oleic acid is a fatty acid, it is a long chain triglyceride and thus, Dl teaches away from the specific use of medium chain triglycerides (i.e., C_6 to C_{12}) in a carrier.

11. The learned Counsel for the Appellants submitted that D2 relates to pharmaceutical formulations that avoid the challenges associated with the use of microsphere delivery vehicles as set out in Paragraph Nos. [0015]-[0017] and [0020]-[0021] and teaches away from the use of a polymer-based formulation.

12. The learned Counsel for the Appellants submitted that the Respondent failed to identify and consider that D2 provides disadvantages to the use of polymer-based microspheres and provides advantages to a low-viscosity, homogeneous solution. Nowhere in the disclosure does it teach or suggest a one-component polymer-based formulation. Accordingly, a PSITA would understand that document D2 provides alternative, non-microsphere formulations. The learned Counsel for the Appellants relied upon Paragraph No. [0023] which is reproduced hereunder:

> "***a preformulation*** *comprising:*
> *a)* ***at least one neutral diacyl lipid*** *and/or a tocopherol;*
> *b)* ***at least onephospholipid****;*
> *c) at least one biocompatible, (preferably oxygen containing) organic solvent;*
> *d) at least one GLP-1 analogue....*
> *wherein the pre-formulation forms, or is capable of forming, at least one*
> *liquid crystalline phase structure* ***upon contact with an aqueous fluid.***"

13. The learned Counsel for the Appellants further submitted that the Respondent has failed to consider that a PSITA would understand that Table 4 of D2 provides twenty-one non-microsphere pre-formulations, each featuring at least 39% of a diacyl lipid (GDO), and where nineteen out of twenty-one (i.e., >90%) comprise GDO3, which has the highest diglyceride content (>95% diglycerides) of the three GDO compositions studied. Further, Examples 5 to 9 describe the preparation of low-viscosity lipid / GLP-1 formulations and Examples 10 to 12 describe the use of the pre-formulations for the preparation of depots; none of the examples in the cited reference report the preparation of microsphere formulations for injection. D2 is silent regarding any teaching or motivation that would have led a PSITA to prepare a manufactured premixed polymer-based suspension of a pharmaceutically acceptable non-aqueous carrier comprising one or more esters of C_6 to C_{12} fatty acids and exenatide as an active pharmaceutical ingredient (e.g., the instantly claimed formulations). Therefore, D2 fails to cure the deficiencies of D1. The abovementioned Table 4 is reproduced hereunder:

TABLE 4

Compositions containing GLP-1

Formulation	GLP-1/wt%	PC/wt%	GDO1/wt%	GDO2/wt%	GDO3/wt%	BtOH/wt%	H_2O/wt%
A	0.5	44.75	44.75	—	—	10	—
B	0.5	44.75	—	44.75	—	10	—
C	0.5	44.75	—	—	44.75	10	—

14. The learned Counsel for the Appellants submitted that the Respondent failed to consider D3 which discloses "*a novel in situ method for the preparation of injectable biodegradable poly(lactide-coglycolide) (PLGA) microspheres for the controlled delivery of drugs, the formulation of a stable dispersion of PLGA microglobule*". D3 does not teach or suggest the amended Claim 1 nor would have it have been obvious to PSITA to arrive at Claim 1 through the disclosure of D3 alone, or in any fair combination. D3 does not teach or suggest a non-aqueous carrier.

15. The learned Counsel for the Appellants submitted that the Respondent has failed to consider that D3 provides cytochrome c and myoglobin as the model drug compounds. These are not in the same class of drugs, structurally related, nor possess the same approximate molecular weight. Therefore, PSITA would not look to the teachings of D3 and have a reasonable expectation of success given that D3 is directed to a different class of compounds.

16. The learned Counsel for the Appellants further submitted that the Respondent in the Hearing contended that D3 "*was in fact concerned with the formulation of a stable dispersion of PLGA 24 microglobule. The drug and the polymer are already contained in the microspheres as can be seen from Figure 1 of D3. Additionally, a nonaqueous carrier is contained.*" However, the Appellant disagreed with the Respondent's characterization of the reference as the Respondent is not comparing the final formulation of D3 with the claimed formulation of the Subject Application. Further, Example 3 as disclosed in the specification of the Subject Application illustrates that the microspheres are combined with a non-aqueous carrier as opposed to an aqueous carrier which is described in D3. Furthermore, D3 still lacks the

active ingredient exenatide and it provides the demerits of the non-aqueous carrier, PSITA would not look to D3 to arrive at the present formulation nor have any expectation of success.

17. The learned Counsel for the Appellants submitted that the Respondent failed to consider D4 which generally relates to a composition directed to a release profile characterized by a ratio of C_{max} to C_{ave} of about 3 or less which can be achieved by controlling the coacervating agent to polymer solvent ratio, such as silicone oil to polymer solvent ratio (in the manufacturing process), thereby achieving a low pore volume. According to the Appellants, D4 is not directed to a manufactured pre-mix formulation for injection comprising microspheres suspended in a non-aqueous carrier comprising one or more triglycerides of C_6 to C_{12} fatty acids. D4 does not teach or suggest the use of a non-aqueous carrier and demonstrates that the formulation of D4 can be achieved without the addition of a carrier. Moreover, there is no teaching or suggestion to provide the use of triglycerides, let alone triglycerides of C_6 to C_{12}, to modify the storage and stability properties of a formulation composition of exenatide.

18. The learned Counsel for the Appellants submitted that the Respondent in the Impugned Order has copied entire written submissions of the Appellants with no effort to provide a reasoned formulation of the invention. As under Section 3(d) of the Act, the Respondent has not cited any closest prior art, the Respondent has also not given any counter arguments to the legal submissions of the Appellant with regards to closest prior art. Despite the fact, the Appellant had submitted the data showing better efficacy of the formulation as claimed in the present invention, which the Respondent has not considered and rejected the Subject Application.

19. The learned Counsel for the Appellants submitted that the Appellants have corresponding foreign patents which have been granted in Australia, Canada, China, Japan, Korea, and United States of America.

20. In view of the above, it was submitted that the present Appeal deserves to be allowed and the Impugned Order be quashed and set aside.

SUBMISSIONS ON BEHALF OF THE RESPONDENT

21. The learned Counsel for the Respondent submitted that D1 discloses pharmaceutical compositions that include an effective amount of calcitonin-containing microspheres as mentioned in Paragraph No. [0061] of D1, sterile injectable aqueous or oleaginous suspensions as mentioned in Paragraph No. [0068] of D1, a pharmaceutically acceptable carrier as mentioned in Paragraph No. [0062] of D1, and microspheres having the active pharmaceutical ingredient dispersed therein as mentioned in the Abstract of D1. Document D1 also discloses the active compounds, the liquid dosage forms may contain oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, fatty acid esters of sorbitan, and mixtures thereof as mentioned in Paragraph No. [0072] of D1, sucrose as mentioned in Paragraph No. [0074] of D1.

22. The learned Counsel for the Respondent submitted that the document D1 particularly discloses a manufactured formulation for injection as mentioned in Paragraph No. [0028] of D1 consisting essentially of a suspension of: (i) a pharmaceutically acceptable carrier which consists essentially of one or more triglycerides of C16 fatty acids as mentioned in Paragraph No. [0062] of D1; and (ii) microspheres which consist essentially of a poly(lactide-co-glycolide) ("**PLGA**") polymer wherein the ratio of lactide : glycolide in the polymer is about 1:1 as mentioned in Paragraph No.

[0031] of D1. Though the cited prior art document D1 does not either discloses exenatide and / or specific amounts of sugar and also shelf life or the viscosity of the carrier, D1 is mostly considered for the technical features of the invention as claimed in Claim 1 like carrier which consists essentially of one or more triglycerides of C_{16} fatty acids as mentioned in Paragraph No. [0062] of D1 and microspheres which consist essentially of a PLGA polymer.

23. The learned Counsel for the Respondent submitted that D2 discloses formulation precursors (pre-formulations) for the *in situ* generation compositions for the controlled release of active agents such as Glucagon-like-peptide-1 (GLP-1) and / or analogues thereof, “native GLP-1” indicates human GLP-1(7-37) and / or human GLP-1(7-36) amide and the terms “Liraglutide”, “CJC-1131”, “AVE-010”,and “exenatide” are used to indicate the respective actives as mentioned in Paragraph No. [0013] of D2. The formulations may include from 0.1 to 10% of exenatide as mentioned in Paragraph No. [0053] of D2.

24. The learned Counsel for the Respondent further submitted that document D2 also teaches, exenatide and / or its analogs dissolved in the lipid formulations gain stability (both storage and in vivo stability) by such stabilizing additives as sugars, e.g., sucrose as mentioned in Paragraph No. [0087] of D2. Document D2 also teaches that said formulations may be stored for at least 6 months at room or refrigerator temperature, without phase separation as mentioned in Paragraph No. [0099] of D2. Further, document D2 also teaches precursor formulations comprising active ingredient exenatide that allow controlling initial release of active agent (observed as C_{max}) providing specific relationship between C_{max} and the

total drug exposure (AUC or mean plateau plasma concentration level; as mentioned in Paragraph No. [0099] of D2. Hence, document D2 also teaches the formulations that are “low viscosity” formulations with a typical range of suitable viscosities ranging from 0.1 to 1000 cP at 20° C as mentioned in Paragraph No. [0051] of D2.

25. The learned Counsel for the Respondent further submitted that D3 discloses a novel *in situ* method for the preparation of injectable biodegradable PLGA microspheres for the controlled delivery of drugs as mentioned in the Abstract of D3, the formulation of a stable dispersion of PLGA microglobule. Document D3 also discloses an injectable dispersion of microspheres comprising a drug and PLGA in a continuous phase consisting of triacetin, PEG400 and miglyol as claimed in present invention.

26. The learned Counsel for the Respondent also submitted that D4 discloses compositions for the sustained release of biologically active polypeptides, and methods of forming and using said compositions, for the sustained release of biologically active polypeptides. The sustained release compositions of this invention comprise a biocompatible polymer having dispersed therein, a biologically active polypeptide and a sugar mentioned in the Abstract, Claim 1 of D4.

27. As per the Respondent, it is obvious to PSITA at the time the invention was made to utilize pre-mixed formulations comprising active pharmaceutical ingredient exenatide and stability agent sugar as taught by document D2 in microsphere delivery systems taught by document D1. Document D2 discloses a pre-mixed formulation having dispersed therein about 5% (w/w) as mentioned in Paragraph No. [0053], exenatide as active pharmaceutical ingredient as mentioned in Paragraph No. [0013] and

sucrose as mentioned in Paragraph No. [0087]. However, it would have been obvious to PSITA at the time of the invention to combine the pre-mixed formulation of document D2 with the invention of document D1 to arrive at the claimed invention without undue experimentation for the purpose of developing a more stable injectable formulation that has a higher rate of patient compliance due to the pre-mixed nature of the formulation.

28. The learned Counsel for the Respondent submitted that it is well within the purview of PSITA to include the limitation of 2% (w/w) sucrose since where the general conditions of the claim are disclosed in the cited prior arts, discovering the optimal or workable concentrations involves only routine skill in the art. D1 might have not contained a specific example, but for the evaluation of non-obviousness, the whole content of D1 has to be considered and as Appellants agree that oleic acid is disclosed, which is a C_{18} fatty acid and also the shortest chain length amongst the mixtures of compositions cited in 29 different forms of excipients are esters made from C_{16} acids. However, document D3 was in fact concerned with the formulation of a stable dispersion of PLGA microglobule and also discloses the same microsphere and carriers as claimed in the present invention. The drug and the polymer are already contained in the microspheres as can be seen from Figure 1 of document D3. Additionally, a non-aqueous carrier is also disclosed in the document D3.

29. The learned Counsel for the Respondent submitted that although the Appellants argued many problems cited in the Complete Specification in order to arrive at the present invention but no such results have been disclosed in the Complete Specification except the storage and stability of exenatide and shelf life or the viscosity of the carrier to make the present

invention inventive over the cited prior art documents. Therefore, the instant alleged set of claims are obvious and does not involve an inventive step under Section 2(1)(ja) of the Act considering the prior art documents D1 to D4.

30. The learned Counsel for the Respondent submitted that the present claims are characterized by the formulation comprising non-aqueous carrier comprising triglycerides of C_6 to C_{12} fatty acids and microspheres comprise a PLGA polymer having dispersed therein 1% to 10% (w/w) of exenatide as an active pharmaceutical ingredient and 0.1% to 5% (w/w) sugar. The present invention does not involve inventive step considering the prior art documents D1 to D4 as the pharmacokinetic profile, storage and *in vivo* stability of the exenatide have already been disclosed in the cited prior art documents. The claims relate to a new form of known active substance i.e., exenatide with no improved therapeutic efficacy and shall be considered as the same substance. The pharmaceutical active ingredient exenatide which is used for the treatment of Diabetes Mellitus Type 2 is known from the prior art document D3.

31. The learned Counsel for the Respondent submitted that the Appellants with respect to better pharmacokinetic profile and stability in purity of exenatide is an argument relating to the bio-availability of the claimed exenatide formulation and not its therapeutic efficacy. No therapeutic efficacy data has been disclosed in the present Complete Specification in order to evidence that the claimed formulation of exenatide comprising non-aqueous carrier comprising triglycerides of C_6-C_{12} fatty acids and microspheres comprise a PLGA polymer having dispersed therein 1% to

10% (w/w) of exenatide as an active pharmaceutical ingredient and 0.1% to 5% (w/w) sugar is improved than the earlier known exenatide formulation.

32. The learned Counsel for the Respondent submitted that the grant of patents by other countries will not by itself present a qualification for the grant of a patent in India. The Subject Application has been examined based on the Act and Rules and the Subject Application has been refused based on the present invention disclosed in the prior art documents cited during the prosecutions of the Subject Application. It is pertinent to be pointed out here that post-grant opposition was filed on the corresponding European Patent Application EP2341905 and decided on 31.01.2023 to grant with auxiliary request 9 which is also altogether a different set of claims.

33. Accordingly, the present Appeal is liable to be set aside.

ANALYSIS AND FINDINGS

35. The disclosure under the Subject Application provides formulations comprising microspheres that contain active pharmaceutical ingredients, where the microspheres are suspended in a non-aqueous pharmaceutically acceptable carrier. The formulations are one-component injectable microsphere formulations, such that they do not require the patient to mix the formulation with a pharmaceutically acceptable carrier prior to injection.

36. The carrier consists of one or more triglycerides, which comprise C_6 to C_{12} fatty acids; and microspheres, which consist essentially of a PLGA polymer having dispersed therein about 1% to 10% (w/w) exenatide and about 0.1% to 5% (w/w) of a sugar. The ratio of lactide : glycolide in the polymer under Claim 1 is about 70:30 to 30:70, or about 1:1.

37. The present invention provides a one-component injectable microsphere formulation which does not require the practitioner to mix the

formulation with the carrier used before injection. The Subject Application also has advantages over two-component formulations as it provides a long shelf-life of the composition in the carrier, sustained release of the active pharmaceutical ingredient, and offers ease of use by patients.

38. The important question here is whether the Impugned Order has provided reasoning while rejecting the Subject Application under Section 2(1)(j) of the Act. The relevant portion of the Impugned Order is reproduced hereunder:

> *"Further, cited prior art document D2: US20080146490 discloses formulation precursors (preformulations) for the in situ generation compositions for the controlled release of active agents such as Glucagon-like-peptide-1 (GLP-1) and/or analogues thereof, "native GLP-1" indicates human GLP-l(7-37) and/or human GLP-l(7-36)amide and the terms "Liraglutide", "aC-1131", "AVE-010", and "exenatide" are used to indicate the respective actives (para [0013] of D2). The formulations may include from 0.1 to 10% of exenatide (Para [0053] of D2). Document D2 also teaches exenatide and/or its analogs dissolved in the lipid formulations gain stability (both storage and in vivo stability) by such stabilizing additives as sugars, e.g. sucrose (Para [0087] of D2). Document D2 also teaches that said formulations may be stored for at least 6 months at room or refrigerator temperature, without phase separation (Para [0099] of D2). Document D2 also teaches precursor formulations comprising active ingredient exenatide that allow controlling initial release of active agent (observed as Cmax) providing specific relationship between Cmax and the total drug exposure (AUC or mean plateau plasma concentration level; Para [0099] of D2). Again, document D2 also teaches the formulations that are "low-viscosity" formulations with a typical range of suitable viscosities ranging from 0.1 to 1000 cP at 20° C (Para [0051] of D2).*
>
> *Moreover, cited prior art document D3: JAIN R A ET AL: "Controlled release of drugs from injectable In situ formed biodegradable PLGA microspheres: effect of various formulation variables", EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 50, no. 2,1 September 2000, pages 257-262; discloses a novel in situ method for the preparation of*

injectable biodegradable poly (lactide-co-glycolide) (PLGA) microspheres for the controlled delivery of drugs (abstract of D3), the formulation of a stable dispersipn of PLGA micrdglobule. Document D3 also discloses an injectable dispersion of microspheres comprising a drug and PLGA in a continuous phase consisting of triacetin, PEG400 and miglyol as claimed in present application (fig. 1 of D3). Whereas, cited prior art document D4: W02005102293 discloses compositions for the sustained release of biologically active polypeptides, and methods of forming and using said compositions, for the sustained release of biologically active polypeptides. The sustained release compositions of this invention comprise a biocompatible polymer having dispersed therein, a biologically active polypeptide and a sugar (abstract, claim 1 of D4). As argued by the Applicant the present invention discloses "A manufactured pre-mixed formulation for injection comprising a suspension of (i) a pharmaceuticaliy acceptable non-aqueous carrier comprising one or more triglycerides of C6-C12 fatty acids; and (ii) microspheres which comprise a biocompatible, biodegradable polymer, wherein the microspheres comprise a poly(lactide-co-glycolide)

As argued by the Applicant the present invention discloses "A manufactured pre-mixed formulation for injection comprising a suspension of (i) a pharmaceuticaliy acceptable non-aqueous carrier comprising one or more triglycerides of C6-C12 fatty acids; and (ii) microspheres which comprise a biocompatible, biodegradable polymer, wherein the microspheres comprise a poly(lactide-co-glycolide) polymer having dispersed therein 1% to 10% (w/w) of exenatlde as an active pharmaceutical ingredient and 0.1% to 5% (w/w) sugar".

The problems cited in the complete specification as argued further by the Applicant are the present invention provides a one-component injectable microsphere formulation which does not require the practitioner to mix the formulation with a pharmaceutically acceptable carrier prior to injection. Additionally, the present application offers advantages over two-component formulations by providing a long shelf-life of the composition in the carrier, sustained release of the active pharmaceutical ingredient, a less complex carrier, a more easily manufactured carrier, a less complex Injection-delivery apparatus, and ease of use by patients. Considering the above facts, it is observed that document D1 is silent regarding the use of exenatlde and/or specific amounts of sugar used in said formulations. Document D1 does not teach a

shelf life of formulations and is also silent regarding the viscosity of the carrier. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize pre-mixed formulations comprising active pharmaceutical ingredient exenatide and stability agent sugar as taught by document D2 in microsphere delivery systems taught by document Dl.

, - Particularly, document Dl does not disclose a pre-mixed formulation having dispersed therein about 5% (w/w) exenatide as active pharmaceutical ingredient and about 2% (w/w) sucrose. However, document D2 discloses a pre-mixed formulation having dispersed therein about 5% (w/w) (para [0053]) exenatide as active pharmaceutical ingredient (para [0013]) and sucrose (para [0087]). Document D2 does not explicitly disclose 2% sucrose (w/w).

i" However, It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the pre-mixed formulation of document D2 with the invention of document, Dl to arrive at the claimed invention without undue experimentation for the purpose of developing a more stable injectable formulation that has a higher rate of patient compliance due to the pre-mixed nature of the formulation.

It Is also well within the purview of one of ordinary skill to Include the limitation of 2% (w/w) sucrose since where the general ^ conditions of the claim are disclosed in the cited prior arts, discovering the optimal or workable concentrations involves only routine skill In the art. Applicant further argued "Dl does not teach or suggest a non-aqueous carrier comprising one more triglycerides of C6- C12 fatty acids". Dl might have not contained a specific example, but for the evaluation of non-obviousness, the whole content of Dl has to be considered and as Applicant is already I - agreed that oleic acid Is disclosed which is a CIS fatty acid and also the shortest chain length amongst the mixtures of compositions cited in 29 different forms of excipients are esters IP made from C16 acids. The applicant further argued that document D3 did not disclose a _ manufactured formulation for injection as claimed, which required a non-aqueous carrier.

However, document D3 was in fact concerned with the formulation of a stable dispersion of PLGA microglobule and also discloses the same microsphere and carriers as claimed In the _ present invention. The drug and the polymer are already contained In the microspheres as can be seen from Figure 1 of document D3. Additionally, a non-aqueous carrier is also ^ - disclosed in the said

> *cited document. Although applicant argued many problems cited In the complete specification In order to arrive at the present invention but no such results have been disclosed In the complete specification* except the storage and stability of exenatide and shelf life or the viscosity of the carrier to make the present invention inventive over the cited prior art documents as the said problems are already have been solved in the said prior art documents. *Hence there is no inventive step can be acknowledged. Therefore instant alleged set of claims are obvious and do not involve an inventive step u/s 2(l)(ja) of the Patents Act considering the prior art documents D1-D4. Hence, the objection raised under Invention u/s 2(l)(j) of the hearing notice is not met."*

39. The first problem that the Subject Application solves is that these formulations provide therapeutic amounts of active pharmaceutical ingredients over an extended period of time from a single injection, thereby eliminating the need for daily injections.

40. The relevant portion of the Complete Specification of the Subject Application is reproduced hereunder:

> *"Injectable sustained release formulations offer the opportunity to provide therapeutic amounts of active pharmaceutical ingredients over an extended period of time from a single injection, thus eliminating the need for once or twice daily injections"*

41. The second problem that the Subject Application solves is overcome the large burst release of injectable microsphere formulations following injection, thereby avoid any deleterious side effects.The relevant portion of the Complete Specification of the Subject Application is reproduced hereunder:

> *"Another disadvantage of presently available injectable microsphere formulations is a large burst release following injection, which causes an undesirable in vivo release of active pharmaceutical ingredient in a single burst. When medications have toxic or deleterious side effects, this is undesirable."*

42. Claim 1 of the Subject Application is reproduced hereunder:

> *"We Claim:*
> *1. A manufactured pre-mixed formulation for injection comprising a suspension of*
> *(i) a pharmaceutically acceptable non-aqueous carrier comprising one or more triglycerides of Ce-Cn fatty acids; and*
> *(ii) microspheres which comprise a biocompatible, biodegradable polymer, wherein the microspheres comprise a poly(lactide-co-glycolide) polymer having dispersed therein 1% to 10% (w/w) of exenatide as an active pharmaceutical ingredient and 0.1% to 5% (w/w) sugar."*

43. The learned Controller has rejected the Subject Application on the basis of Section 2(1)(j), more specifically, Sections 2(1)(ja) and 3(d) of the Act. Therefore, it is important to examine whether the claimed invention exhibits an inventive step under Section 2(1)(ja) of the Act, in the light of Documents D1 to D4. This analysis would be carried out in the light of ***Hoffmann-La Roche Ltd. v. Cipla Ltd***., (2016) 65 PTC 1 (Del.), which provides the procedure for assessing the inventive step.

PRIOR ART DOCUMENT D1

44. Document D1, pertains to the microsphere delivery systems in which the microspheres include blended PLGA copolymers and a biologically active agent. The learned Counsel for the Appellants submitted that documents D2 and D3 do not talk about a non-aqueous carrier and the Subject Application have a non-aqueous career, which is not present in documents D1 to D4. It was also submitted that fatty acid, in the main claim of the Subject Application, is not mentioned in D1 to D4. The learned Counsel for the Appellants also referred to Paragraph No. [0062] of D2 and argued that Exenatide is not mentioned in D1.

45. *Per contra*, the learned Counsel for the Respondent, referring to Paragraph No. [0068] of D1, submitted that C_{18} acid is mentioned, and the Appellants are claiming the C_6 to C_{18} fatty acids under the Subject Application. The learned Counsel for the Respondent, therefore, submitted that since document D1 mentions that C_{18} is a career, it is obvious for PSITA to take C_6 to C_{12} fatty acids as a career. The learned Counsel for the Respondent has relied on Paragraph No. [0068] which is reproduced hereunder:

> *"[0068] For example, sterile injectable aqueous or **oleaginous suspensions** may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water. Ringer's solution, U.S.P., and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as **oleic acid** are used in the preparation of injectables."*

46. The learned Counsel for the Respondent, while referring to Paragraph No. [0062] of D1, submitted that the oils mentioned in Paragraph No. [0062] of D1 are non-aqueous. It also mentions Ethyl Oleate, which is a derivative of fatty acid. The Paragraph No. [0062] is reproduced hereunder:

> *"[0062] As described above, the pharmaceutical compositions of the present invention additionally include a pharmaceutically acceptable carrier, which, as used herein, include any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or*

emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Fifteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the microspheres of the invention, such as by producing any undesirable biological effect or otherwise interacting in «, deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention. ***Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, sugars such as lactose, glucose and sucrose;*** *starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt;* ***gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, com oil, and soybean oil, glycols, such a propylene*** *glycol;* ***esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminium hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible*** *lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening agents, flavoring agents, and perfuming agents, preservatives, and antioxidants can also be present in the composition, according to the judgment of the formulator."*

47. The learned Counsel for the Respondent further submitted that D1 also discusses the use of microspheres, regarding which Paragraph No. [0002] of the D1 was referred, which is reproduced hereunder:

"[0002] An important factor in the successful treatment o:; long-term chronic disease, such as osteoporosis, diabetes, asthma, hepatitis, and arteriosclerosis etc., is patient compliance to the prescribed treatment regimen. However, the. protein and peptide drugs often used to treat chronic diseases typically require multiple doses by injection, which are painful to the patient and often

> *dramatically decreases compliance.* ***Although a variety of delayed release microspheres of poly(DL-lactide-co-glycolide) (PLGA) copolymers are available in the art, there exists the need for improved PLGA microspheres containing biologically active agents that have controlled release profiles."***

PRIOR ART DOCUMENT D2

48. Document D2 pertains to GLP-1 Analogue Formulations, and the subject matter of the invention relates to compositions forming a low viscosity mixture and methods of treatment comprising administration of such compositions, especially in treating diabetes, and to pre-filled administration devices and kits containing the formulations. Paragraph No. [0027] of D2 discloses the microsphere which is reproduced hereunder:

> *"[0027] The present invention further provides methods of preparing microspheres having controlled release profiles. According to the present invention, the timing, rate, quantity, and/or duration of release of a biologically active agent from a microsphere can be controlled or modulated by optimization of the microsphere copolymer ratio. In certain preferred embodiments, the microspheres contain a blend of particular copolymers having different lactide to glycohde ratios. Without limitation, the lactide:glylcolide ratio deter mines the release profile of the microsphere."*

49. The learned Counsel for the Appellants submitted that D2 does not disclose non-aqueous carrier, as well as fatty acid claims under the Subject Application.

50. Referring to Paragraph No. [0024] of D2, the learned Counsel for the Appellants contended that, unlike the Subject Application, the water presence is mandatory in D2. The Paragraph No. [0024] of D2 is reproduced hereunder:

"[0024] In one preferred embodiment, this pre-formulation will comprise a low-viscosity mixture of:
a) at least one diacyl glycerol;
b) at least one phosphatidyl choline;
c) at least one oxygen containing organic solvent;
d) at least one GLP-1 analogue;
wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid."

51. Referring to Paragraph Nos. [0013], [0015], and [0018] of D2, the learned Counsel for the Respondent submitted that exenatide is disclosed. Further, this court has noted that Paragraph No. [0014] discloses the scope for GLP-1 being long-acting and sustained formulations. The relevant Paragraph Nos. [0013], [0015] and [0018] are reproduced hereunder:

"[0013] As used herein, "native GLP-1" indicates human GLP-1 (7-37) and/or human GLP-1 (7-3 6)amide and the terms "Liraglutide", "CJC-1131", "AVE-010", and ***"exenatide"*** *are used to indicate the respective actives above, including their physiologically acceptable salts, esters and derivatives when! context allows.*

[0014] ***With regard to administration, conditions such as type-2 diabetes are ongoing, and any treatment regime will typically involve long-term, ongoing therapy, for periods of months or years.*** *Currently available GLP-1 therapies are typically injectables which require administration around twice a day for the period of treatment.* ***This will generally be by patient self-administration. Since frequent injection over a long period is not an optimal administration strategy, there is clearly scope for GLP-1 users to benefit from long-acting, sustained formulations, which might be administered much less frequently.***

[0015] The only long-acting GLP-1 product known to be in development is ***Exenatide LAR****, developed by a collaboration of Alkermes, Amylin and Lilly. This uses the Alkermes Medisorb ® delivery system consisting of microspheres of biodegradable polymers. Tlie release system comprises a poly(DLlactide) (PDLL)*

polymer microsphere formulation suspended in water, which entraps the GLP-1 analogue exenatide.

*** *** ***

[0018] From a drug delivery point of view, polymer depot compositions generally have tire disadvantage of accepting only relatively low drug loads and having a "burst/lag" release profile. The nature of the polymeric matrix, especially when applied as a solution or pre-polymer, causes an initial burst of drug release when the composition is first administered. This is followed by a period of low release, while the degradation of the matrix begins, followed finally by an increase in the release rate to the desired sustained profile. ***This burst/lag release profile can cause the in vivo concentration of active agent to burst above the functional window immediately following administration, and then drop back through the bottom of the functional window during the lag period before reaching a sustained functional concentration for a period of time. Evidently, from a functional and toxicological point of view this burst/lag release profile is undesirable and could be dangerous.*** *It may also limit the equilibrium concentration which can be provided due to the danger of adverse effects at the "peak" point. The presence of a lag phase may furthermore require supplementary dosing with repeat injections during the start-up period of depot treatment in order to maintain a therapeutic dose while the concentrations of active provided from the depot are sub-functional."*

52. Hence, Paragraph No. [0014] discloses the scope for GLP-1 users to benefit from long-acting, sustained formulations, which might be administered much less frequently. It is also important to note that Paragraph No. [0018] discusses the burst / lag issues.

53. Further, Paragraph No. [0053] of the D2 discloses the concentration of GLP-1 analogue (Exenatide) as present at 0.1% to 10%. The Paragraph [0053] of D2 is reproduced hereunder:

[0053] The present invention provides a pre-formulation comprising components a, b, c and at least one GLP-1 analogue as indicated herein. ***The amounts of these components will typically be in the***

range 30-70% a), 30-60% b) and 0.1-20% c), witli the GLP-1 analogue present at 0.01% to 10%, (such as 40-70% a), 30-60% b) and 0.1 -10% c), with the GLP-1 analogue present at 0.1% to 10%). *All % being by weight herein throughout, unless otherwise indicated. The formulations may consist of essentially only these components and in one aspect consist entirely of such components. Preferable ranges for component a) are 33-60% (e.g". 43-60%), particularly 35-55% (e.g. 45-55%) and preferable ranges of component b) are 33-55% (e.g. 35-55%), particularly 35-50% (e.g. 40 to 50%).”*

54. The learned Counsel for the Respondent also mentioned Paragraph No. [0087] of D2 which discloses the sugar. The relevant Paragraph No. [0087] is reproduced hereunder:

> *“[0087] The GLP-1 as a powder (e.g. in the kit of the invention), as well as GLP-1 dissolved in the lipid formulation) may gain stability (both storage and in vivo stability) by certain stabilising additives.* ***Such additives include sugars*** *(e.g. sucrose, trehalose, lactose etc.), polymers (e.g. polyols such as carboxy methyl cellulose), small amounts of surface active agents (e.g. P80—see above), antioxidants (such as ascorbic acid, EDTA and citric acid), amino acids (such as methionine, glutamate, lysine etc.) and anionic lipids and surface active agents (such as dioleoyl phosphatidyl glycerol (DOPG), palmitoyloleoyl phosphatidylglycerol (POPG) and oleic acid (OA)).”*

55. The learned Counsel for Respondent further submitted that Claims 12 and 14 of the Subject Application claims that the medicine under the Subject Application does not need to be taken twice-a-day because the active pharmaceutical ingredients are available for longer. This is already disclosed under Paragraph No. [0099] of D2 which is reproduced hereunder:

> *“[0099] A considerable advantage of the depot precursors of the present invention is that they are stable homogeneous phases. That is to say, they may be stored for considerable periods (preferably at least 6 months) at room or refrigerator temperature, without phase separation. As well as providing advantageous storage and facile administration, this allows for the dose of GLP-1 analogue to be selected by reference to the species, age, sex, weight, and/or*

physical condition of the individual subject, by means of injecting a selected volume. Furthermore, the present inventors have surprisingly found that the initial release of active agent (observed as is not proportional to dose volume, in ranges of at least 10-fold in sample volume injection, while the total drug exposure (observed as .AUC or mean plateau plasma concentration) is proportional to the injection volume. On the contrary, it has been shown that can be correlated to the surface area of the injected dose volume, is proportional to the two-third power of the injected dose volume. Increasing the dose volume by a factor of 10 will not increase the 10 times and the relationship between and the total drug exposure (AUC or mean plateau plasma concentration level) will thus decrease with increasing dose volume. This is highly advantageous, because this property reduce the risk of reaching potentially toxic plasma drug concentrations even if the total dose is significantly increased. ***As considered above, this may be a key concern in going from a twice-daily administration to a sustained formulation without provoking hypoglycaemia.*** *Even in situations where dosing is not directly proportional to injection volume, however, the homogenous nature of the depot precursors importantly allow for partial administration of a pre-measured dose and this administration may he made by reference to a dosing table, chart, software calculation etc. which may take into account any or all relevant subject variables."*

PRIOR ART DOCUMENT D3

56. Document D3 pertains to "*Controlled release of drugs from injectable In situ formed biodegradable PLGA microspheres: effect of various formulation variables."* Referring to Page No. 216 of D3, the learned Counsel for the Appellants submitted that D3 use a hydrophilic career while in the Subject Application, a hydrophobic career is used. Contrary to this, the learned Counsel for the Respondent, while referring to the Abstract of D3, argued that it discusses the same problem as the present invention claims under the Subject Application. D3 discloses / uses the PLGA microsphere. This is exactly the present invention of the Appellants under the Subject Application. The Abstract of D3 is reproduced hereunder:

"Abstract

A novel in situ method for the preparation of injectable biodegradable poly(lactide-co-glycolide) (PLGA) microspheres for the controlled delivery of drugs is described here. *A stable dispersion of PLGA microglobules ('premicrospheres' or 'embryonic microspheres') in a vehicle mixture on injection, comes in contact with water from aqueous buffer or physiological fluid, thereby hardening the microglobules into solid matrix type microparticles entrapping the drug (in situ formed microspheres). The drug is then released from these microspheres in a controlled fashion. The effect of the following formulation variables on the characteristics of the novel drug delivery system (NDDS) was investigated: (i) the concentrations of polyethylene glycol 400 (PEG 400), the encapsulated drug, and the hydrophilic excipient (mannitol); and (ii) the types of encapsulated drug (micromolecules and macromolecules such as protein) and vehicles (replacing triacetin and Miglyol 812 by triethyl citrate and soybean oil respectively). Also, the effect of formulation, process, and storage (15 days/4°C) conditions on the physical stability of the encapsulated protein was evaluated. The in vitro drug release was enhanced with decrease in the PEG 400 concentration and increase in the drug and mannitol concentration. The drug release was retarded with increase in the molecular weight of the encapsulated drug. Substitution of triacetin by triethyl citrate and miglyol 812 by soybean oil resulted in variation in the release of the drug from the in situ formed microspheres. A preliminary investigation of the physical stability of the myoglobin revealed that the α-helical structure was unaffected by the formulation, process, and the storage conditions"*

PRIOR ART DOCUMENT D4

57. Document D4 pertains to *"Poly (lactide-co-glycolide)-based sustained release microcapsules comprising a polypeptide and a sugar"*. Document D4 relates to compositions for the sustained release of biologically active polypeptides, and methods of forming and using the compositions for the sustained release of polypeptides that are biologically active. The compositions of the present invention are comprised of a bio-compatible polymer having dispersed therein a biologically active

polypeptide and a sugar. The learned Counsel for Appellants, while referring to Page No. 33 of D4 submitted that it does not disclose the active compound exenatide. The relevant portion is reproduced hereunder:

> *"That the Respondent has also failed to consider that the cited prior art document WO 2005/102293 A1 (hereinafter mentioned as D4) (annexed as Exhibit E-11 with Affidavit in support of Appeal), which generally relates to a composition directed to a release profile characterized by a ratio of Cmax to Cave of about 3 or less which can be achieved by controlling the coacervating agent to polymer solvent ratio, such as silicone oil to polymer solvent ratio (in the manufacturing process), thereby achieving a low pore volume."*

58. On the other hand, the learned Counsel for the Respondent referred to Page No. 10 of D4 and submitted that the sugar and the weight is the same as claimed under the Subject Application. The relevant portion is reproduced hereunder:

> *"The Sugar*
> *A sugar, as defined herein, is a monosaccharide, disaccharide or oligosaccharide (from about 3 to about 10 monosaccharides) or a derivative thereof. For example, sugar alcohols of monosaccharides are suitable derivatives included in the present definition of 5 sugar. As such, the sugar alcohol mannitol, for example, which is derived from the monosaccharide mannose is included in the definition of sugar as used herein. Suitable monosaccharides include, but are not limited to, glucose, fructose and mannose. A disaccharide, as further defined herein, is a compound which upon hydrolysis yields two molecules of a monosaccharide. Suitable disaccharides include, but are not 10 limited to, sucrose, lactose and trehalose. Suitable oligosaccharides include, but are not limited to, raffinose and acarbose.*
> ***The amount of sugar present in the sustained release composition can range from about 0.01% (w/w) to about 50% (w/w), such as from about 0.01% (w/w) to about 10%***
> ***(w/w), such as from about 0.1% (w/w) to about 5% (w/w) of the total weight of the 15 sustained release composition. Excellent release profiles were obtained incorporating about 2% (w/w) sucrose.***

Alternatively, the amount of sugar present in the sustained release composition can be referred to on a weight ratio with the agent or biologically active polypeptide. For example, the polypeptide and sugar can be present in a ratio from about 10:1 to about 1:10 2:0 weight:weight. In particularly preferred embodiments, the ratio of polypeptide (e.g., exendin-4) to sugar (e.g., sucrose) is about 3:2 (w/w), 4:2 (w/w), and 5:2 (w/w). Combinations of two or more sugars can also be used. The amount of sugar, when a combination is employed, is the same as the ranges recited above. When the polypeptide is exendin-4, the sugar is preferably sucrose, mannitol or a 25 combination thereof."

59. Further, the Abstract and Claim 1 of D4 discuss the sustained release compositions of the present invention, which comprises of a bio-compatible polymer having dispersed therein a biologically active polypeptide and a sugar. Additionally, microspheres are disclosed at Page Nos. 26 and 27 and Exenatide at Paragraph Nos. [0010] and [0015] at Page No. 6 of D4.

60. The table below shows the disclosure made in the documents D1 to D4:

Technical Feature of Subject Application	**D1**	**D2**	**D3**	**D4**
Non-aqueous carrier comprising one or more triglycerides of C6 to C12 fatty acids	No But at Paragraph No. [0068] discloses "*Oelic Acid*" is closed which is a C18 Fatty Acid. The paragraph also suggests using "*sterile, fixed oils*" that overlaps with the description of oils in the Complete Speciation of the Subject Application.	No	No	No

Exenatide as an active pharmaceutical ingredient	No	Yes Paragraph Nos. [0013] and [0015]	No	Yes Page No. 6, Paragraph Nos. [0010] and [0015]
Sugar	No	Yes Paragraph No. [0087]	No	Yes The sugar and the weight is same as mentioned in the Subject Application at Page No. 10
Microspheres	Yes Paragraph No. [0002]	No	Yes Abstract	Yes Page Nos. 26 and 27

61. As discussed above, document D1, pertains to the microsphere delivery systems in which the microspheres include blended PLGA copolymers and a biologically active agent. The delivery of a biologically active agent to a specific *in vivo* location can be accomplished through the administration of the microspheres in a pharmaceutical composition. The purpose of the non-aqueous carrier, i.e., oil, is to so that it does not solubilise the polymer(s) that form the microspheres. Non-aqueous carrier will not solubilise Exenatide or other water-soluble therapeutic peptides or proteins. Paragraph No. [0062] of D1 states that any standard pharmaceutical carrier in the formulation can be used, unless that carrier is incompatible with the microspheres used. For example, if it causes an unwanted biological effect or interferes harmfully with the microspheres or other components. Therefore, one of the suggestions of Paragraph No. [0062] of D1 is to use a non-aqueous carrier.

62. The summary of the Complete Specifications of the Subject Application discloses the various oils as career in the following language:

"Further, although the microspheres are formulated in oil (i.e. a

> *carrier as disclosed herein), in some embodiments the microspheres do not have oil contained within the interior spaces or pores, or do not have oil within a substantial number of interior spaces or pores of the microspheres, and yet can achieve the surprising properties disclosed herein. The formulation is a suspension whereby the microspheres are suspended in the carrier. The non- aqueous carrier may be an oil, such as fractionated oils, triglyccrides, diglyccrides, monoglyccridcs, propylcne glycol fatty acid dicsters, and the like."*

63. Further, under the heading "carrier" the Complete Specification of the Subject Application discusses which is reproduced hereunder:

> *"In one embodiment, the carrier is a medium chain triglyceride. The medium chain triglyceride may be synthetic or natural (e.g., produced from fractionated oils, such as coconut oil and/or palm kernel oil). "Medium chain triglyceride" refers to esters of glycerol having three Cf to Cii fatty acid chains, where the three fatty acid cliains may be the same or different."*

64. The purpose of the non-aqueous carrier, i.e., oil, is to so that it does not solubilise the polymer(s) that form the microspheres. Non-aqueous carrier will not solubilise exenatide or other water-soluble therapeutic peptides or proteins.

65. Paragraph No. [0068] of D1 suggests the use of sterile, fixed oils. Although the paragraph suggests employing synthetic mono- or diglycerides. The statement "*In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium*" can reasonably be understood as suggesting the use of triglyceride oils, as "*fixed oils*" in ordinary usage refers to fats/oils whose principal constituents are triglycerides. The next line of the paragraph adds specific examples in the fixed-oil domain while not replacing the baseline understanding that fixed oils, which is predominantly triglyceride oils in natural form. Therefore,

"teaching away" argument will not apply here.

66. In ***Astrazeneca AB and Another v. Torrent Pharmaceuticals Ltd,*** 2020 SCC OnLine Del 1446, this Court held that merely because there is teaching towards one solution (ethoxy) and not another (methoxy), does not mean that there is "teaching away" from the later. The relevant paragraph is reproduced hereinunder:

> *"105. According to the plaintiff there is no motivation to look at Example 12 when 80 examples have been given of which Examples 1 and 2 were synthesized on a large scale, there is no motivation to change methyl group, there are no teachings towards substitution with ethoxy, efficacy data of Example 12 was not known, the teaching of IN '147 were to have hydrogen on central phenyl ring and no ethoxy on the distal phenyl in any of the 80 examples. As noted above, for preparation of the structure in Example 12, four methods have been noted and in the said example though methoxy was used and even though there was no teaching towards ethoxy, there were no teachings even away from ethoxy. Both ethoxy and methoxy being lower alkyl, a person with ordinary skill in the art would have been motivated to bring this single change of substitution of methoxy to ethoxy to find out if predictable results ensue. Consequently, this Court is of the prima facie opinion that the suit patent is vulnerable on the grounds of obviousness in view of Example 12 of IN '147."*

67. Similarly, in ***Fresenius Kabi Oncology Limited v. Glaxo Group Limited & Anr,*** 2013 SCC Online IPAB, the Intellectual Property Appellate Board held that if a prior art reference teaches two alternative methods to reach the same result, while indicating that one method gives better result than other, and the alternative carries several disadvantages, the person skilled in the art would read the statements neutrally in such a way that he would neither picking out the "teaching towards" statement nor seeking out the "teaching away" statement.

68. Therefore, the oils mentioned in the Paragraph No. [0068] of D1

would also include the specified oils mentioned in the Complete Specification of the Subject Application under the heading's "summary" and "carrier". Additionally, at Paragraph No. [0068] of D1 specifically discloses the oleic acid. The disclosed oleic acid is a C_{18} fatty acid and also the shortest chain length amongst the mixtures of compositions cited in 29 different forms of excipients are esters made from C_{16} acids. Therefore, in the light of the above reasoning, it would be obvious for PSITA to use the triglyceride fatty acid of carbon chain lengths ranging from 6 to 12, which is claimed under Claim 1 of the Subject Application. Therefore, the submission of the Appellants that Dl is silent regarding any non-aqueous carrier comprising triglycerides, much less the carbon range as set out in Claim 1, cannot be accepted.

69. Further, Document Dl provides an example of microspheres present in the formulation at a concentration of 10 mg/ml as claimed in the present application. Document Dl also discloses a manufactured formulation for injection as mentioned under Paragraph No. [0028] of Dl consisting essentially of a suspension of:

(i) a pharmaceutically acceptable carrier which consists essentially of one or more triglycerides of CIS fatty acids;

(ii) microspheres consisting essentially of a PLGA polymer; and

(iii) wherein the ratio of lactide : glycolide in the polymer is about 1:1.

70. It is clear that the Paragraph Nos. [0013] and [0015] of D2 discloses Exenatide. Further, Paragraph No. [0087] of D2 also discloses the sucrose, trehalose, lactose, etc. The summary of the Complete Specification of the Subject Application also discloses the different types of sugars and the relevant portion of the Complete Specification reproduced hereunder:

> *"The sugar may be, e.g., glucose, dextrose, galactose, maltose, fructose, mannose, sucrose, lactose, trehalose, raffinose, acarbose, glycol, glycerol, erythritol, threitol, arabitol, ribitol, sorbitol, dulcitol, iditol, isomalt, maltitol, lactitol, mannitol, xylitol, or a combination of two or more thereof. In one embodiment, the sugar is sucrose."*

71. Therefore, D2 discloses formulation precursors (preformulations) for the *in situ* generation compositions for the controlled release of active agents such as Glucagon-like-peptide-1 (GLP-1) and / or analogues thereof, "native GLP-1" indicates human GLP-l(7-37) and / or human GLP-l(7-36) amide and the terms "Liraglutide", ''a C-1131", ''AVE-010", and "Exenatide'' are used to indicate the respective actives. The formulations may include from 0.1% to 10% of Exenatide. Paragraph No. [0087] of D2 also teaches, exenatide and/or its analogues dissolved in the lipid formulations gain stability (both storage and *in vivo* stability) by such stabilising additives as sugars. Further, Paragraph No. [0099] also disclose that said formulations may be stored for at least six months at room or refrigerator temperature, without phase separation.

72. Document D3, in its Abstract, discloses a novel in situ method for the preparation of injectable biodegradable PLGA microspheres for the controlled delivery of drugs the formulation of a stable dispersion of PLGA microparticles. D3 also discloses an injectable dispersion of microspheres comprising a drug and PLGA in a continuous phase consisting of triacetin, PEG400 and miglyol as claimed in the present application. Under Document D4, preferably, the compositions are formulated for injection and controlled release of the active compound to the body. Further, D4 discloses exendin-4 at several places, which is nothing but Exenatide. The Complete

Specification of the Subject Application under the heading "Detailed Description" states that Exenatide has the same meaning and amino acid sequence as exendin-4.

73. In ***Bristol-Myers Squibb Holdings Unlimited Company and Others v. BDR Pharmaceuticals International Pvt. Ltd.***, 2020 SCC OnLine Del 1700, it is held that mosaic of prior arts may be done while claiming obviousness, however the party claiming must be able to demonstrate that how the person of ordinary skill in the art would have been led to combine the relevant components relied from the mosaic of prior art. The relevant paragraph is reproduced hereunder:

> *"36. From the judgments as noted above, some of the principles which govern the field to find out whether an invention is obvious or not can be summed up as under: —*
>
> *(i)A hindsight reconstruction by using the patent in question as a guide through the maze of prior art references in the right way so as to achieve the result of the claim in the suit, is required to be avoided.*
>
> *** *** ***
>
> *(v)* ***Though mosaic of prior art documents may be done in order to claim obviousness, however, in doing so, the party claiming obviousness must be able to demonstrate not only the prior art exists but how the person of ordinary skill in the art would have been led to combine the relevant components from the mosaic of prior art.***
>
> *** *** ***
>
> *(vii) Though it would be tempting to put together a combination of prior arts but this requires a significant degree of hindsight, both in selection of relevant disclosures from these documents and also in disregarding the irrelevant or unhelpful teachings in them.*
>
> *Emphasis supplied"*

74. Therefore, it would have been obvious to PSITA to arrive at the present invention, which was made to utilize pre-mixed formulations comprising active pharmaceutical ingredient Exenatide and stability agent sugar as taught by D2 in microsphere delivery systems taught by Dl.

75. Therefore, the claimed invention under the Subject Application is obvious and does not involve an inventive step under Section 2(l)(ja) of the Act in the light of the prior art documents D1 to D4, and no inventive step can be acknowledged. Hence, the objections raised under Section 2(l)(j) of the Act at the time of the Hearing is not met.

76. This Court finds it important to address that does the PSITA seek to refer Document D2, D3 and D4 after referring to Document D1? The phrase in Paragraph No. [0002] of D1 discloses the microspheres of PLGA copolymers and discusses the need for improved PLGA microspheres containing biologically active agents that have controlled release profiles. The statement in the said Paragraph that *"there exists the need for improved PLGA microspheres containing biologically active agents that have controlled release profiles."*, would make the PSITA refer to other cited Documents to find a solution. Further, the discussion under Paragraph No. [0014] of D2 discloses the scope for GLP-1 being long-acting and sustained formulations, which would, along with D1, suggest coming to the present invention. Additionally, Paragraph No. [0018] of D2, which discusses the burst / lag issues, would teach to refer to other cited documents like D4.

77. In view of the above conclusion, the Subject Application has rightly been refused by the learned Controller under Section 2(1)(j) of the Act, and does not require interference.

78. In view of the above, the Subject Application of the Appellant cannot

be termed as an invention under Section 2(1)(j) of the Act. Accordingly, the Impugned Order dated 10.07.2018 passed by the learned Controller does not require interference and is hereby upheld. The present Appeal is dismissed.

TEJAS KARIA, J

NOVEMBER 24, 2025
'KC'/'N'