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Nanomedicine in Chemistry Education: Development of a Digital Learning Module with Real Life Experiments

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Abstract This publication introduces a digital learning module on the topic of **nanomedicine** for chemistry education in **high schools** and for student laboratories. **Nanoparticles** provide a modern approach for treating diseases. By encapsulating active ingredients in **nanoparticles** the ingredients are not distributed in the entire body, but can be specifically transported and released to the target organs and tissues. The advantage of this approach is that a higher dose can reach the designated target while minimizing the overall dosage and resulting side effects. This research topic offers excellent links to classical school chemistry contents such as polymer chemistry, polymerization, ester formation and cleavage, polarity, and solubility. The digital learning module is based on a **differentiation grid** that offers students with varying learning backgrounds an individual way to access and engage with the module.

Keywords: *drug delivery, nanomedicine, digitalization, polyesters, nanoparticle, esterification, hydrolysis, high school / introductory chemistry, first-year undergraduate / general laboratory, differentiation grid.*

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1. Introduction

Successful disease control, not least the SARS-CoV-2 pandemic, confronts us with new challenges all the time. Conventional **drug delivery systems** (DDS) have numerous disadvantages that complicate targeted, individualized therapy. The effect is mostly systemic, potentially harming the entire body due to the high dose administered and side effects in non-targeted regions and organs. However, at the targeted site in the body, the concentration of the active ingredient is often not high enough to control the disease. This dilemma can be resolved by using modern targeted DDS. The aim is to transport and release active ingredients only at the affected organ, leading to a high local concentration, which can additionally be maintained over a longer period of time. The suitable properties required for these "smart" carrier materials are provided by polymeric **nanoparticles** [1,2].

Teaching this current and research-related subject area offers interesting connection points for chemistry education in **high schools**. Supported by digital media and based on a **differentiation grid** [3], students learn facts about **nanomedicine** in general and specifically how DDS works in their own, individual way. The newly created digital learning module contains real-life experiments as well as a variety of different task formats. It highlights the potential of **nanoparticles** in medical applications, introduces a possible method for synthesizing polymers as well as formulating polymeric **nanoparticles** suited for **drug delivery**, and includes the loading of **nanoparticles** as drug carriers with a dye as a model substance. Finally, the targeted release of the drug can be simulated due to a pH value change. The experiments can be carried out with harmless and inexpensive chemicals, and initial implementations show the successful realization with groups of students. [4]

2. Experimental Basis

The development of the experimental series was a collaboration between the department of chemistry didactics and the chemical research within the Collaborative Research Center 1278 PolyTarget. The aim was to develop a series of experiments that introduce students to targeted DDS: From the synthesis of the polymer to the formulation and loading of the nanocarriers to the targeted release. The Model of Educational Transfer Research (see Figure 1) was chosen as the research method for the transfer of current scientific knowledge into the school context. Within a cyclical process involving students, student teachers, and teachers, conception, testing, evaluation, and optimization take place before the newly created material is disseminated to interested audiences.

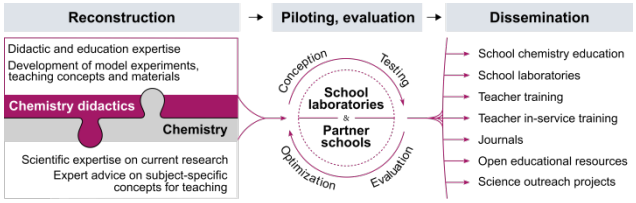

Figure 1. Model of Educational Transfer [4].

Information on the development of the series of experiments, the scientific background as well as the recorded measured values have been published in the Journal of Chemical Education [4]. The series of experiments is structured in three parts (see Figure 2) and analogous to a taxi ride, where the cab represents the drug carrier, *i.e.*, the polymeric **nanoparticles** and the passenger embodies the drug.

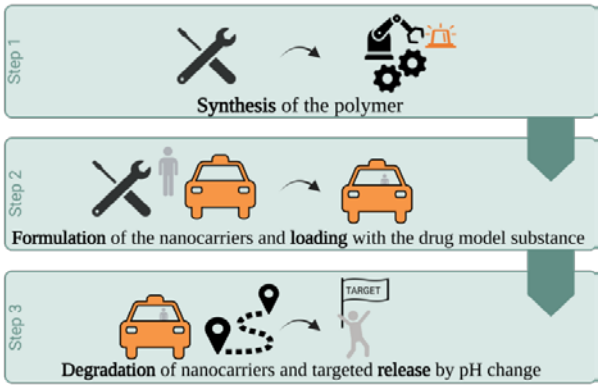

Figure 2. Taxi analoge overview setup of the series of experiments: (1) synthesis of the polymer, (2) formulation and loading of the nanocarriers, (3) degradation of the nanocarriers and drug release.

Within the first step of the test series (1), the synthesis of the polymer takes place - as the basis for the formulation of the **nanoparticles**. Using the taxi analogy, the starting material for the vehicle is provided here. The students synthesize the polymer poly(*δ*-valerolactone) (P*δ*VL) themselves from the monomer *δ*-valerolactone (*δ*VL) by a ring-opening polymerization (ROP) (see Figure3). **Polyesters** are one of the most frequently used polymer classes for the encapsulation of hydrophobic active ingredients. The reasons for this are the properties of the used polymers: They are non-toxic, biocompatible and biodegradable [5]. For the student experiment, the monomer *δ*VL is used because the reaction to form the polymer occurs within a few minutes at room temperature by using the organocatalyst 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD). Thus, the experiment is well-suited in terms of time for the school context [6,7]. The ROP is initiated by the addition of ethanol.

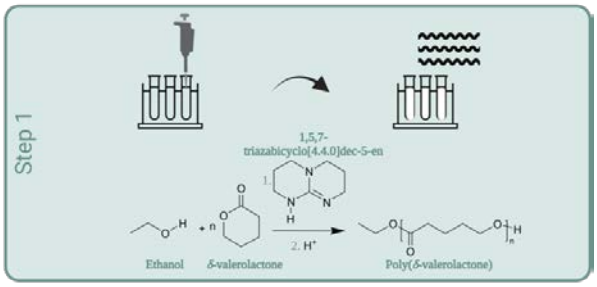

Figure 3. Schematic representation of the ROP of *δ*VL.

In step (2) of the series of experiments, the method of nanoprecipitation, also called solvent evaporation method [8,9,10], based on Fessi *et al.* [11], is used to formulate the **nanoparticles** and to encapsulate the model substance nile red instead of an active ingredient [4]. In the taxi analogy, this step represents the assembly of the vehicle as well as the boarding of the passenger. Nile red offers the advantage of being allowed as a chemical in the school context and increases the visualization of the process.

For the formulation (2), the hydrophobic polymer P*δ*VL previously synthesized by the students themselves in step (1) is used and dissolved in the solvent acetone. When choosing the solvent, it is important to ensure that it is miscible with water. After injection of the organic phase into water. Nile red is also dissolved in acetone. Together, the dissolved polymer and the nile red acetone solution are dropped into an excess of water. Subsequently the acetone evaporates due to its low boiling point at ambient temperature. This process can be accelerated by a slight increase in temperature to about 50 °C. The water-insoluble polymer forms the particles in the aqueous environment and the hydrophobic dye nile red is encapsulated (see Figure 4).

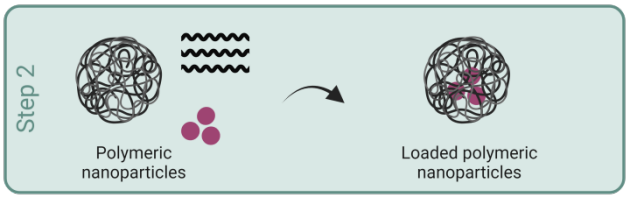

Figure 4. Formulation and loading of the polymeric nanoparticles.

Finally, step (3) of the series focuses on the degradation of the particles and the release as an important step to ensure the targeted effect (see Figure 5).

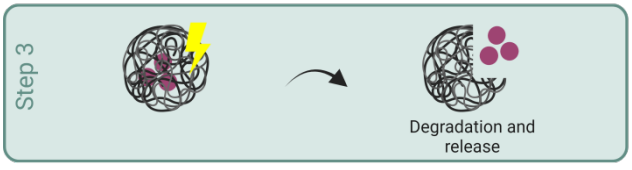

Figure 5. Degradation of the polymeric nanoparticles and release of nile red.

In principle, the release can be induced by different stimuli, such as magnetism, light, use of enzymes, heat or pH value changes [12,13]. For the implementation in school, the degradation of particles and the release of nile red is realized under alkaline conditions. Addition of sodium hydroxide solution to the particle suspension results in saponification of the hydrophobic polymer PδVL and finally release of the dye. Because nile red is not soluble in water, it precipitates over time, which can be followed visually after about 30 minutes. The ester **hydrolysis** responsible for the degradation of the particles links to the students' prior knowledge in chemistry [4].It is also known from biology lessons that there are different pH ranges [14,15,16,17,18] in the body and in cells (see Figure 6). This represents the content-related background for the pH-dependent release. Transferred to the taxi analogy, the release represents the arrival at the destination, destruction of the vehicle and the passenger getting out of the taxi.

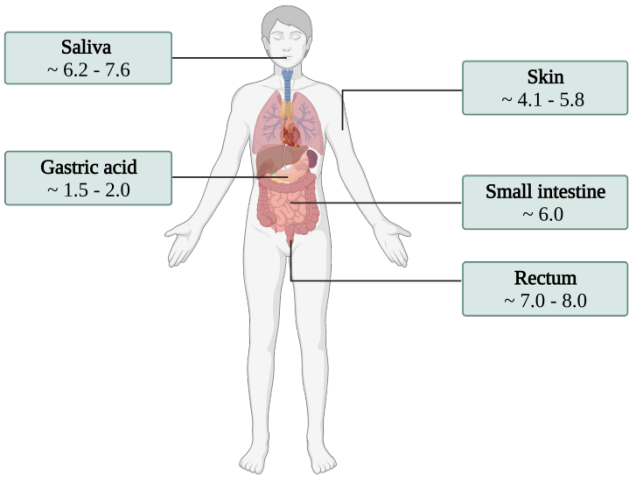

Figure 6. Some exemplary pH values in the human organism.

3. Digital Learning Module

After introducing the topic of **nanomedicine** and displaying the experiments developed for school usage, a digital learning module will be presented that was created to enhance students' engagement with the topic. First, the basis of the digital learning module, a **differentiation grid**, and the layout of the module will be explained. Second, the different tasks of the learning module and the material used for it will be described. Finally, results of first testing will be presented, and an outlook will be given concerning the further usage of the module.

3.1. Creation of a Digital and Complexity-Differentiated Learning Module

3.1.1. What is a Differentiation Grid?

A **differentiation grid** is a model that combines cooperative and individual aspects of learning. It has been developed for planning lessons in heterogenic learning groups as part of a school trial [19] and was adapted later on for the usage in different subjects [20]. While all students participate in the same topic, planning this topic according to a differentiation grid provides the students with the opportunity to engage with the topic in their own individual way [3]. In order to do so, first, the topic and its different aspects are cooperatively analyzed for fitting and useful learning content (*i.e.* in form of a Mind- or Concept-Map). While doing so, the learning contents can already be divided into multiple possible sub-topics, summarizing, and including some of the relevant aspects that have just been analyzed. Secondly, from these possible sub-topics a few are chosen to represent an increasing thematic complexity of a topic. This means that the topic is divided into several different sub-topics with growing complexity, ranging from a superficial to a deep understanding of the topic [21]. From the point of view of chemistry education, a contextual approach [22] can be a good introduction point, with connections to students' everyday life. After that the sub-topics gradually go deeper, from developing the chemical aspects of the context to a more abstract understanding of the science behind it. Finally, aspects of these sub-topics are subsequently differentiated according to a growing cognitive complexity [23]. While there are different approaches on how to measure this cognitive complexity, we mainly focus on Bloom's revised learning taxonomy as suggested by Anderson *et al.* [24]. These considerations result in a grid with fields arranged horizontally by thematic complexity on the x-axis and fields arranged vertically by cognitive complexity on the y-axis (see Figure7).

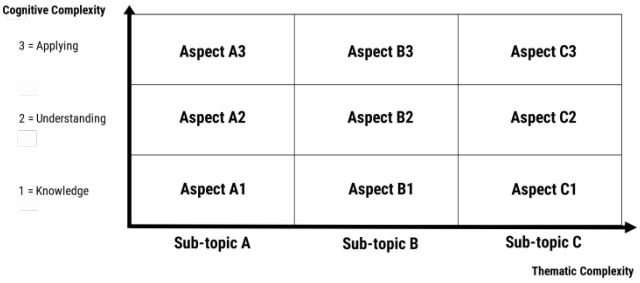

Figure 7. General layout of a differentiation grid.

For each field a learning task is constructed [25]. This means that from the differentiated aspects of the sub-topics learning goals for each field are derived and learning material is constructed. This results in tasks of varying complexity, with the supposedly easiest tasks in the lower left corner and the supposedly most difficult tasks in the upper right corner. This way, learners can self-assess their best approach to the topic and can freely choose the fields they like to carry out. Obligatory and facultative fields can be named, the grid can also vary in size. The duration for conducting a **differentiation grid** varies depending on the size and number of compulsory fields selected.

3.1.2. From the Differentiation Grid to a Digital and Complexity-Differentiated Learning Module

For our purposes a 3 x 3 **differentiation grid** is used as the basis to create a digital and complexity-differentiated learning module. This means that this module includes nine tasks of different cognitive and thematic complexity. Two task types have been distinguished: One that includes an experiment as an integral part of knowledge acquisition

and another that focuses mainly on theoretical aspects and uses models and other info material.

The learning goals of each task of the grid have been chosen so that they tie closely to our local curriculum [26] but also include aspects of general interest to the public. Titles of the tasks have been chosen to spark interest and further engagement while also hinting at the contents or the goal of the task. Each task is structured into four steps [27]: (1) The learners familiarize themselves with the relevant aspect of the sub-topic. Depending on the level of cognitive complexity this can be used for *e.g.*, conceptualization, exploration or problematization of the relevant aspect [28]. (2) The learners create a learning product. This means that they (a) document their learning results from step (1) (b) build up knowledge from theses learning results and (c) solidify their new knowledge. Scaffolded exercises are often used to support this process. Step (3) is optional and includes further help or assistance in conducting step (2). In the last step (4) learners can compare their learning product with a suggested solution, correct possible mistakes or check alternatives.

A Multitouch Learning Book [29] was then chosen to construct a digital and complexity-differentiated learning module: By using the app "Pages" (only available on devices with iOS) an interactive eBook can be created that uses internal and external links for navigation. The grid itself serves as a table of contents; students can choose each task by clicking on the respective title of the task in the grid. Each page of a task includes all material needed for solving all four steps of the task (see Figure 8).

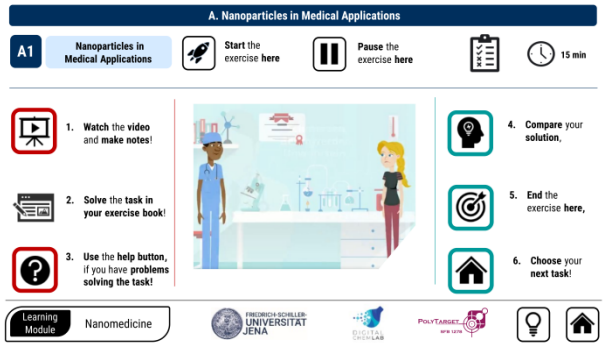

Figure 8. Exemplary page of task A1 of the digital learning module.

The eBook has been created with the intention of reducing possible extraneous cognitive load to a minimum and using principles researched by Mayer *et al.* [30]. Buttons surrounded by a rounded square can be clicked on. Black squares signal general function, red squares (on the left) represent material needed for solving the task, turquoise squares (on the right) signal actions needed to finish the task. Symbols were used to represent the meaning of the buttons (*e.g.*, a rocket for starting the task or a question mark for a help button). Colours were used as scarcely as possible and mainly for colour coding the sub-topics and their tasks (A = blue, B = green, C = gold). Central to each page is a representative picture for the task. The headline shows the sub-topic, name and number of the task as well as the button for starting and pausing the field and general information (type of task and approximate duration). The foot line holds the name of the module and logos of the associated research initiatives plus two general buttons (overview of the symbols, return to **differentiation grid**).

The learning material was created using the Microsoft Office Suite (Words, PowerPoint) and in the case of the learning videos additional software (OBS Studios, Adobe Premiere Pro). Interactive tasks and help buttons were created using external websites (learnignapps.org, thinglink.com). Videos and documents can be accessed using the cloud service of our university (*via* Nextcloud, cloud.uni-jena.de). The eBook is accompanied by a small analogue exercise book with a page for each task of the grid (as described above in step (2)).

The students each use an iPad and the app „Books" for accessing the digital learning module. Apart from the eBook itself, access to the internet and a web broser (*e.g.*, Safari) are necessary to work with the learning module. A self-created online tool is used for documenting the order and length of the tasks and can also provide a small evaluation tool upon completing the task. Students work in pairs and also start, pause, and end their field manually. The estimated time for conducting this learning module is roughly three hours. A minimum of four tasks is expected to be completed in this time.

Consulting the SAMR-model [31] we tried to use digital media in the most advantageous way: Some aspects of the digital learning module improve the tasks (*e.g.*, digital experimental instructions) and some modify or even redefine the tasks (e.g. learning videos, interactive tasks and fields). An analogue exercise book was chosen, because there was no specific advantage in a digital variant. The students can take the exercise book home and use the exercises as a basis for further engagement with the topic in regular school lessons.

The usage of a digital and complexity differentiated learning module, according to our new concept for the organic integration of digital media into all areas of chemistry education (digitalchemlab [32]), has been successfully tested within our work group and the student laboratory affiliated to it [33]. The differentiation matrix for the digital learning module **"Nanomedicine"** and its contents will be described in the following.

3.2. Description of Tasks and Experiments

The **differentiation grid** is composed of three sub-topics each containing three tasks with increasing complexity. The grid and its nine tasks can be seen below (see Figure 9).

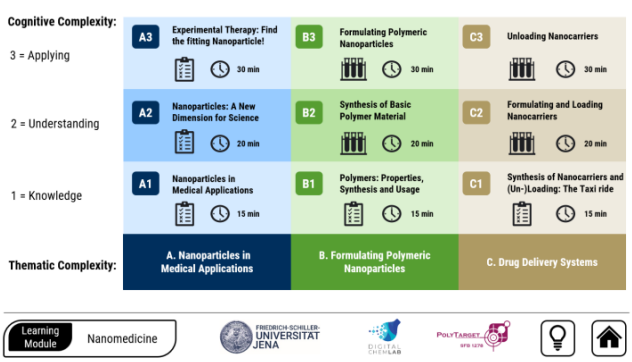

Figure 9. Differentiation grid on the topic "Nanomedicine".

3.2.1. A: "Nanoparticles in Medical Appplications"

Sub-topic A is composed of tasks treating the topic "**Nanoparticles** in Medical Applications".

Using a video in cartoon style displaying a doctor-patient conversation, task A1 introduces basic ideas of **drug delivery**. It thus introduces issues of the systemic use of medical drugs such as side-effects and high doses of the active substance. This problem-oriented approach leads to a tangible access to the topic of **drug delivery**. The learning target of task A1 is as follows: Students can describe the problems of systematic medical drug usage and explain the advantages of targeted **drug delivery**.

Task A2 introduces the size dimension "nano" and **nanoparticles**. The key properties of **nanoparticles**, namely their size make them very suitable for their application in **drug delivery** processes. The learning target of task A2 is as follows: Students can estimate the dimension "nano" and can illustrate useful properties of **nanoparticles**.

Task A3 is a fictional case study in which the students have to select the correct combination of a fictional carrier material and a fictional medical drug. The DDS is supposed to be used in the treatment of a patient's pancreatic cancer. The task is built up as a puzzle in which the students must combine the fitting properties of the carrier material, the medical drug, and the human body. The learning target of field A3 is as follows: Students can determine a suitable DDS by analysing the properties that have an influence on the selection of a **DDS**.

3.2.2. B: "Formulating Polymeric Nanoparticles"

Sub-topic B is composed of fields treating the topic "Formulating Polymeric **Nanoparticles**".

Task B1 deals with the class of polymers in general. Basic terms, properties and concepts are explored in a short learning video, while the students have to solve a cloze text. The learning target of task B1 is as follows: Students can explain fundamental properties of the class of polymers and are able to illustrate the reaction type "polymerization".

Task B2 includes the experiment above described as step (1) in which the polymer PδVL is synthesized *via* ROP from the monomer δVL. Because these processes are invisible from just the observations of the experiments, a commented animation video illustrates the process on a molecular level. The learning target of task B2 is as follows: Students can synthesize the starting materialPδVL for formulating **nanoparticles** and describe the process on a molecular level.

Task B3 includes an experiment in which PδVL-**nanoparticles** are formulated by using the solvent exchange method similar to step (2) but without nile red. A model experiment in which the different states of the system ((a) polymer, (b) polymer in solvent and (c) polymer in non-solvent) are compared with each other supports the students in understanding this approach of formulating **nanoparticles**. The learning target of task B3 is as follows: Students can formulate polymeric **nanoparticles** *via* the solvent exchange method and analyse the process on a molecular level.

3.2.3. C: "Drug Delivery Systems"

Sub-topic C is composed of fields treating the topic "**Drug Delivery Systems**".

Task C1 depicts the formulation and loading of **nanoparticles** on the molecular level and combines it with the experimental procedure as described above in step (3). The learning objective of task C1 is as follows: Students can explain the formulation and loading of **nanoparticles** with an active substance (or dye) on the molecular level.

Task C2 includes an experiment in which PδVL-**nanoparticles** are formulated and loaded with nile red using the solvent exchange method, as described above in step (2). The existence of the loaded **nanoparticles** can be made visible by the Tyndall-Effect. The learning target of task C2 is as follows: Students can formulate and load PδVL-**nanoparticles** *via* the solvent exchange method and can interpret their observations made *via* laser pointer.

Task C3 includes an experiment in which the release of loaded **nanoparticles** is explored. For this, **nanoparticles** loaded with the dye nile red are treated with a sodium hydroxide solution, as described above in step (3). The polymeric **nanoparticles** are saponified and thus degraded leading to the release of nile red. The learning target of task C3 is as follows: Students can experimentally degrade the polymeric **nanoparticles,** release dye from loaded **nanoparticles,** and discuss how a different pH value leads to different results.

3.3. Planned Usage and Outlook

The included experiments and their accompanying tasks have been already tested (see Figure 10) with various student groups [4].

Figure 10. A student who is checking the Tyndall effect after formulation of polymeric nanoparticles.

The digital learning module **"Nanomedicine"** itself will be first tested with teachers and fellow researchers in September 2023. Due to the novelty and complexity of the subject and the used methods we first want to capture the

perspective of experts on the matter. After a short revision phase the module will be evaluated with students in our student laboratory. The evaluation will focus on the interest and experienced emotions while conducting the learning module. Furthermore, understanding of the knowledge and concepts regarding **nanomedicine** will be tested. Quantitative and qualitative methods will be used.

After a short revision phase in accordance with the cyclic design of the Model of Educational Transfer Research, the module will be disseminated to students, student teachers, and teachers. The goals is to familiarize a wider audience with both the topic and the learning module itself. After that the digital learning module on **nanomedicine** will be used regularly in our student laboratory and the included materials will be applied in a variety of ways in courses for (student) teachers. You will be able to find the material *via* a CC-BY-licence on our website (https://www.chemgeo. uni-jena.de/chemiedidaktik).

4. Conclusion

This article aims to introduce interested readers to the topic of **nanomedicine** and to show applications for using this current and research-related topic for chemistry education. In order to do so, experiments were created that show the synthesis of a base polymeric material, the formulation of polymeric **nanoparticles** and the loading of a model active substance (dye). The destruction of the nanocarriers and the targeted release of the dye can also be shown in an experiment. These experiments and further learning material were then used to create a digital learning module on the topic of **nanomedicine** implementing the model of a (digital) differentiation grid. As this topic, the developed experiments and the newly created digital learning module are all subject to further research, it remains to be seen how this topic and the developed materials can be introduced into regular chemistry lessons. First results from conducting the experiments in our student laboratory show much promise that this topic has great potential for interested students and teachers to engage in this area of current research. By developing a digital and complexity-differentiated learning module we hope to enhance students' motivation to interact with the science underlying it and thus make this topic accessible to learners of all different backgrounds.

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References

[1] Behnke, M., Holick, C. T., Vollrath, A., Schubert, S., Schubert, U. S., "Knowledge-Based Design of Multifunctional Polymeric Nanoparticles," in Michel, M. C. (Eds.), Handbook of experimental pharmacology. Springer Verlag, Berlin, 1-24, 2023.

[2] Englert, C., Brendel, J. C., Majdanski, T. C., Yildirim, T., Schubert, S., Gottschaldt, M., Windhab, N., Schubert, U. S., "Pharmapolymers in the 21st century: Synthetic polymers in drug delivery applications," *Progr. in Polym. Sci*., 87, 107–164, 2018.

[3] Sasse, A., Schulzeck, U., "Die Differenzierungsmatrix als Rahmen für Planung und Reflexion inklusiven Unterrichts," in Sasse, A., Schulzeck, U. (Eds.), *Inklusiven Unterricht planen, gestalten und reflektieren: Die Differenzierungsmatrix in Theorie und Praxis; Lernen inklusiv und kooperativ*, Vol. 1, Verlag Julius Klinkhardt, Bad Heilbrunn, 11–34, 2021.

[4] Fruntke, A., Behnke, M., Stafast, L. M., Träder, T., Dietel, E., Vollrath, A., Weber, C., Schubert, U. S., Wilke, T., "Targeted Drug Delivery: Synthesis of Smart Nanocarriers for School Chemistry Education," *J. Chem. Educ.*, 100 (2), 751–759, 2023.

[5] Musyanovych, A., Schmitz-Wienke, J., Mailänder, V., Walther, P., Landfester, K., "Preparation of biodegradable polymer nanoparticles by miniemulsion technique and their cell interactions," *Macromol. Biosci.*, 8 (2), 127–139, 2008.

[6] Lohmeijer, B. G. G., Pratt, R. C., Leibfarth, F., Logan, J. W., Long, D. A., Dove, A. P., Nederberg, F., Choi, J., Wade, C., Waymouth, R. M., Hedrick, J. L., "Guanidine and amidine organocatalysts for ring-opening polymerization of cyclic esters," *Macromolecules* 39 (25), 8574–8583, 2006.

[7] Simón, L., Goodman, J. M., "The mechanism of TBD-catalyzed ring-opening polymerization of cyclic esters," *J. Org. Chem*, 72 (25), 9656–9662, 2007.

[8] Martínez Rivas, C. J., Tarhini, M., Badri, W., Miladi, K., Greige-Gerges, H., Nazari, Q. A., Galindo Rodríguez, S. A., Román, R. Á., Fessi, H., Elaissari, A., "Nanoprecipitation process: From encapsulation to drug delivery," *Int. J. Pharm.* 532 (1), 66–81, 2017.

[9] Miladi, K., Sfar, S., Fessi, H., Elaissari, A., "Nanoprecipitation Process: From Particle Preparation to In Vivo Applications," in Vauthier, C., Ponchel, G. (Eds.), *Polymer Nanoparticles for Nanomedicines*, Springer International Publishing, Cham, 17–53, 2016.

[10] Zielińska, A., Carreiró, F., Oliveira, A. M., Neves, A., Pires, B., Venkatesh, D. N., Durazzo, A., Lucarini, M., Eder, P., Silva, A. M., Santini, A., Souto, E. B., "Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology," *Molecules*, 25 (16), 3731-3751, 2020.

[11] Fessi, H., Puisieux, F., Devissaguet, J., Ammoury, N., Benita, S., "Nanocapsule formation by interfacial polymer deposition following solvent displacement," *Int. J. Pharm.* 55 (1), R1-R4, 1989.

[12] Pham, S. H., Choi, Y., Choi, J., "Stimuli-Responsive Nanomaterials for Application in Antitumor Therapy and Drug Delivery," *Pharmaceutics* 12 (7), 630-648, 2020.

[13] Knutson, C. M., Hilker A. P., Tolstyka, Z. P., Anderson, C. B., Wilbon, P. A., Mathers, R. T., Wentzel, M. T., Perkins, A. L., & Wissinger, J. E., "Dyeing to Degrade: A Bioplastics Experiment for College and High School Classrooms," *J. Chem. Educ.* 96 (11), 2565–2573, 2019.

[14] Schulte to Brinke, A., Mehlich, A., Doberenz, C., Janssens-Böcker, C., "Acidification of the Skin and Maintenance of the Physiological Skin pH Value by Buffered Skin Care Products Formulated around pH 4," *J. Cosmet. Dermatol. Sci. Appl.*, 11 (1), 44–57, 2021.

[15] Fujimori, S., "Gastric acid level of humans must decrease in the future," *World J. Gastroenterol.*, 26 (43), 6706–6709, 2020.

[16] Fallingborg, J., "Intraluminal pH of the human gastrointestinal tract," *Dan. Med. Bull.*, 46 (3), 183–196, 1999.

[17] Hua, S., "Physiological and Pharmaceutical Considerations for Rectal Drug Formulations," *Front. Pharmacol.*, 10, 1196, 2019.

[18] Baliga, S., Muglikar, S., Kale, R., "Salivary pH: A diagnostic biomarker," *J. Indian Soc. Periodontol.*, 17 (4), 461–465, 2013.

[19] Sasse, A., Schulzeck, U., "Differenzierungsmatrizen als Modell der Planung und Reflexion inklusiven Unterrichts – zum Zwischenstand in einem Schulversuch," in Jantowski, A., (Ed.), *Gemeinsam leben. Miteinander lernen.*, Impulse, Vol. 58, Thüringer Institut für Lehrerfortbildung, Lehrplanentwicklung und Medien (Thillm), Bad Berka, 13–22, 2013.

[20] Woest, V., Engelmann, P., „Fächerverbindender naturwissenschaftlicher Unterricht," in Sasse, A., Schulzeck, U. (Eds.), *Inklusiven Unterricht planen, gestalten und reflektieren:*

Die Differenzierungsmatrix in Theorie und Praxis, Lernen inklusiv und kooperativ, Vol. 1, Verlag Julius Klinkhardt, Bad Heilbrunn 125–142, 2021.

[21] Sasse, A., Schulzeck, U., "Die thematische Komplexität des gemeinsamen Lerngegenstandes - Differenzierungsmatritzen aus subjektwissenschaftlicher Perspektive," in *Sasse, A., Schulzeck, U. (Eds.), Inklusiven Unterricht planen, gestalten und reflektieren: Die Differenzierungsmatrix in Theorie und Praxis, Lernen inklusiv und kooperativ*, Vol. 1, Verlag Julius Klinkhardt, Bad Heilbrunn, 51–77, 2021.

[22] Parchmann, I.,Gräsel, C.,Baer, A.,Nentwig,P., Demuth,R.,Ralle, B. andthe ChiK ProjectGroup, " 'Chemie im Kontext': A symbiotic implementation of a context-based teaching and learning approach," *Int J Sci Educ*, 28,1041–1062, 2006.

[23] Krackel, B., "Die kognitive Komplexität des gemeinsemn Lerngegenstands - Differenzierungsmatritzen aus lernpsychologischer Perspektive," in Sasse, A., Schulzeck, U. (Eds.), *Inklusiven Unterricht planen, gestalten und reflektieren: Die Differenzierungsmatrix in Theorie und Praxis*, Lernen inklusiv und kooperativ, Vol. 1, Verlag Julius Klinkhardt, Bad Heilbrunn, 35–50, 2021.

[24] Anderson, L. W., Krathwohl, D. R., *A taxonomy for learning, Teaching, and Assessing. A revision of Bloom's taxonomy of Educational Objectives: Complete Edition*, Longman, New York, 2001.

[25] Blömeke, S., Risse, J., Müller, C., Eichler, D., Schulz, W., „Analyse der Qualität von Aufgaben aus didaktischer und fachlicher Sicht. Ein allgemeines Modell und seine exemplarische Umsetzung im Unterrichtsfach Mathematik,", Unterrichtswissenschaft 34 (4), 330-357, 2006.

[26] Thüringer Ministerium für Bildung, Wissenschaft und Kultur, *Lehrplan für den Erwerb der allgemeinen Hochschulreife Chemie*, 2012.

Leisen, J., „Lernprozesse mithilfe von Lernaufgaben strukturieren. Informationen und Beispiele zu Lernaufgaben im kompetenzorientierten Unterricht," *NiU Physik*, 21 (117/118), 9–13, 2010.

[27] Oser, F. K., Baeriswyl, F. J., "Choreographies of Teaching: Bridging Instruction to Learning," in Richardson, V. (Ed.), *Handbook of research on teaching*, 4. ed., American Educational Research Association, 1031–1065, 2002.

[28] Seibert, J., Luxenburger-Becker, H., Marquardt, M., Lang, V., Perels, F., Kay, C. W. M., Huwer, J., "Multitouch Experiment Instruction for a Better Learning Outcome in Chemistry Education," *World J. Chem. Educ.*, 8 (1), 1–8, 2020.

[29] Mayer, R. E., Fiorella, L., "Principles for Reducing Extraneous Processing in Multimedia Learning: Coherence, Signaling, Redundancy, Spatial Contiguity, and Temporal Contiguity Principles," in Mayer, R. E., (Ed.), *The Cambridge handbook of multimedia learning, Second edition;* Cambridge handbooks in psychology; Cambridge University Press, Cambridge, 279–315, 2014.

[30] Hamilton, E. R., Rosenberg, J. M., Akcaoglu, M., "The Substitution Augmentation Modification Redefinition (SAMR) Model: a Critical Review and Suggestions for its Use," *TechTrends* 60 (5), 433–441, 2016.

[31] ter Horst, N., Wilke, T., "Digital and differentiated learning in student laboratories: the concept of digitalchemlab," *CHEMKON*, 29 (S1), 227–232, 2022.

[32] ter Horst, N., Wilke, T., „Digital-differenzierende Lernmodule im Schülerlaborkontext: eine Pilotstudie," in *Conference Proceedings DiCE-Tagung 2023*, Thüringer Universitäts- und Landesbibliothek, *in revision*.