VNIVERSITAT DE VALÈNCIA

Course Guide
44714 Industrial synthesis of drugs

COURSE DATA

Data Subject	
Code	44714
Name	Industrial synthesis of drugs
Cycle	Master's degree
ECTS Credits	3.0
Academic year	2020 - 2021

Study (s)

Degree	Center	Acad. year	Period
2226 - M.D. in Organic Chemistry	Faculty of Chemistry	1	Second term

Subject-matter

Degree	Subject-matter	Character
2226 - M.D. in Organic Chemistry	10 - Industrial synthesis of drugs	Obligatory

Coordination

Name	Department
DEL POZO LOSADA, CARLOS	325 - Organic Chemistry

SUMMARY

This subject is divided in two parts: “Pharmaceutical products scale up” (1,5 credits) together with “New methodologies in the drug synthesis” (1,5 credits). Both parts constitute the topic Industrial Drug Synthesis. This subject in addition with Industrial Organic Chemistry will provide a global perspective of the aspects that one professional could find in either chemical or pharmaceutical industry. This involves the project approach, the implementation, scale up following the current regulations and finally patent publication. Despite those aspects are related to pharmaceutical industry, as a global vision could be applied to other industrial branches.

The subject “Pharmaceutical product scale-up” shows in detail all aspects necessaries to transfer the knowledge of manufacturing from a laboratory until production plant. This knowledge and its philosophy are applicable to other industries that develop processes.

PREVIOUS KNOWLEDGE

Relationship to other subjects of the same degree

There are no specified enrollment restrictions with other subjects of the curriculum.

Other requirements

A good background in organic chemistry is highly desirable.

OUTCOMES

2226 - M.D. in Organic Chemistry

- Students should apply acquired knowledge to solve problems in unfamiliar contexts within their field of study, including multidisciplinary scenarios.
- Students should be able to integrate knowledge and address the complexity of making informed judgments based on incomplete or limited information, including reflections on the social and ethical responsibilities associated with the application of their knowledge and judgments.
- Students should communicate conclusions and underlying knowledge clearly and unambiguously to both specialized and non-specialized audiences.
- Students should demonstrate self-directed learning skills for continued academic growth.
- Students should possess and understand foundational knowledge that enables original thinking and research in the field.
- Use different presentation formats (oral, written, slide presentations, boards, etc.) to communicate knowledge, proposals and positions.
- Be able to access to information tools in other areas of knowledge and use them properly.
- Ability to design synthetic sequences for the preparation of some active ingredients, by using methodologies previously described along the course.
- Saber participar en debates y discusiones, dirigirlos y coordinarlos y ser capaces de resumirlos y extraer de ellos las conclusiones más relevantes y aceptadas por la mayoría.
- Poseer habilidades sociales, un buen nivel de comunicación oral y escrita, así como capacidad para trabajar en equipo y con personas de diferentes procedencias.
- Competencias de gestión tales como la capacidad para la planificación y gestión de tiempo y recursos, así como para dirigir y tomar decisiones.
- Ser capaces de valorar la necesidad de completar su formación científica, en lenguas, en informática, asistiendo a conferencias o cursos y/o realizando actividades complementarias, autoevaluando la aportación que la realización de estas actividades supone para su formación integral.
- Comprender los problemas del escalado de las reacciones en la industria.

LEARNING OUTCOMES

The final aim with this subject is to achieve, together with the subjects that form Industrial Organic Chemistry, that the students will obtain a series of knowledge directly related with the chemical industry in general, and particularly, with the pharmaceutical industry, that will qualify them to access a professional career in those types of companies with guaranties. Nowadays, the academic formation of the students in the University does not reach some aspects directly related with industry, and this master pretends to fill this gap.

DESCRIPTION OF CONTENTS

1. Route selection

Laboratory synthetic methodology to access new molecules are not applicable to an industrial scale in the 99% of the cases. A series of principles are detailed to be able to choose a new synthetic protocol at industrial scale.

2. Reagents selection

Once the synthetic route is defined, there are a wide variety of possibilities to develop the process just by changing the reagents. Here we will describe details to how to choose among all of those possibilities on the basis of availability, economy, riskiness, etc.

3. Solvent selection

Solvents selection of a synthetic sequence is one of the main aspects since, in general, they are the reagents employed in higher volume, and therefore, their influence in the environmental issues and security is very high. Here we will detail the security features and toxicity of a wide variety of solvents. Several solvents, with widespread usage in the 20th century, are nowadays not recommended or prohibited for the different regulating agencies. More secure and economic alternatives will be discussed.

4. Reaction development

For the correct development of a named reaction, the following aspects have to be considered: determination of the reaction security, confirm a secure equipment for the operations, scale-up selection, election of the equivalents of all starting materials, determination of the need of inert atmosphere, stablish the adition sequence, set the temperature and speed of addition, selection of the pressure, set the stirring and monitorize the reaction.

5. Water influence

The water is or could be the main source of problems in the scale-up of a reaction. Is considered as the most frequent impurity, but on the other hand, it could be necessary for the normal development of a process.

6. Monitoring during the process

Process control is crucial for the perfect monitoring of a reaction; here some of the aspects that could be overseeing with controls during the process, together with the normal techniques employed to perform them: end of the reaction (GC, HPLC, IR, TLC, etc.). Keeping of aceptable levels of water. Appropiate reagent loading. Control of the pH in neutralizations, extractions, etc. Ensure the complete elimination of a solvent. Confirm the complete washing of a precipitate (HPLC, pH). Ensure complete dryness (GC).

7. Process Optimization

Process optimization has a high influence in the following aspects: Improve eficiency, improve yield and quality, reduce costs, improve productivity and reduce waste.
Several different forms of optimization are described, the impact of those changes as a consequence of the optimization, in the subsequent steps of the synthesis, in the impurity profile of the active pharmaceutical ingredient and how to choose the adequate optimization depending on the time.

8. Catalytic reactions optimization

The same aspects described in the previous section but with catalytic reactions.

9. Work-up

Work-up is described as: collective Word for the treatment applied to a process since the reaction was completed until the product is isolated.
Some aspects related to the work-up are: quenching or treatment of the reaction mixture por prevent or minimize side reactions, provide secure conditions for the staff that takes care of the process, suppres impurities, provide final product in the adequate conditions for its purification, neutralize waste and minimize operations and reactors.
The fundamental operations of the work-up will be studied: quenching, extraction, treatment with activated carbón, filtration, condentracion, solvent removal, deionization and metal elimination, waste elimination, derivatization and solid supported reagents.

10. Final aspect and impurities

The final aspect that a drug reach the market is very important. For its eficacy. Aspects to consider: importance of the final process, formulation (pills), stability tests, degradation (oxidation, hydrolysis, fotolysis, rearrangement, reaction with additives), control of the size of particle, polimorf selection (optimun stability, good bioavailability, easy of formation) and purity and impurities (toxicologic essays, minimize).

11. Anticipation and problem solving

The best way to avoid problems is to anticípate its appearance. Some aspects that could help as, are: deep knowledge of the process, confirm that is secure, discuss possible problems with the scale-up team, control in process performing, ensure the quality of the raw materials, ensure the availability of the adequate equipment, after the process, ensure que quality and discuss future optimizations.

12. Chiral synthesis

New drugs posses more and more chiral centers. Here we will detail different forms to access those productos: fermentation (natural product isolation antibiotics, pravastatin, lovastatin-; semisynthetic-simvastatin, penicillins, cephalosporins-), exploitation of the natural resources of chiral compounds: preparation of intermediates chiral carbon pool-. (enalapril, aztreonam, naproxen), separation of racemates, preferent cristallization of one enantiomer (kinetic resolution chemical or enzimatyc-, cristallization of diastereoisomers, chromatography), asymmetric synthesis (stoichiometric, catalytic).

13. Practical examples of drug synthesis

In this chapter, which constitutes the second part of the subject, we will provide practical examples of the synthesis and process optimization in the drug synthesis. Scale-up and process improvement will be also considered from a Green chemistry perspective.

WORKLOAD

ACTIVITY	Hours	% To be attended
Theory classes	16,00	100
Seminars	14,00	100
TOTAL	**30,00**	

TEACHING METHODOLOGY

The subject is formulated in a manner that the student is the principal actor of its own learning. From the beginning of the course, students will have the whole didactic material necessary and the teaching will be structured in the following manner:

• Master classes (in person): In those classes basic concepts of the subject will be introduced. Active participation of the students will be encouraged by means of question proposal related to the application of previously acquired concepts.

• Seminars.- This teaching assignment will be dedicated to problem resolution and questions with the active participation of students.

• Written assignment.- Additionally, when the teacher will consider it, some assignments will be proposed, normally related to the study of a practical case, connected with one of the themes of the program, that will be detailed in a scientific publication.

EVALUATION

The assessment of student learning will be performed in a continuous manner for the teacher throughout the course, and it will contain the following points:

● **Direct assessment of the professor:** 15% of the final grade will come from the direct evaluation of the professor both in theoretical and practical classes. In this evaluation, some different aspects will be considered. Among them, we outlined the following:

- Attendance and participation in the discussions.

- Progress in the use of the proper language of the field.

- Problem resolution and question proposal

- Critic spirit

- presentation of the exercices.

● **Assessment of the word performed by the student.** The contents and the form will be considered at this stage. The weighting of this part will be 25% of the total grade.

● **Written exams.** 60% of the final grade will come from the grades obtained in those written exams.

- in person examination (traditional style) with both theoretical and practical questions of contents related to the subject. The nature of those questions and problems will force the students to connect several aspects that come from different themes of the subject, or if the teacher considers it convenient, from different subjects.

- Not in person exams. The teacher will give to the students directly or by electronic mail, a series of questions that the students have to complete, either individually or in group, depending on the decision of the teacher. In any case, the answers will be sent to the teacher again in person or by electronic mail, in the period previously stipulated.

REFERENCES

Basic

- Practical Process Research & Development, N.G.Anderson Academic Press, 2000
- Organometallics in Process Chemistry, Ed. R.D.Larsen, Springer, 2004
- The Chemistry of Process Development in Fine Chemical & Pharmaceutical Industry, C.Someswara, Rao, Asian Books, 2004

Additional

- Chemical Process Research. The Art of Practical Synthesis, Ed. A.F.Abdel-Magid, 2004
- Green Chemistry,.Theory and Practice, P.Anastas, Oxford University Press, 2000
- Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions, Ed. H.U.Blaser and E.Schmidt. 2004. Weinheim, Wiley
- webs for safety information : www.fmclithium.com ; www.dechema.de

ADDENDUM COVID-19

This addendum will only be activated if the health situation requires so and with the prior agreement of the Governing Council

● **Second call evaluation**

Due to the alarm state imposed by the sanitary situation, the second call evaluation will be performed in the not in person mode. The face to face theoretical classes and the evaluation of the first call was already finished when the alarm state was ordered.

To this end, the tools stipulated in the platform “Aula Virtual” will be employed. In the same token, the integrity of the exams will be verified with the software provided by the UVEG. The students will identify themselves by means of the password necessary to access the “Aula Virtual” platform.