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

% Judgement reserved on: 07.05.2026
Judgment delivered on: 07.08.2026

\+ C.A.(COMM.IPD-PAT) 118/2022

ESTEVE PHARAMACEUTICALS S.A. ....Appellant

versus

CONTROLLER OF PATENTS AND DESIGNS ....Respondent

Advocates who appeared in this case:

For the Appellant: Mr. J. Sai Deepak, Senior Advocate with Ms. Mehak Rahul Chaudhry, Ms. Ekta Sarin and Ms. Mugdha Palsule, Advocates.

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

CORAM:
HON'BLE MR. JUSTICE TUSHAR RAO GEDELA

J U D G M E N T

TUSHAR RAO GEDELA, J.

1. The present appeal has been filed under Section 117A of the Patents Act, 1970 (hereinafter referred to as '*the Act*') assailing the order dated 12.02.2020 (hereinafter referred to as *'the impugned order'*) refusing the Patent Application No.1435/DELNP/2012 titled "*Co-crystals of Tramadol and Coxibs*" (hereinafter referred to as '*subject application*') on the ground of lack of inventive step under Section 2(1)(ja) and lack of patentability under Sections 3(d) and 3(e) of the Act.

2. Briefly, the facts stated in the appeal are as under:-

2.1. On 15.02.2012, the appellant filed a national phase patent application at the Indian Patent Office, New Delhi bearing

no.1435/DELNP/2012 based on PCT application no.PCT/EP2010/002385 dated 19.04.2010.

2.2. On 18.09.2013, the Request for Examination (hereinafter referred to as *'RFE'*) was filed. Thereafter, on 30.10.2017, First Examination Report (hereinafter referred to as *'FER'*) was issued by the respondent raising the objections under Section 2(1)(ja) for lack of novelty and lack of inventive step citing the prior art documents D1 and D2, Section 3(d) and Section 3(e) of the Act. On 30.04.2018, the appellant had filed its response to the said FER alongwith amended claims.

2.3. Thereafter, on 13.11.2019 and 17.12.2019, hearing notices were issued to the appellant raising additional objections by citing prior art documents D3-D7 as well as sufficiency of disclosure under Section 10(4) of the Act. The agent of the appellant attended the hearing on 17.01.2020. Subsequently on 29.01.2020, the appellant had filed its written submissions alongwith a further set of amended claims.

2.4. Consequent thereto, the impugned order dated 12.02.2020 was passed by the respondent whereby the subject application was rejected on the ground that the claimed subject matter of the subject patent does not constitute an invention under Section 2(1)(ja), Section 3(d) and Section 3(e) of the Act. Aggrieved thereof, the present appeal has been preferred.

CONTENTIONS OF THE APPELLANT:-

3. Opening for the appellant, Mr. J. Sai Deepak, learned senior counsel, adumbrates the brief background of the appeal and submits that the priority date of the patent is 16.10.2009 while the date of filing of the

patent application is 15.02.2012. The patent has been applied for *"Co-Crystals of Tramadol and Coxibs"*. He would submit that the subject patent application has been rejected on account of non-fulfilment of objections under Section 2(1)(ja) for lack of inventive step as well as Sections 3(d) and 3(e) of the Act. He submitted that though an objection under Section 2(1)(j) for lack of novelty was indeed raised, however, in the impugned order, the said objection has not been sustained. Thereby indicating that the initial objection under Section 2(1)(j) of the Act has been met with by the appellant. While arguing, learned senior counsel referred to the impugned order as also the Complete Specifications (hereinafter referred to as *'CS'*) alongwith the subject application and the prior art documents D1 to D7 etc.

Expanding his arguments, learned senior counsel would submit as under:-

3.1. Alluding to the First Examination Report (hereinafter referred to as 'FER') dated 30.10.2017 as well as the Hearing Notice dated 13.11.2019, learned senior counsel would submit that the respondent raised objections on account of lack of novelty. He would submit that in response thereto, the appellant amended its claims and limited the same to *"a co-crystal of tramadol and celecoxib"*. Drawing attention to the impugned order dated 12.02.2020, he would contend that while rejecting the subject patent application on other grounds, the objection of lack of novelty was not taken. Learned senior counsel pointed out and read the concerned paragraphs which clearly indicate that the rejection is not based on lack of novelty. In other words, it is contended that the objection under Section 2(1)(j) of the Act for

lack of novelty was met with by the appellant post amendment of its claims. Thus, to that extent, the impugned order can be deemed to have accepted that the claimed invention possesses novelty.

3.2. Stringing with the aforesaid submission, learned senior counsel would contend that the next objection raised under Section 3(d) of the Act would itself be unsustainable. According to learned senior counsel, having regard to the fact the respondent itself has conceded and accepted that the subject matter of the claimed invention is "novel", the objection under Section 3(d) of the Act i.e., the claimed invention is a mere discovery of a new form of a known substance, would be unsustainable. Learned senior counsel would contend that there is no evidence to establish that as on the priority date of the claimed invention, there existed a combination of tramadol and celecoxib against which the efficacy of the co-crystal of tramadol and celecoxib could be tested. He would further stoutly contend that the prior arts D5 and D7 only generally disclose celecoxib as one of the Non-Steroidal Anti-Inflammatory Drugs (hereinafter referred to as *'NSAIDS'*) which may be used with tramadol and there is no specific disclosure in the said prior arts. Relying upon the judgment of this Court in ***D.S. Biopharma Ltd. vs. The Controller of Patents and Designs & Ors.: MANU/DE/3418/2022***, learned senior counsel would contend that to validate the objections under Section 3(d) of the Act, the respondent must specify (i) the "known-substance"; (ii) how and why the claimed molecule or substance is a derivative or is otherwise a new form of a known substance; and (iii) the basis to assert that the alleged 'known' substance and the claimed

molecule or substance have the same 'known' efficacy. It cannot be left to the applicant to deduce as to what is the known substance and thereafter, give efficacy data. Since the known substance was not identified in the Hearing Notice, the objection under Section 3(d) of the Act would be unsustainable.

3.3. In the context of Section 3(d) of the Act, in addition to the aforesaid argument, learned senior counsel would invite attention of this Court to the other limb of the objection under Section 3(d) i.e., enhanced therapeutic efficacy over the known substances which are tramadol and celecoxib. Relying on the data provided along with Figure 6, learned senior counsel invited attention to the results obtained on mechanical allodynia for co-crystal of (rac)-tramadol-HCl-celecoxib (1:1), tramadol and celecoxib expressed as ED50. According to the learned senior counsel, the said Figure displays a comparison of the effects of co-crystal of (rac)-tramadol-HCl-celecoxib (1:1) of tramadol and celecoxib on reversal of incision-induced mechanical allodynia in the incised rat hind paw following a single dose (8-10 per group). He would contend that Figure 6 clearly demonstrates that co-crystal of (rac)-tramadol-HCl-celecoxib (1:1) has a higher percentage of anti-allodynia as compared to celecoxib and tramadol individually.

3.4. Dilating further on the aforesaid, learned senior counsel relied on Figure 8 which shows results obtained on the effect of co-crystal of (rac)-tramadol-HCl-celecoxib (1:1), tramadol and celecoxib expressed as ED50 in the incision-induced thermal hyperalgesia in the rat hind paw. According to learned senior counsel, the result clearly establishes that the co-crystal of (rac)-tramadol-HCl-

celecoxib (1:1) was more potent than tramadol and celecoxib individually. He relied upon the judgment of ***Merck Sharp and Dhome Corp. Vs. Glenmark Pharmaceutical Ltd.: MANU/DE/0852/2015*** and ***F. Hoffman La Roche vs. Cipla Ltd.: MANU/DE/3672/2015***, to submit that it was the duty of the respondent to identify the "known substance" as also to indicate how the patent did not exhibit enhanced efficacy over such known substance. Thus, according to learned senior counsel, the respondent failed to meet the requirements for raising an objection under Section 3(d) of the Act. Additionally, learned senior counsel would forcefully contend that the respondent failed in considering and analysing the data provided in the CS which demonstrated the enhanced therapeutic efficacy of the co-crystal compared to that of tramadol and celecoxib individually. Thus, the objection under Section 3(d) is unsustainable.

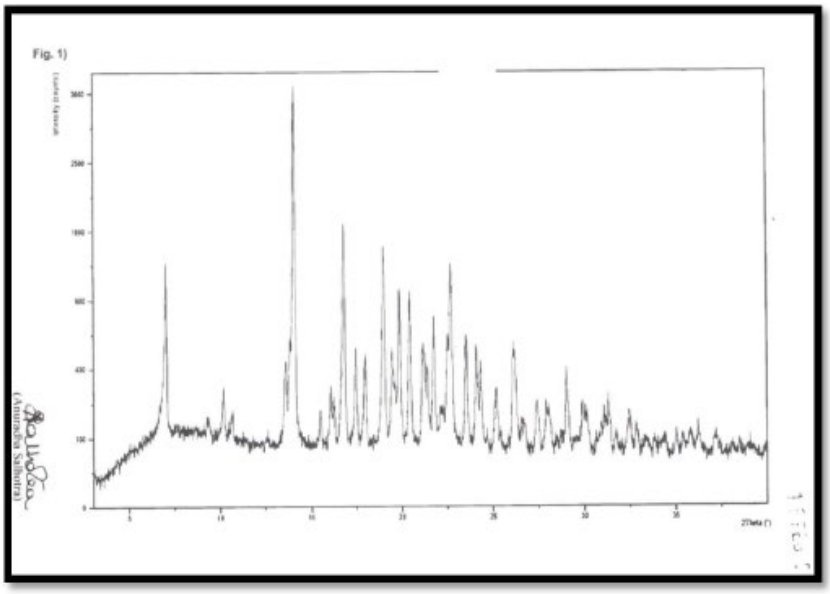
3.5. Mr. J. Sai Deepak, learned senior counsel next challenged the rejection of the subject patent application under Section 3(e) of the Act by the respondent. He would contend that the premise of the respondent that the claimed invention is a mere admixture of known substances resulting in the aggregation of the properties of such components and thus non-patentable, is entirely misplaced. Referring to the conclusion arrived at by the respondent in the impugned order, learned senior counsel would contend that the reasoning provided therein in respect of objection under Section 3(e) of the Act is entirely vague and without any cogent material or analysis to support the same. It is stated that for objection under

Section 3(e) to sustain, the claimed invention must be a mere aggregation of known components without any synergistic effect.

3.6. According to learned senior counsel, the aforesaid objection under Section 3(e) is not tenable for the reason that the claimed invention is directed to a co-crystal and not an admixture. While an admixture is obtained by physically mixing two or more components, a co-crystal on the other hand, is a single, homogeneous crystalline phase formed through specific and directional intermolecular interactions between the Active Pharmaceutical Ingredient (hereinafter referred to as *'API'*) and the conformer in a defined stoichiometric ratio. He invites attention to the relevant paragraph of the CS which defines a co-crystal, as extracted hereunder:-

> *""Co-Crystal" as used herein is defined as a crystalline material comprising two or more compounds at ambient temperature (20 to 25°C, preferably 20°C), of which at least two are held together by weak interaction, wherein at least one of the compounds is a co-crystal former. Weak interaction is being defined as an interaction which is neither ionic nor covalent and includes for example: hydrogen bonds, van der Waals forces, and n-n interactions." (Last Paragraph on Page 35 PDF Pg. 38 of the Appeal Paperbook)*
>
> *A recent article by Zawarotko (Zwarotko, Crystal Growth & Design, Vol. 7, No. 1, 2007, 4-9) gives a definition of co-crystal which is in line with the definition given above and thus also is a definition of "cocrystal" according to this invention. According to this article "a cocrystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components consist of a target molecule or ion and a molecular cocrystal former(s); when in a co-crystal, they coexist at a molecular level within a single crystal" (Second Paragraph on Page 36 PDF Pg. 39 of the Appeal Paperbook)"*

3.7. Apart from the above, learned senior counsel would also submit that the difference between a co-crystal and an admixture is also clear from their Powder X-ray Diffraction pattern (hereinafter referred to as *'PXRD'*). According to learned senior counsel, while the PXRD pattern of an admixture would have characteristic peaks of each individual component, the PXRD pattern of a co-crystal would show a new and unique set of diffraction peaks for a single substance indicating a new crystalline phase. The Figure 1 provided in the CS relied upon by the learned senior counsel is extracted hereunder:-



Thus, according to learned senior counsel, the aforesaid PXRD pattern establishes that a co-crystal is not a mere physical admixture but structurally distinct solid form having its own crystal lattice and psychochemical characteristics and thus, cannot fall within the scope of Section 3(e) of the Act. As per the learned senior counsel, the claimed co-crystal clearly demonstrates synergistic effect and improved pharmacokinetic properties

compared to tramadol alone as also good synergistic activity, all of which are clear from Figure 6 and Figure 8. In view of the above, it is submitted that the findings in the impugned order with respect to Section 3(e) of the Act are arbitrary and unfounded.

3.8. Mr. J. Sai Deepak, learned senior counsel next referred to the objection of lack of inventive step sustained in the impugned order. Before referring to the grounds of challenge, learned senior counsel would refer to the law laid down by Courts as to the fundamental principles for determining the existence of an inventive step and lack of obviousness. In that context, he relies upon the judgment in ***Avery Dennison Corporation vs. Controller of Patents and Designs: MANU/DE/4319/2022***.

3.9. Having referred to the law, learned senior counsel would contend that the respondent relied upon disclosures in prior arts D5 and D7 along with D4A to reject the subject patent application on the ground of lack of inventive step and obviousness. In regard to the prior art D4A, learned senior counsel would submit that it discloses a pharmaceutical composition comprising acetaminophen and tramadol components which are both analgesics and as such, directed to an entirely different combination of APIs. He would stoutly contend that D4A does not mention celecoxib at all. Therefore, according to the learned senior counsel, the said prior art possibly cannot reach a combination or co-crystal of celecoxib with tramadol.

3.10. Learned senior counsel would submit that the prior art D5 discloses a slow-release pharmaceutical composition comprising (a) a core comprising therapeutically effective amount of tramadol

or its pharmaceutically equivalent salt thereof and at least one pharmaceutically acceptable excipient; (b) a slow-release coat; and (c) an immediate release layer comprising therapeutically effective amount of Naproxen or its pharmaceutically equivalent salt thereof and at least one pharmaceutically acceptable excipient. Further to that, it is contended that the respondent has observed that in prior art D5, naproxen is only used as an illustrative example, and a "Person Skilled in the Art" (hereinafter referred to as *'PSITA'*) would know how the combination may be modified using other NSAIDs such as celecoxib.

3.11. To the aforesaid narrative in D5, learned senior counsel would contend that apart from naproxen, D5 lists a number of NSAIDs in addition to celecoxib like Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac and Tolmetin, which itself demonstrates that there is no enabling disclosure for a specific combination of tramadol and celecoxib. He would contend that there is neither any teaching nor a suggestion in D5 of a co-crystal of tramadol and any NSAID. Thus, according to learned senior counsel, there is no motivation in D5 to select tramadol and celecoxib to arrive at the claimed co-crystal. The motivation, if any, should appear and exist in the prior art in order to defeat the inventive step. A mere suggestion of a combination of tramadol and celecoxib amongst a number of components referred to above without providing an enabling disclosure would not constitute motivation.

3.12. Learned senior counsel next referred to prior art D7, submitting that it discloses a pharmaceutical co-crystal composition comprising an API and a co-crystal former (another API) wherein the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature, and wherein the API and co-crystal former are hydrogen bonded to each other. Learned senior counsel would stoutly contend that given the aforesaid background of D7, a PSITA, while referring to the teachings contained therein, would be required to try iterations numbering about 10485910 combinations to select tramadol and celecoxib among 4580 APIs, to arrive at the claimed co-crystal. In order to substantiate and support his contention, learned senior counsel relied upon the affidavit of the investigator who clearly mentioned that out of approximately 500 API-API candidates tested by the appellant, only 13 of them formed a co-crystal and rest of the compounds formed slurries, crystalline salts or combinations. According to learned senior counsel, the occurrence of API-API co-crystal with the features and properties shown by 1:1 co-crystal of rac-tramadol-HCl and celecoxib is rare with less than 0.1% probability of fulfilling all the criteria. Thus, according to learned senior counsel, prior art D7 neither provides any motivation to PSITA nor makes the claimed invention obvious.

3.13. Learned senior counsel considerably relied upon the judgment of this Court in ***Biomoneta Research Pvt. Ltd. vs. Controller General of Patents Designs & Anr.: 2023/DHC/001816***.

CONTENTIONS OF THE RESPONDENT:-

4. In response to the arguments of the appellant, Ms. Rukhmini Bobde, learned CGSC appearing for the respondent submitted as under:-

4.1. Ms. Bobde briefly alludes to the prior art documents D1 to D7 as also claims 1, 10 & 11 of the subject patent application. She would submit that the subject patent application claims the co-crystals of the known therapeutic active agents like tramadol and celecoxib which are well known and cited in the prior art referred to in the impugned order. She would stampede that even the salts thereof are used as therapeutically active agents for pain relief.

4.2. Without prejudice to the contentions of the respondent, Ms. Bobde would submit that even if documents D1-D4A and D6 are assumed to not disclose or teach the combination of tramadol with NSAIDs like celecoxib, the disclosure in prior arts D5 and D7 are cumulatively sufficient to reject the subject patent application of the appellant on lack of inventive steps and obviousness. According to her, the restriction to prior art documents D5 & D7 is only for the reason that while the initial claims of the appellant were broad and covering a combination of tramadol with coxibs, the amended claims restricted themselves to the specific combination of tramadol with celecoxib. She would contend that though D1 to D4A and D6 do not disclose or teach specific combination of tramadol with celecoxib, the said documents provide general disclosure to the PSITA about the need for the combination of drugs and definitely provide combination of tramadol with other APIs.

4.3. Ms. Bobde would contend that tramadol is a synthetic opioid analgesic which has reported side effects including nausea, constipation, dizziness, headache etc. However, such side effects are preventable by prescribing lower doses of tramadol without compromising the pain relief. In order to reduce the side effects, opioids like tramadol are combined with other drugs including non-opioids analgesic agents. As an example, Ms. Bobde refers to D5 which discloses a combination of tramadol with other NSAIDs. In order to make good her submissions, she referred to the list of NSAIDs found in D5 which also includes celecoxib.

4.4. Dilating further on prior art D5, she would submit that D5 discloses not only the combination of naproxen (NSAIDs) with tramadol but also describes examples illustrating the invention related to a combination comprising a slow released tramadol and an NSAID. The invention in D5 clearly mentions that naproxen is used only as an example for illustrative purposes which in no way limits the scope of the invention and that a PSITA would know how the combination may be modified using any other NSAID like celecoxib etc. to arrive at the same/similar combination. Thus, according to her, D5 not only motivates a PSITA to prepare an alternative combination of tramadol with other NSAIDs but also renders the claimed invention obvious.

4.5. She laid great stress on the following description found in D7:-

> *"...it would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the*

processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to increase or decrease the dissolution rate of API-containing pharmaceutical compositions in water, increase or decrease the bioavailability of orally-administered compositions, and provide a more rapid or more delayed onset to therapeutic effect…
… It has now been found that new co-crystalline forms of APIs can be obtained which improve the properties of APIs as compared to such APIs in a non-co-crystalline slate (free acid, free base, zwitter ions, salts, etc.)…"

According to her, D7 in claims 5 & 6 provides the co-crystal composition of API-API wherein the first API and the second API are selected from Table-IV. She would submit that D7 describes the API-API co-crystal and the chemical and physical properties of an API in the form of co-crystal may be compared to a reference compound that is the same API in a different form.

4.6. Ms. Bobde would submit that D7 describes the solubility modulation, dissolution modulation, bioavailability modulation, dose response modulation and stability increased of the co-crystals of APIs and also preparation of co-crystals of unsaltable APIs, decreased hygroscopicity of co-crystals of APIs, decreased form diversity of co-crystals of APIs and morphology modulation of co-crystals of APIs. Furthermore, D7 exemplified some of the API-API co-crystals with each API selected from the Table-IV and co-crystals composition of the API-co-crystals former. Thus, according to her, predicated on the aforesaid, it is obvious for a PSITA to prepare co-crystals of API as taught in D5 using the methods disclosed in D7. Applying the same to the present subject

patent application, the claimed invention only provides an alternative tramadol combination with atleast one coxib i.e., celecoxib in co-crystal form.

4.7. That apart, she emphasized that D5 teaches the synergistic combination of tramadol and NSAIDs and has actually exemplified the combination of tramadol with naproxen. D5 also teaches and enlists other NSAIDs like celecoxib etc. which can be used as an alternative in place of naproxen. Thus, the teaching in D5 and the methods of preparation found in D7 together render the claimed invention obvious.

4.8. She further submitted that the disclosure in D7 that co-crystals has an improved property as compared to the free form or a salt would be known to a PSITA, who would be well aware of the potential advantages of the co-crystals in APIs and would obviously use the teachings and suggestions of D5 and D7 with common general knowledge to prepare tramadol and NSAIDs.

4.9. Learned CGSC would contend that the process claimed in Claim 10 is obvious for a PSITA in view of the processes disclosed and described in D7 by dissolving the separate components in a solvent and adding one to the other and co-crystal may then precipitates or crystallizes as the solvent mixtures is evaporated slowly and alternatively, the co-crystal may also be obtained by dissolving the two components in the same solvent.

4.10. Referring to Figure 5 indicating bio-availability of a co-crystal of (rac)-tramadol HCI-celecoxib (1:1) in dogs compared to celecoxib alone and to the combination of both APIs, she would contend that the said figure only shows the comparison and does

not provide bio-availability data for tramadol in comparison to the claimed cocrystal of (rac)-tramadol HCI-celecoxib (1:1). While relying on the judgment of the Division Bench in ***F. Hoffmann-La Roche Ltd. & Ors. vs. Cipla Limited: 2016(65)PTC1(Del)***, she would submit that the procedure prescribed to ascertain whether an invention has an inventive step or not as laid down by the judgment has strictly been followed by the respondent. In fact, according to her, it is the appellant which has failed to establish inventive steps in the claimed invention. She would vehemently contend that both the drugs tramadol and celecoxib are well known in the art for pain relief and the common general knowledge in the art at the priority date is known because the number of combinations of tramadol with other NSAIDs was already known to avoid the side effects of tramadol, based on the prior art documents. The silence of mention about the co-crystal formation of tramadol with celecoxib in D5 may not be of much relevance as the said difference is obvious for a PSITA in view of the detailed disclosure provided in D7 for preparation of API - API co-crystals and the suggestion of possibility of a combination of tramadol and celecoxib. In order to support her contention, she invited the attention of this Court to Table IV to demonstrate that both celecoxib and tramadol as APIs are clearly mentioned in Table IV of D7.

4.11. Predicated on the above, Ms. Bobde would contend that D5 and D7 clearly disclose to the persons skilled in PSITA that in preparation of API cocrystals, the desired properties like dose response, dissolution, bio-availability and stability will be

increased in comparison to API alone and would also show synergy.

4.12. So far as the challenge to objection under Section 3(d) of the Act is concerned, Ms. Bobde would contend that the claimed cocrystals are a mere new form of known substance and do not show any enhanced efficacy over the known substance. She would reiterate that APIs like tramadol and celecoxib are well known in the prior art for the purpose of pain relief and thus, the co-crystallization of two well known drugs is considered as a mere new form. Thus, the objections under Section 3(d) are sustainable as the new form i.e. the cocrystals of the known APIs i.e. tramadol and celecoxib, particularly in the absence of enhanced therapeutic efficacy. She would contend that though Figure 5 shows the comparison of celecoxib with claimed cocrystal only, it does not provide bio-availability data for tramadol in comparison to claimed cocrystals (rac)-tramadol HCI-celecoxib (1:1). That when read with the fact that it is already disclosed in D7 that on forming co-crystals of APIs, the dose response and bio-availability is increased in comparison to the API alone, clearly establishes that the requirement under Section 3(d) of the Act has not been met with. According to her, the appellant has not placed on record any data in the CS that the therapeutic efficacy of the known drugs i.e. tramadol and celecoxib is actually increased or not when taking the cocrystals of both the drugs.

4.13. With respect to the sustainability of objections under Section 3(e) of the Act, Ms. Bobde would submit that a combination of two active agents is considered as a mere admixture particularly in

the absence of any synergy between them and thus, non-patentable.

4.14. Ms. Bobde would refer to Figures 6 & 7 and Table III of the CS relied upon by the appellant to submit that the results of combination of cocrystals of tramadol and celecoxib are not found synergistic as the ED50 for celecoxib if 2.35 and ED50 for cocrystal is 2.26 which is considered comparable only. She would submit that it is not clear from the CS that the alleged cocrystals which shows synergy in all the conditions for which the appellant is seeking protection i.e., the treatment of pain, acute pain, chronic pain, neuropathic pain, severe to moderate pain, hyperalgesia, allodynia or cancer pain, diabetic neuropathy or diabetic peripheral neuropathy and osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica.

4.15. To support the above contentions, reliance was also placed on ***Novartis AG vs. Union of India & Ors.: (2013) 6 SCC 1.***

4.16. Predicated on the above, Ms. Bobde, learned counsel would pray that the present appeal be dismissed.

REJOINDER ON BEHALF OF THE APPELLANT:-

5. Mr. J. Sai Deepak, learned senior counsel reiterated his submissions and contended that the learned Controller failed to consider the data submitted by the appellant demonstrating the enhanced therapeutic efficacy of the claimed invention. He further submitted that in any case, the learned Controller had abandoned the objection pertaining to lack of novelty while passing the impugned order.

6. Addressing the issue of inventive step, learned senior counsel emphasised on the fact that the priority date of the prior art D7 is of the

year 2004 whereas the present invention claims priority from the year 2010. He contended that while D7 generally discloses co-crystalline forms, it neither teaches nor suggests the specific co-crystal combination comprising tramadol and celecoxib as claimed in the present application. Learned senior counsel submitted, *arguendo* that if D7 indeed disclosed or made obvious the claimed combination, there exists no plausible explanation as to why no person skilled in the art conceived or developed the specific co-crystal combination of tramadol and celecoxib for nearly six years following the publication of D7. Thus, he contended that the prolonged absence of such development is indicative of the non-obvious nature of the claimed invention.

7. It was also contended that the prior arts D5 and D7 were cited during the prosecution of corresponding patent applications of the appellant before multiple jurisdictions such as Israel, Brazil and USA, however, the patents were granted in favor of the appellant.

8. Predicated on the aforesaid contentions, he prayed that the present appeal be allowed and the impugned order, being devoid of merits, be set aside.

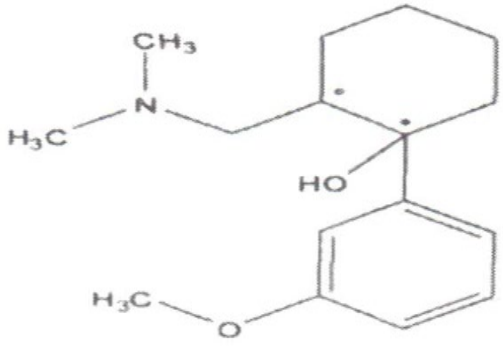
ANALYSIS & CONCLUSION:-

9. The present invention is titled "*CO-CRYSTALS OF TRAMADOL AND COXIBS".* The subject application provides a co-crystal comprising tramadol either as a free base or as a physiologically acceptable salt and at least one coxib, being selected from celecoxib/salts thereof and a pharmaceutical composition comprising said co-crystal. The field of invention is provided as follows:-

> *"The present invention relates to co-crystals of tramadol and NSAIDs - like coxibs processes for preparation of the*

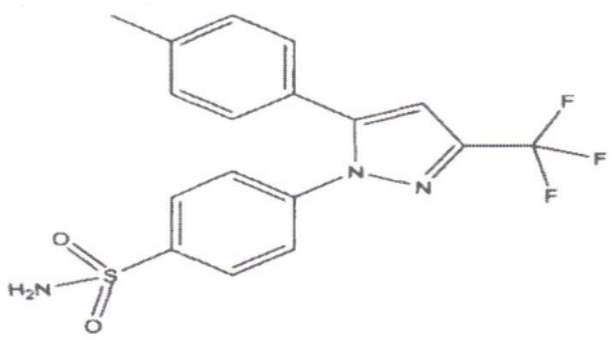
same and their uses as medicaments or in pharmaceutical formulations, more particularly for the treatment of pain."

10. A perusal of the CS of the subject application, would disclose that there are several drugs which are known to be useful in the treatment/management of pain. The CS further discloses one of the morphinic derivatives that has shown improved results when administered orally, is tramadol. It would be beneficial to reproduce hereunder the structure of tramadol :-



Tramadol

11. The CS further discloses that coxibs are NSAIDs used as the co-crystal former with tramadol. Coxibs are selective COX-2 inhibitors and one of the important of these, is the drug celecoxib which is widely marketed. Its chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-pyrazol-1-yl] benzenesulfonamide. It has an empirical formula - C17H14F3N302S. The structure of celecoxib is reproduced hereunder:-



Celecoxib

The CS of the subject application specifies that due to their drawbacks, opioids like tramadol cannot always be given repeatedly or at higher doses as analgesics to treat the pain. Therefore, the CS proposes to combine opioids with other drugs which are non opioid analgesic agents, so as to lower the amount of opioids that is needed to produce an equivalent degree of analgesia. Thus, the objective of the subject application, gathered from the CS is to provide new means of improving the properties of tramadol, especially with respect to the treatment of pain, by providing new drugable forms of tramadol.

12. The present invention under the CS describes the desirable improvements/advantages of the new druggable form that are as follows:-

> *"Especially desirable improvements/advantages of the new drugable form would include:*
>
> *• improvement of physicochemical properties in order to facilitate the formulation, the manufacture, or to enhance the absorption and/or the bioavailability: thus*
> *• being more active when compared to tramadol base or hydrochloride salt: or*
> *• providing a form of tramadol with a further active agent having a beneficial pharmacological effect in itself, thus allowing for a highly efficient dose/weight relation of the final active principle or even*
> *• allowing the use of a lower therapeutic dose of either tramadol and the further active agent, an NSAID - the coxib -, or of both:*

• having a synergistic effect through the combination of tramadol and the further active agent, an NSAID - the coxib -, the same new druggable form: or further
• having the bitter taste of tramadol removed or ameliorated;
• being easily obtainable, easy to manufacture or
• allowing more flexibility in formulating, or facilitating its formulation,
• being highly soluble, thus allowing better dissolution rates, especially if dissolving in an aqueous physiological surrounding, or
• improving stability of the co-crystal in comparison to the physical mixture of Tramadol/Active Agent (an NSAID - the coxib -) at the same ratio;
• allowing new routes of administration; also
• allowing - if necessary - to combine tramadol with a chemically usually non-compatible active agent in the same formulation or even in immediate contact, without having to isolate tramadol; or finally
• minimizing/reducing the side effects, especially the severe side effects, assigned to tramadol.

Other desirable improvements/advantages of the new druggable form would include being active in diseases or symptoms being or related to pain and its subtypes, especially those in which current treatment is insufficient like sciatica or frozen shoulder or pain related to central sensitization (central pain syndrome).

Most desirably the new drugable forms should combine more than one, most of these advantages."

13. It is asserted in the CS that the claimed co-crystals show improved properties as compared to tramadol used individually and simultaneously demonstrate good analgesic activity. It is also claimed that the new drugable form may have another advantage which is possibly achieving some modulation of the pharmacological effects. As per the CS of the present application, the main object of the present invention is a co-crystal comprising tramadol either as a free base or as a physiologically acceptable salt and at least one NSAID/coxib. For clarity, the objective of the present invention is reproduced as under:-

"This objective was achieved by providing new co-crystals of tramadol. It was found that tramadol was able to form co-crystals with NSAIDs - like coxib-, especially with celecoxib. These co-crystals show improved properties if compared to tramadol alone, and also good analgesic activity. The co-crystals thus obtained have a specific stoichiometry. Under the proper circumstance this is also another advantage of these new solid drugable forms possibly achieving some modulation of the pharmacological effects. While APIs (Active Pharmaceutical Ingredients) like tramadol in general have been recognized to form crystalline polymorphs, solvates, hydrates and amorphous forms for a number of years, there is little knowledge about which APIs will form co-crystals. Co-crystals are a specific type of crystalline form which provide a new avenue to modulate the API form and thus to modulate API properties. Co-crystals contain an API and at least one other component which crystallize together. Selection of the other component helps determine whether a co-crystal will form and what properties the co-crystal will have. Just as a polymorph, solvate, hydrate or amorphous form of an API can modulate stability, solubility, and hygroscopicity. a cocrystal can modulate those same properties.

Thus the main object of the present invention is a co-crystal comprising tramadol either as a free base or as a physiologically acceptable salt and at least one NSAID/coxib."

14. In order to understand the claimed invention, it is important to examine the claims of the subject application. The claims filed by the appellant along with written submissions are as follows:-

"We Claim:

I. A co-crystal comprising tramadol either as a free base or as a physiologically acceptable salt and at least one coxib, being selected from celecoxib or salts thereof.

2. The co-crystal as claimed in claim 1 wherein the tramadol is (-)-tramadol or (+)-tramadol or is (rac)-tramadol or a salt thereof.

3. The co-crystal as claimed in claim 2, selected from:
• a co-crystal comprising (rac)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib;

• a co-crystal comprising (+)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib;
• a co-crystal comprising (-)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib; or preferably
• a co-crystal comprising (rac)-tramadol-HCl and celecoxib.

4. The co-crystal as claimed in any of claims 1 to 3, comprising (rac)-tramadol.HCl and celecoxib.

5. The co-crystal as claimed in claim 4, wherein the molecular ratio between the (rac)tramadol. HCl and celecoxib is 1 :1.

6. The co-crystal as claimed in claim 5, comprising (rac)-tramadol-HCI and celecoxib in a molecular ratio of 1:1, characterized in that it shows a Powder X-Ray Diffraction pattern with peaks [20] at 7.1, 9.3, 10.2, 10.7, 13.6, 13.9, 14.1, 15.5, 16.1 16.2, 16.8, 17.5, 18.0, 19.0, 19.5, I 9.9, 20.5, 21.2, 21.3, 21.4, 21.8, 22.1, 22.6, 22.7, 23.6, 24.1 24.4, 25.2, 26.1, 26.6, 26.8, 27.4, 27.9, 28.1, 29.1, 29.9, 30.1, 31.1, 31.3, 31.7, 32.5, 32.8, 34.4, 35.0, 35.8, 36.2 and 37.2[0], with the 20 values being obtained using copper radiation (CuKat 1.54060A).

7. The co-crystal as claimed in claim 5, comprising (rac)-tramadol-HCI and celecoxib in a molecular ratio of 1:1characterized in that it shows a Fourier Transform Infra Red pattern with absorption bands at 3481.6 (m), 3133.5 (m), 2923.0 (m), 2667.7 (m), 1596.0 (m), 1472.4 (m), 1458.0 (m), 1335.1 (m), 1288.7 (m), 1271.8 (m), 1168.7 (s), 1237.3 (m), 1168.7 (s), 1122.6 (s), 1100.9 (m), 1042.2 (m), 976.8 (m), 844.6 (m), 820.1 (m), 786.5 (rn) 625.9 (rn) cm-

8. The co-crystal as claimed in claim 5, comprising (rac)-tramadol-HCI and celecoxib in a molecular ratio of 1:1, characterized in that it has an orthorhombic unit cell with the following dimensions:
a = 11.0323(7) A
b = 18.1095(12) A
c = 17.3206(12) A.

9. The co-crystal as claimed in claim 5, comprising (rac)-tramadol-HCI and celecoxib in a molecular ratio of 1:1, characterized in that the endothermic sharp peak corresponding to the melting point has an onset at 164°C.

10. A process for the production of a co-crystal as claimed in claim 1 comprising the steps of:
(a) dissolving or suspending the coxib, being selected from celecoxib or salts thereof in a solvent; heating the solution or dispersion to a temperature above ambient temperature and below the boiling point of the solution or dispersion;
(b) dissolving together with, or after, or before step (a) tramadol either as a free base or as a salt in a solvent, combined with step (a) by dissolving tramadol already together with the coxib in step (a)
(c) adding the solution of (b) to the solution of (a) and mixing them;
(d) adding a solvent to the solution of (a), (b) or (c) and mixing them;
(e) cooling the mixed solution/dispersion of step (a), (b), (c) or (d) to ambient temperature or below;
(f) evaporating part or all of the solvent; and
(g) filtering-off the resulting co-crystals.

11. A pharmaceutical composition characterized in that it comprises a therapeutically effective amount of 1-60 % by weight of the co-crystal as claimed in any of claims I to 9 in a physiologically acceptable medium."

Having examined the above background and objective of the present invention in the light of the CS of the subject application, it would be apposite to now consider the objections raised by the respondent. In the humble opinion of this Court, it would be relevant and pertinent to first examine and appreciate the controversy regarding the objections of lack of inventive step under Section 2(1)(ja) of the Act.

Objection under Section 2(1)(ja) of the Act:-

15. During the arguments, learned counsel for the appellant emphasised that D7 is the strongest/closest prior art cited by the Patent Office, which possibly discloses the co-crystal, however, insisted that unlike the claimed invention under the subject application, it does not disclose the efficacy. Referring to Figure 6 from the CS of the subject application, it was

submitted that ED50 value for tramadol and celecoxib is 5.41 and 3.03 respectively, while that for co-crystal of (rac)-tramadol-HCl-celecoxib (1:1) is 2.04, and therefore, the composition shows synergy.

16. To examine the objection to lack of inventive step under Section 2(1)(ja) of the Act, it appears crucial to first discuss the prior arts cited by the Patent Office. This Court would consider the prior arts D5 and D7, which are most relevant among the cited prior arts.

17. The prior art D5 (US 2008/0031950 A1) was greatly relied upon by the respondent. D5 relates to a method of treating pain and pain related conditions by administering a therapeutically effective amount of an NSAID and a slow-release tramadol combination to the subject. The field of invention of D5 is reproduced hereunder:-

> *"[0001] The present invention provides a method of treating pain and pain related conditions by administering to a patient in need thereof, a therapeutically effective amount of an NSAID and a slow release tramadol combination. The present invention further a pharmaceutical composition comprises of a slow-release Tramadol and an immediate release NSAID such as Naproxen."*

18. Para [0011] of D5 admits that opioids such as tramadol were used as analgesics to treat severe pain in the past, however, have significant side effects. Subsequently, in para [0012], it discloses that in order to reduce such side effects, opioids have been combined with other drugs including non-opioid analgesic agents which lower the amount of opioid needed to produce an equivalent degree of analgesia. It may be of relevance to note that the said para also discloses that some of these combination products also have the advantage of producing a synergistic analgesic effect. For clarity, paras [0011] and [0012] of D5 are extracted below:-

"[0011] Opioids have for many years been used as analgesics to treat severe pain. They, however, produce undesirable side effects and as a result cannot always be given repeatedly or at high doses. The side effect problems are well documented in the literature. See, for example, J. Jaffe in "Goodman and Gilman's, The Phannacological Basis of Therapeutics", 8th edition; Gilman et al.; Pergamon Press, New York, 1990; Chapter 22; pages 522-57310 wherein it is disclosed that morphine and its congeners, e.g., codeine, hydrocodone and oxycodone, are opioid agonist analgesics that exhibit side effects such as respiratory depression, constipation, tolerance and abuse liability. As alternatives to using opioids, non-opioids such as aspirin and ibuprofen are used as analgesics. Ibuprofen, like aspirin, is not subject to the tolerance, addiction and toxicity of the opioid analgesics, However, ibuprofen, aspirin and other non-steroidal anti inflammatory drugs (commonly referred to as NSAIDs) are only useful in relieving pain of moderate intensity, whereas the opioid analgesics are useful in relieving more intense pain; See Woodbury, D. and Fingl, E. in "The Pharmacological Basis of Therapeutics", 5th Ed.; Goodman, L. and Gilman, A., Chapter 15, (1975)[11].

[0012] To reduce the side effect problems of opioids, opioids have been combined with other drugs including non-opioid analgesic agents, which lower the amount of opioid needed to produce an equivalent degree of analgesia. It has been claimed that some of these combination products also have the advantage of producing a synergistic analgesic effect. *For example, A. Takemori, Annals New York Acad. Sci., 281,262 (1976)[12] discloses that compositions including combinations of opioid analgesics with dn1gs other than analgesics exhibit a variety of effects, i.e., sub additive (inhibitory), additive or super additive. R. Taber et al., J. Pharm. Expt. Thera., 169(I), 29 (1969)13 disclose that the combination of morphine and methadone, another opioid analgesic, exhibits an additive effect. U.S. Pat. No. 4,571, 400 discloses that the combination of dibydrocodcinc, an opioid analgesic, and ibuprofen, a non-opioid analgesic, provides super additive effects when the components are within certain ratios. See also U.S. Pat. Nos. 4,587,252 and 4,569,937, whicb disclose other ibuprofen opioid combinations. A. Pircio et al., Arch. Int. Phannacodyn., 235, 116 (1978) report super additive analgesia with a 1:125 mixture of butrn:phanol, another opioid analgesic, and acetaminophen, a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant super*

> *additive analgesia.* ***Combinations of non-opioid analgesics have also been prepared to avoid the side effects associated with opioids, and the combinations are noted to have the benefit of requiring less of each ingredient and producing super additive effects. G. Stacher et. al.. Int. J. Clin. Pharmacol. Biopbarmacy, 17, 250 (1979)15 report that the combination of non-opioid analgesics, i.e., tolmetin (another NSAID) and acetaminophen, allows for a marked reduction in the amount of tolmetin required to produce analgesia. In addition, U.S. Pat. No. 4,260,629 discloses that an orally administered composition of acetaminophen and zomepirac, a non-opioid analgesic, in a particular weight ratio range produces a superadditive relief of pain in mammals.*** *Furthermore, U.S. Pat. No. 4,132,788 discloses that 5-aroyl-1-(lower) alkylpyrrole- 2-acetic acid derivatives, non-opioid analgesics, when combined with acetaminophen or aspirin exhibit superadditive ant arthritic activity. However, there have been warnings against the daily consumption of non-opioid analgesic mixtures and of the consumption of a single nonopioid analgesic in large amounts or over long periods (see, D. Woodbury and E. Fingl al page 349)11. In addition, ibuprofen, aspirin and some other NSAIDs may cause gastrointestinal side effects especially if used repeatedly. See, for e:Kample, M. J. S. Langman, Am. J. Med. 84 (Suppl. 2A): 15-19, 1988)16 ; P. A. Insel in "The Pharmacological Basis of Therapeutics" 8th Ed.; Gilman, A. G. et al., Chapter. 26, pp. 664-668, 199017."*

[Emphasis supplied]

19. Apart from the above, para [0043] of D5 enlists the NSAIDs which can be selected from celecoxib, diclofenac, diflunisal, etc., to be used in combination with tramadol. The same is reproduced hereunder:-

> *"[0043] The term "effective amount" as used herein means a dosage which is sufficient in order for the treatment of the patient to be effective compared with no treatment. The term "NSAID" as used in this specification means any non-steroidal anti-inflammatory drug including but not limited examples such as Celecoxib, Diclofenac, Diflunisal, Etod-olac, Fenoprofen, Flurbirofen, Ibuprofen, Jndometlrocin, Ketoprofen, Ketorolac, Mefenam.icAcid, Meloxicam, Nabu-metone, Neproxen, Oxaprozin, Piroxicam, Sulindac and Tolmetin."*

20. Thus, the prior art D5 does disclose celecoxib as one such NSAID which may be used in combination with tramadol. As per Para [0012], the combination may have some synergistic effect. Further, in para [0068], D5 notes that Examples 1 and 2 illustrate the invention related to a combination comprising of a slow release tramadol and an NSAID. It also notes that the person skilled in the art (hereinafter referred to as "PSITA") will know how this combination may be modified using other NSAIDs such as celecoxib from the prior art. It is imperative to extract para [0068] hereunder:-

> *"[0068] The following Examples 1 and 2 are shown for illustrating the invention related to combination comprising a slow release tramadol and an NSAID. According to this invention where we have used a specific NSAID Naproxen only as an example for illustrative purposes and these examples in no way limit the scope of the invention.* ***The person skilled in the art will know how the combination may be modified using other NSAIDs such as Celecoxib, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbirofen, Ibuprofen, Indometltacin, Ketoprofen, Ketorolac, Mefenrunic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicaru, Sulindac and Tolmetin and using other manufacturing methods known in the art.*** *In general, the invention disclosed in this patent can be manufactured using the range listed in Table 1."*

[Emphasis supplied]

21. Another prior art cited and heavily relied upon by the respondent is document D7 (WO 2004/078163 A2). The invention under D7 relates to co-crystal API-containing compositions, pharmaceutical compositions comprising such APIs, and methods for preparing the same. It is noted that prior art D7 discloses that it would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. It is of some significance to observe that D7 also notes that needle-like crystal forms/habits of APIs can lead to aggregation, even in

cases where the composition is composed of the API mixed with other substances such that a non-uniform mixture is obtained. The background of D7 cited below, also notes that it is desirable to identify improved forms of APIs which exhibit significantly improved properties that include increased aqueous solubility and stability. The background of D7 is reproduced as follows:-

> *"It would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a nonuniform mixture is obtained. It is also desirable to increase or decrease the dissolution rate of API-containing pharmaceutical compositions in water, increase or decrease the bioavailability of orally-administered compositions, and provide a more rapid or more delayed onset to therapeutic effect. It is also desirable to have a form of the API which, when administered to a subject, reaches a peak plasma level faster or slower, has a longer lasting therapeutic plasma concentration, and higher or lower overall exposure when compared to equivalent amounts of the API in its presently-known form. The improved properties discussed above can be altered in a way which is most beneficial to a specific API for a specific therapeutic effect."*

22. The summary of CS of D7 also discloses that a new co-crystalline form of APIs can be obtained which improves the properties of APIs as compared to such APIs in a non-co-crystalline state. For the purposes of clarity, the summary of the CS of D7 is reproduced as follows:-

> *"SUMMARY OF THE INVENTION*
>
> *It has now been found that new co-crystalline forms of APIs can be obtained which improve the properties of*

APIs as compared to such APIs in a non-co-crystalline state (free acid, free base, Zwitter ions, salts, etc.).

Accordingly, in a first aspect, the present invention provides a co-crystal pharmaceutical composition comprising an API compound and a co-crystal former, such that the API and cocrystal former are capable of co-crystallizing from a solid or solution phase under crystallization conditions."

[Emphasis supplied]

23. Further, the claim 5 of D7 claims that the APIs are hydrogen bonded to a molecule. Claim 6 of D7 specifies that the composition has improved properties such as increased solubility, better bioavailability, increased stability of the co-crystals as compared to an API and decrease in hygroscopicity. Further, Claim 16 of D7 claims a process for preparing a pharmaceutical co-crystal composition comprising a first and a second API. Claims 5, 6, 16 and 17 of the prior art D7 provides the following co-crystal composition:-

"5. A pharmaceutical co-crystal composition, comprising: a first and a second API, wherein each API is either a liquid or a solid at room temperature, and wherein the APIs are hydrogen bonded to a molecule.

6. The pharmaceutical co-crystal composition according to claim 5, wherein:

(a) the first API is hydrogen bonded to the second API;
(b) an API is selected from an API of Table IV;
(c) each API is selected from an API of Table IV;
(d) an API is a liquid at room temperature, and the other API is a solid at room temperature;
(e) each API is a solid at room temperature;
(f) an API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-

heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;
(g) each API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cynamide, oxime, nitrite, diazo, organohalide, nitro, S-beterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;
(h) the difference in pKa between the first API and the second API does not exceed 2;
(i) the solubility of the co-crystal is increased as compared to an API;
(j) the dose response of the co-crystal is increased as compared to an API;
(k) the dissolution of the co-crystal is increased as compared to an API;
(1) the bioavailability of the co-crystal is increased as compared to an API;
(m) the stability of the co-crystal is increased as compared to an API;
(n) a difficult to salt or unsaltable API is incorporated into the co-crystal;
(o) the hygroscopicity of the co-crystal is decreased as compared to an API;
(p) an amorphous API is crystallized as a component of the co-crystal;
(q) the form diversity of the co-crystal is decreased as compared to an API; or (r) the morphology of the co-crystal is modulated as compared to an API.

xxx xxx xxx

16. A process for preparing a pharmaceutical co-crystal composition comprising a first and a second API, comprising:
(a) providing the first and a second API, wherein each API is either a liquid or a solid at room temperature;
(b) grinding, heating, co-subliming, co-melting, or contacting in solution the APis under crystallization conditions, so as to form a solid phase, wherein the APis are hydrogen bonded to a molecule;
(c) isolating co-crystals formed thereby; and
(d) incorporating the co-crystals into a pharmaceutical composition.

17. The process of claim 16, wherein:
(a) the first API is hydrogen bonded to the second API;
(b) an API is selected from an API of Table IV;
(c) each API is selected from an API of Table IV;
(d) an API is a liquid at room temperature and the other API is a solid at room temperature;
(e) each API is a solid at room temperature;
(f) an API has at least one functional group selected from the group consisting of: ether, bioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid. phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;
(g) each API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrite, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-beterocyclic ring, pyrrole, O-heterocyclic ring. furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or
(h) the difference in pK. between the first API and the second API does not exceed 2."

[Emphasis supplied]

24. The aforesaid needs to be read in conjunction with the disclosure of celecoxib as also tramadol made by D7 in Table 4, the relevant part whereof is extracted hereunder:-

celecoxib	Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)- [CAS]
tramadol	Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, cis-(+/-)-[CAS]

25. The claim 6 of D7 specifies that each API is selected from an API of Table IV and the said Table IV discloses both celecoxib as well as tramadol. Additionally, relevant Examples i.e., examples 1 and 2 of D7 which discuss the preparation of the co-crystals are reproduced as follows:-

> *"Example 1*
>
> *1:1 celecoxib:nicotinamide co-crystals were prepared. Celecoxib (100 mg, 0.26 mmol) and nicotinamide (32.0 mg, 0.26 mmol) were each dissolved in acetone (2 mL). The two solutions were mixed and the resulting mixture was allowed to evaporate slowly overnight. The precipitated solid was redissolved in acetone a second time and left to evaporate to dryness. The powder was collected and characterized. Detailed characterization of the celecoxib:nicotinamide co-crystal is listed in Table XXIV. Fig. 1A shows the PXRD diffractogram after subtraction of background noise. Fig. 1B shows the raw PXRD data. Fig. 2 shows a DSC thermogram of the celecoxib:nicotinamide cocrystal. Fig. 3 shows a TGA thermogram of the celecoxib:nicotinamide co-crystal. Fig. 4 shows a Raman spectrum of the celecoxib:nicotinamide co-crystal.*
>
> *Example 2*
>
> *Co-crystals of celecoxib and 18-crown-6 were prepared. A solution of celecoxib (157.8 mg, 0.4138 mmol) in Et20 (10.0 mL) was added to 18-crown·6 (118.1 mg, 0.447 mmol). The opaque solid dissolves immediately and a white solid subsequently began to crystallize very rapidly. The solid was collected via filtration and was washed with additional diethyl ether (5 mL). Detailed characterization of the celecoxib:18-crown-6 co-crystal is listed in Table XXIV. Fig. SA shows the PXRD diffractogram after subtraction of background noise. Fig. 5B shows the raw PXRD data. Fig. 6 shows a DSC thermogram of the celecoxib:18-crown-6 co-crystal. Fig. 7 shows a TGA thermogram of the celecoxib:18-crown-6 co-crystal."*

26. It is necessary to also note that prior art D7 on page 11 describes the API-API co-crystal and the chemical and physical properties of an API in the form of a co-crystal which may be compared to a reference

compound. Besides, at pages 5 and 6, the prior art D7 under the heading 'Summary of the Invention', describes the solubility modulation, dissolution modulation, bioavailability modulation, dose-response modulation and increased stability.

27. Additionally, D7 discloses several methods for the preparation of co-crystals including the "Crystallization from Solution". The methods are extracted as follows:-

> *"EXEMPLIFICATION*
>
> *General Methods for the Preparation of Co-Crystals*
>
> *a) High Throughput crystallization using the CrystalMax ™ platform*
>
> *CrystalMax™ comprises a sequence of automated, integrated high throughput robotic stations capable of rapid generation, identification and characterization of polymorphs, salts, and co-crystals of APIs and API candidates. Worksheet generation and combinatorial mixture design is carried out using proprietary design software Architect™. Typically, an API or an API candidate is dispensed from an organic solvent into tubes and dried under a stream of nitrogen. Salts and/or co-crystal formers may also be dispensed and dried in the same fashion. Water and organic solvents may be combinatorially dispensed into the tubes using a multi-channel dispenser. Each tube in a 96-tube array is then sealed within 15 seconds of combinatorial dispensing to avoid solvent evaporation. The mixtures are then rendered supersaturated by heating to 70 degrees C for 2 hours followed by a 1 degree C/minute cooling ramp to 5 degrees C. Optical checks are then conducted to detect crystals and/or solid material. Once a solid has been identified in a tube, it is isolated through aspiration and drying. Raman spectra are then obtained on the solids and cluster classification of the spectral patterns is performed using proprietary software (Inquire™).*
>
> *b) Crystallization from solution*
>
> *Co-crystals may be obtained by dissolving the separate components in a solvent and adding one to the other. The co-crystal may then precipitate or crystallize as the solvent mixture is evaporated slowly. The co-crystal may*

<u>also be obtained by dissolving the two components in the same solvent or a mixture of solvents.</u>

c) Crystallization from the melt (Co-melting)

A co-crystal may be obtained by melting the two components together (i.e., co-melting) and allowing recrystallization to occur. In some cases, an anti-solvent may be added to facilitate crystallization.

d) Thermal microscopy

A co-crystal may be obtained by melting the higher melting component on a glass slide and allowing it to recrystallize. The second component is then melted and is also allowed to recrystallize. The co-crystal may form as a separated phase/band in between the eutectic bands of the two original components.

e) Mixing and/or grinding

A co-crystal may be obtained by mixing or grinding two components together in the solid state.

f) Co-sublimation

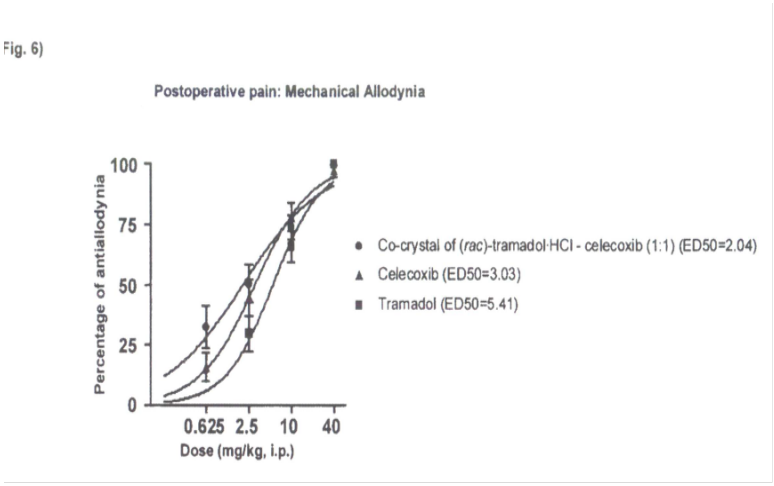
A co-crystal may be obtained by co-subliming a mixture of an API and a cocrystal former in the same sample cell as an intimate mixture either by heating, mixing or placing the mixture under vacuum. A co-crystal may also be obtained by co-sublimation using a Kneudsen apparatus where the API and the co-crystal former are contained in separate sample cells, connected to a single cold finger, each of the sample cells is maintained at the same or different temperatures under a vaccum atmosphere in order to co-sublime the two components onto the cold-finger forming the desired co-crystal."

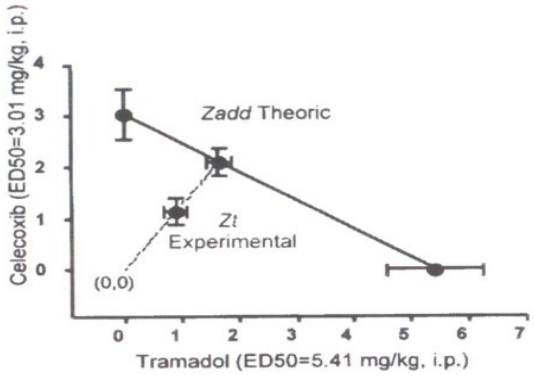
[Emphasis supplied]

28. While submitting that the present invention shows synergistic effect, the appellant had referred to Fig.6 and Fig.7 of the CS of the subject application. The appellant had submitted that the lower the ED50 would be, the higher is the efficacy. According to the appellant, the graphs show that the individual efficacy is less than the combined, and therefore there is synergy.

29. As per the appellant, this data was available with the Patent Office, yet the respondent did not provide any reasoning as to how this data is

inadequate to overcome the objection under Section 2(1)(ja) of the Act. For clarity, the said graphs are extracted below:-





30. Contrary to this, the respondent submitted that under the data submitted by the appellant, there is no appreciable change in the dosage. The respondent further submitted that the peak reached is almost the same in tramadol as in the composition, and therefore, there are no significant improvements. However, according to the appellant, the data provided is ED50=2.04 which is better than the performance of the other two products taken individually.

31. The appellant also vehemently contended that if the combination is disclosed in one prior art and co-crystals in other, the learned controller is mandated to provide the teaching as to how one cited document motivates/suggests to refer to the other, in order to reach the invention claimed under the subject application.

32. To examine the objection of lack of inventive step of the present invention, this Court has analysed the above mentioned disclosure of D5 and D7 in comparison to the present invention, which is depicted in the following table:-

SUBJECT APPLICATION	***D7***	***D5***	***COMMENTS***
Claim 1. *"We Claim:* *I. A co-crystal comprising* ***tramadol*** *either as* ***a free base*** *or as* ***a physiologically acceptable salt*** *and at least one* ***coxib****, being selected from* ***celecoxib or salts thereof****.*	***Claim 5*** *5. A pharmaceutical co-crystal composition, comprising: a first and a second API, wherein each API is either a liquid or a solid at room temperature, and* ***wherein the APIs are hydrogen bonded to a molecule****.* ***Claim 6*** *6. The pharmaceutical co-crystal composition according to claim 5, wherein:* *(a) the first API is hydrogen bonded to the second API;* *(b) an API is selected from an API of Table*	*"**[0068]** The following Examples 1 and 2 are shown for illustrating the invention related to combination* ***comprising a slow release tramadol and an NSAID.*** *According to this invention where we have used a specific NSAID Naproxen only as an example for illustrative purposes and these examples in no way limit the scope of the invention.* ***The person skilled in the art will know how the combination may be modified using other NSAIDs such as Celecoxib,***	**Claim 6 of D7** disclosed the pharmaceutical co-crystal composition, comprising compounds given under table IV, which included tramadol and celecoxib. Further, **Para [0068] of D5**, discloses that tramadol and celecoxib can be used together. **Therefore, the composition of tramadol and celecoxib is disclosed.**

	IV; *(c)* ***each API is selected from an API of Table IV;*** *(d) an API is a liquid at room temperature, and the other API is a solid at room temperature;* *(e) each API is a solid at room temperature;* *(f) an API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;* *(g) each API has at*	*Diclofenac, Diflwusal, Etodolac, Fenoprofen, Flurbirofen, Ibuprofen, Indometltacin, Ketoprofen, Ketorolac, Mefenrunic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicaru, Sulindac and Tolmetin and using other manufacturing methods known in the art. In general, the invention disclosed in this patent can be manufactured using the range listed in Table 1."* *"[0043] The tenn "effective amount" as used herein means a dosage which is sufficient in order for the treatment of the patient to be effective compared with no treatment. The term "NSIAD" as used in this specification means any non-steroidal anti-inflammatory drug including but not limited examples such as* ***Celecoxib****, Diclofenac,*	

	least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cynamide, oxime, nitrite, diazo, organohalide, nitro, S-beterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; *(h) the difference in pKa between the first API and the second API does not exceed 2;* ***(i) the solubility of the co-crystal is increased as compared to an API;*** ***(j) the dose response of the co-crystal is increased as compared to an API;*** *(k) the dissolution of*	*Diflunisal, Etodolac, Fenoprofen, Flurbirofen, Ibuprofen, Jndometlrocin, Ketoprofen, Ketorolac, Mefenamic Acid, Meloxicam, Nabumetone, Neproxen, Oxaprozin, Piroxicam, Sulindac and Tolmetin."*	

	*the co-crystal is **increased** as compared to an API;* *(l) the **bioavailability** of the co-crystal is increased as compared to an API;* *(m) the **stability** of the co-crystal is increased as compared to an API;* *(n) a difficult to salt or unsaltable API is incorporated into the co-crystal;* *(o) the **hygroscopicity of the co-crystal is decreased as compared to an API**;* *(p) an amorphous API is crystallized as a component of the co-crystal;* *(q) the form diversity of the co-crystal is decreased as compared to an API; or* *(r) **the morphology of the co-crystal is modulated as compared to an API.***		
Claim 10. *10. A **process for the production of a co-crystal as claimed in claim 1 comprising the steps of:*** *(a) **dissolving or suspending the coxib**, being selected from celecoxib or*	***Claim 16.*** *A process for preparing a pharmaceutical co-crystal composition comprising a first and a second API, comprising:-* ***(a) providing a first and a second API, wherein each API is***		**As per D7, Co-crystals may be obtained by dissolving separate components in a solvent and thereafter, adding one to the other.** **The D7 also**

salts thereof in a solvent; heating the solution or dispersion to a temperature above ambient temperature and below the boiling point of the solution or dispersion; *(b)* ***dissolving together with, or after, or before step (a) tramadol*** *either as a free base or as a salt in a solvent, combined with step (a) by dissolving tramadol already together with the coxib in step (a)* *(c)* ***adding the solution of (b) to the solution of (a) and mixing them;*** *(d)* ***adding a solvent to the solution of (a), (b) or (c) and mixing them;*** *(e)* ***cooling the mixed solution/dispersion*** *of step (a), (b), (c) or (d) to ambient temperature or below;* *(f)* ***evaporating*** *part or all of the solvent; and* *(g)* ***filtering-off*** *the resulting co-crystals.*	***either a liquid or a solid at room temperature;*** *(b)* ***grinding, heating, co-subliming, co-melting, or contacting in solution the APIs under crystallization conditions, so as to form a solid phase, wherein the APIs are hydrogen bonded to a molecule;*** *(c)* ***isolating co-crystals formed thereby;*** *and* *(d) incorporating the co-crystals into a pharmaceutical composition."* *"EXEMPLIFICATIO N* *General Methods for the Preparation of Co-Crystals* b*) Crystallization from solution* ***Co-crystals may be obtained by dissolving the separate components in a solvent and adding one to the other. The co-crystal may then precipitate or crystallize as the solvent mixture is evaporated slowly. The co-crystal may also be obtained by dissolving the two***		**disclosed that the co-crystal may then precipitate/crys tallize as the solvent mixture is evaporated slowly.**

	components in the same solvent or a mixture of solvents.		

[Emphasis supplied]

33. In order to ascertain the question as to whether the improvements or advantages sought under the present invention are already described or disclosed in D7, it would appropriate to first note the desirable improvements/advantages of the new drugable form as described in the CS of the present invention and hitherto discussed in para 12 of this judgment above. Those are summarized as follows:-

> *"• improvement of **physicochemical properties** in order to facilitate the formulation, the manufacture, or **to enhance the absorption and/or the bioavailability:** thus*
> *• **being more active***
> *• beneficial pharmacological effect in itself, thus allowing for a **highly efficient dose/weight** relation of the final active principle or even*
> *• allowing the use of a lower therapeutic dose of either tramadol and **- the coxib -, or of both**:*
> *• having a **synergistic effect** through the combination of tramadol and coxib*
> *• bitter taste of tramadol removed or ameliorated;*
> *• being easily obtainable, easy to manufacture or*
> ***• allowing more flexibility in formulating***
> *• **being highly soluble, thus allowing better dissolution rates**,*
> ***• improving stability of the co-crystal in comparison to the physical mixture of Tramadol/Active Agent (an NSAID - the coxib -)***
> *• allowing **new routes of administration**; also*
> ***minimizing/reducing the side effects, especially the severe side effects, assigned to tramadol."***

34. It flows from para 33 above that the objective of the CS of the subject application specifies that the claimed co-crystals show improved properties as compared to tramadol alone and also show good analgesic activity. Additionally, another advantage of these new solid drugable

forms claimed is possibly achieving some modulation of the pharmacological effects. It also notes that the co-crystals thus obtained have a specific stoichiometry and possibly achieve some modulation of the pharmacological effects. In comparison, Claim 6 of the D7 claims as under:-

- Compared to an API, the solubility of the co-crystal is increased.
- The dose response of the co-crystal is also increased as compared to an API.
- Compared to an API, the dissolution of the co-crystal is increased
- As compared to an API, the bioavailability of the co-crystal is increased.
- The stability of the co-crystal is increased as compared to an API;
- Hygroscopicity of the co-crystal is decreased as compared to an API.
- The form diversity of the co-crystal is decreased as compared to an API.
- Compared to an API, the morphology of the co-crystal is modulated.

The aforesaid comparison would amply suggest that the disclosure in D7 also specifies (i) increased bioavailability in the co-crystals compared to the individual APIs; (ii) dose response of the co-crystal is increased as compared to an API; (iii) increase in stability of the co-crystal. These parameters are also claimed in the present invention.

35. As per the Summary of the Invention of D7, the new co-crystalline forms of APIs can be obtained which improves the properties of APIs as compared to such APIs in a non-co-crystalline state.

36. D7 under claim 1 discloses the hydrogen bonding between the first API and the second API. Further, claim 5 of D7 specifies that the APIs are hydrogen bonded to a molecule. It is significant to note that at page 5 of

the CS of the present invention, it is clearly specified that the two compounds are held together by weak interaction, and the interaction is neither ionic nor covalent and includes hydrogen bonds. The relevant para of the present invention is reproduced as follows:-

> *‘"Co-Crystal" as used herein is defined as a crystalline material comprising two or more compounds at ambient temperature (20 to 25°C, preferably 20°C) of which at least two are held together by weak interaction, wherein at least one of the compounds is a co-crystal former. Weak interaction is being defined as an interaction which is neither ionic nor covalent and includes for example; hydrogen bonds, van der Waals forces, and π -π interactions.’’*

[Emphasis supplied]

37. Therefore, reading of the prior art D5 (para 68) which discloses the combination of tramadol and celecoxib as a method of treating pain, along with the disclosure under prior art D7, would render the present invention obvious.

38. That apart, the improvements specified under claim 6 of the prior art D7 provides teaching/motivation/suggestion to apply the co-crystal disclosed under D7 to improve the treatment under D5. Significantly, para 12 of D5 discloses that some of the combination products also have the advantage of producing a synergistic analgesic effect. Such disclosure under prior art D5 would motivate PSITA to apply the co-crystal disclosed under D7 for better improvements.

39. Additionally, D7 under general methods of preparation as well as claim under 16, discloses that Co-crystals may be obtained by dissolving separate components in a solvent followed by the addition of one component to the other. The D7 further discloses that thereafter co-crystal may then precipitate/crystallize as the solvent mixture evaporated slowly.

Thus, the process disclosed in D7 and that in the present invention also overlap.

40. In light of the above discussion and consideration of prior art documents D5 and D7, the invention claimed under the subject application lacks inventive step and therefore, barred under Section 2(1)(ja) of the Act.

41. Since this Court has, on merits, upheld the objection raised by the learned Controller on the ground of lack of inventive step under Section 2(1)(ja) of the Act, this Court is of the considered opinion that there is no requirement of examining the other objections raised under Section 3(d) and 3(e) of the Act. (See: ***Kroll Information Assurance, LLC vs. The Controller General of Patents, C.A.(COMM.IPD-PAT) 439/2022)***.

42. Both parties had relied on certain judgements in support of their respective contentions as noted above however, having regard to the fact that this Court has examined and analysed the objection under Section 2(1)(ja) of the Act on merits in detail, this Court is of the considered opinion that the said judgements need no reference.

43. In view thereof, the present appeal stands dismissed, alongwith pending applications, with no order as to costs.

TUSHAR RAO GEDELA
(JUDGE)

AUGUST 07, 2026/*rl/aj*