PHARMACEUTICAL EXCIPIENTS FROM THE POINT OF VIEW OF A MEDICINAL CHEMIST

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Abstract. A new elective discipline of pharmaceutical study – *Chemistry of pharmaceutical excipients*, which could present structural and analytical profiles of the most interesting and important groups of pharmaceutical excipients has been established at the Pharmaceutical faculty of Veterinary and Pharmaceutical University in Brno, Czech Republic. The discipline consists of 2 hours of lectures per week and 16 hours of laboratory per semester. The matter of study is divided into 6 themes of lectures and 2 thematic sections of laboratory. Examination is performed orally and students can randomly choice two of 15 questions which also cover up whole the matter of the discipline. The courses have begun since the session 2007/2008 and the interest of students in them gradually growths. The first students passed the courses with excellent rating.

Keywords: pharmaceutical excipients, structure, SAR, synthesis, analytical specifics

Introduction

Pharmaceutical excipients are inorganic or organic compounds, which are necessary for formulation of medicinal preparations suitable for direct aplication to a patient, although, they are not holders of any pharmacological activity. In the study program of pharmacy in the Czech Republic, such substances are the matter of interest predominantly from the point of view of their use in application forms, and from

the point of view of physico-chemical properties related to it. Pharmaceutics, in the middle Europe often called pharmaceutical technology or galenic pharmacy, is the discipline which deals with them applying such approaches. Medicinal chemistry had been marginally interested in structures, syntheses and partially structure-activity relationships of some selected classes of excipients like preservatives, colorants and sweeteners and appropriate chapters in older textbooks of medicinal chemistry had been also devoted to them [1] but increasing number of chemical drugs crowded out stepwisely these topics. Indeed, neither any of these above mentioned nor other discipline offers a comprehensive view to chemical structures, synthetic ways and typical analytical procedures of these compounds. It is in contradiction to the fact that most of modern pharmacopeias have for excipients the same requierements on purity as for active ingredients. Chemistry of pharmaceutical excipients could be a discipline capable to fill out this blank and build a bridge between pharmaceutics on one side and medicinal chemistry together with pharmaceutical analysis on another one. It will also have a small overlap with margins of pharmacognosy in fields of natural sweeteners, dyes and antioxidants.

Results

The *Chemistry of pharmaceutical excipients* is an elective discipline recommended for students of the fourth year of master of pharmacy study program, but it is suitable also for students of the third year. For choosing of this discipline, knowledges of fundamentals of inorganic, organic, physical and analytical chemistry are proposed, not necessarily those of medicinal chemistry, drug analysis and pharmaceutics. The discipline of value of 2 credits of the European Credits Transfer System (ECTS) has been beeing taught in the spring semester (the summer semester according to Czech usances) since 2007. It consists of both lectures and laboratories. The topics of 6 two-hours lectures are as follows:

1. Circumscription of the concept of pharmaceutical excipients. Their fundamental division from the points of view of their usage and structure. Compounds at the border between drugs and excipients.
2. Compounds enhancing disintegration of tablets. Stabilizers of physico-chemical properties of dispersion systems: viscosity-increasing, emulsifying and suspending agents. Oligo- and polysacharides and their semisynthetic derivatives. (Starch, alkylated starches, cellulose, cellulose ethers and esters, cyclodextrines). Specific methods of their pharmacopeial analysis including applications of NMR spectroscopy. (Determination of substitution grade of hydroxypropylbetadex, i.e. hydroxypropyl- β-cyclodextrine according to European (PhEur)[1]) and Czech (CzPh)[2]) pharmacopeias (Fig. 1).
3. Stabilizers of chemical composition of medicinal preparations: antioxidants (inorganic and organic compounds suitable for either hydrophilic or hydro-

phobic media), antimicrobial and antifungal preservatives (organic compounds containing heavy metals in their molecules, phenolic compounds including a homologic series of parabens (nipagins), carboxylic acids, quarternary ammonium salts, aldehydes and their precursors). Dependence of activity of preservatives on pH. Structure-activity relationships including selected QSAR regression models, syntheses of principal compounds.

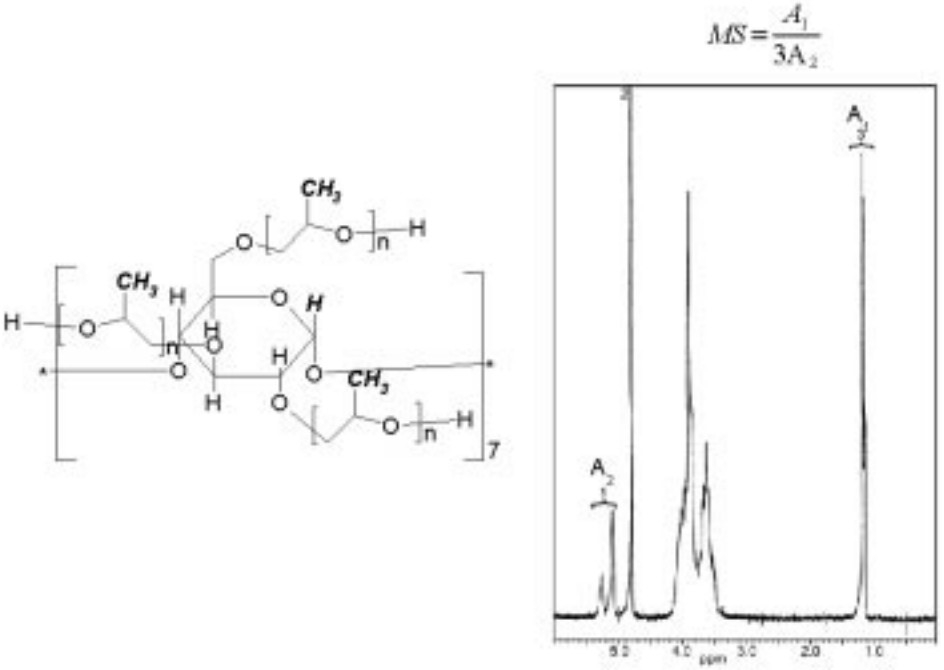

Fig. 1. Molar substitution of hydroxypropylbetadex is calculated as a ratio of area of methyl hydrogens of isopropyl moiety and a treble of area of hemiacetale hydrogen in 2-position of glucose unit

4. Selected compounds controling bioavailability of drugs. Transdermal, buccal and gastro-intestinal penetration enhancers. (Percutaneous permeation accelerants, which have been beeing most widely studied, are accentuated.) Overview of basic structural groups, proposed and particularly evidenced mechanisms of their actions, special demands of enhancers used in topical application forms, methods of determination and quantitative expression of their activity. Compounds triming taste and flavour of medicinal preparations. Sweeteners of natural origin: carbohydrates, alcoholic sugars, glycosides useful as sweeteners. Alternate sweeteners: basic structural types, their toxicity, syntheses of some principal compounds. Quantitative expression of sweeten-

ing ability, its relationship to structure. Volatile compounds of both natural and synthetic origin suitable as odour regulating agents.

5. Colour corrigentia – pharmaceutical dyes and colouring agents. Specific methods of analysis of colour substances. Quantitative description of a colour in CIE L*a*b* system and similar systems according to *USP* Chapter 1061, "Color – instrumental measurement."[3]) Overview of approved dyes of both natural and synthetic origin, their toxicity, lipohilicity and spectral properties (absorption extremes). Structure-colour relationships of anthocyanines.

The topics of 24 hours sections of laboratory are as follows:

1. Synthesis of an antimicrobial preservative – paraben with longer and/or branched alkyl chain. (Alternative: synthesis of an artificial sweetener – sacharine.)
2. Analysis of pharmaceutical colorants. Quantitative description of a colour in CIE L*a*b* system (for example see Fig 2) and evaluation of purity and homogenity of colour substances (for better exploitation of time, the work on both topics overlaps).

Except the above mentioned pharmacopeas, the compendium of Rowe et al.[2], the review articles[3-5], the author's PhD thesis [6] and the chemical databases ChemDat[4]) of Merck KGaA, Darmstadt, Germany and ChemID plus the databases[5]) of the the U.S. National Library of Medicine were used as principal resources for preparation of both lectures and laboratory.Whole the course is finished with an oral exam, in which students randomly elect two of 15 examination areas which reflect topics of both lectures and laboratories. In accordance with the Study Order of the Veterinary and Pharmaceutical University[6]) they have 15 minutes for written preparation and additional 15 minutes for oral answering: (1) Concept of pharmacetical excipients and their basic division; (2) Examples of compounds at the border between active ingredients and excpients; (3) Cellulose and cellulose derivatives. Their structures, basic properties and use as excipients; (4) Starch and its semi-synthetic derivatives. Cyclodextrines. Their structures, basic properties, their use as excipients. Analytical characterization of selected substituted cyclodextrines using NMR spectroscopy; (5) Antimicrobial and antifungal preservatives; (6) Antioxidants; (7) Transdermal penetration enhancers – requests on their properties, determination and expression of their activity; (8) Transdermal penetration enhancers – fatty acids, long-chain alcanols, simple alifatic esters; (9) Transdermal penetration enhancers – sulfoxides and their derivatives; (10) Transdermal penetration enhancers – terpenes; (12) Transdermal penetration enhancers – amino acids derivatives including lactames; (13) Compounds masking unpleasant taste of medicines. Overview of sweeteners of both natural and synthetic origin; (14) Overview of compounds masking unpleasant odour of medicinal preparations; (15) Overview of pharmaceutical dyes and their important physico-chemical and biological properties; (16) Instrumental colour measurement – expression of a colour by coordinates of a colour space.

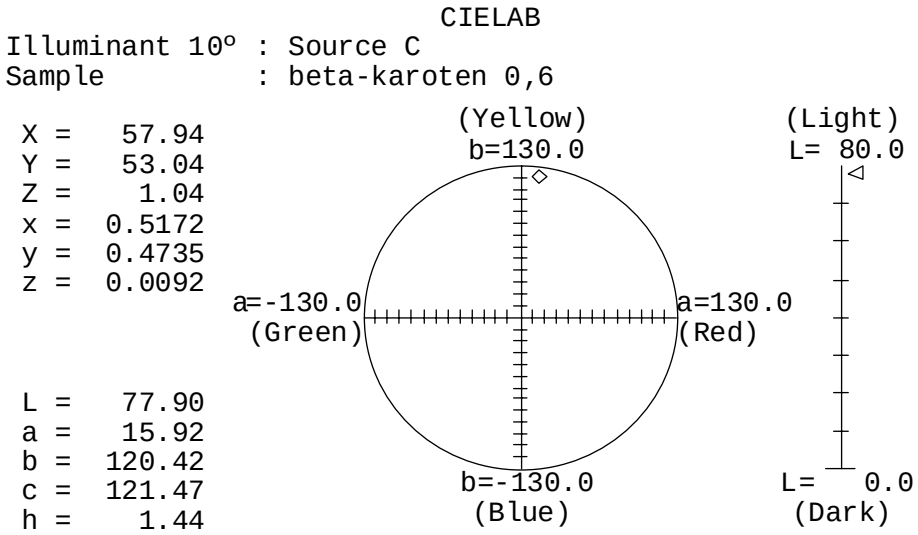

Fig. 2. An example of deremination of colour coordinates in CIE L*a*b* system: solution of β-carotene of concentration 0.6 mg/ml in 96% ethanol. Transmission Spectrum was determined on Helios Beta UV-VIS spectrophotometer (Unicam, G.B.) and processed to colour coordinates using Chroma software from the same firm

Discussion

In the Czech university system, every new discipline must be approved by the Scientific Council of a faculty which is an advisory board of the Dean. The Council consists of profesors and other teachers of the Faculty and extramural and also experts and other celebrities. Members of the Coucil are established by the Dean himself. The syllabus of this discipline has been disputed at the Council twice since October 2006. The final approval of his discipline was qualified by narrowing of the syllabus, which originally involved also field of tensides and emulsifiers and incorporation of the discipline in the fall (winter) semester of the fourth year of study. Although, emplacement of a discipline in a concrete year of study is, according to our credit system, only recommendation, students theoretically can choice any dicscipline in any year if they have space in their schedules and necessary entering knowledges. The submitter, which is identical with the author of this article, self excluded the topic of vehicula and constituents from the syllabus because of lower structural and analytical interestingness of this theme and also to avoid a needless overlap with courses of pharmaceutics. Thus, the more accurate name for this discipline could be Selected

chapters from chemistry of pharmaceutical excipients. The courses have started in the spring semester 2007/2008. The first time, only three students found courage to choice this completly novel discipline, but all passed it out excelently. (Our faculty is comparatively small; there are about 130 students in each year of study.) For current study year 2008/2009, 16 students have been enrolled for this discipline. This is maximal number with regard to time possibilities of teachers of these courses – the author and one his Ph.D. student. Currently, the study program of pharmacy at our university runs only in Czech. However, the english study program has been recently approved by the accreditation commision of the Ministry of Education, Youth and Physical Training so that the study of pharmacy in our faculty including this elective discipline will became available for foreing students since the study year 2009/2010 and it will be necessary to prepare also an english version of this discipline. For future, we also plan to broaden the field of this discipline to selected additives used cosmetics, foods and beverages. There are many compounds used in pharmaceutical as well as in cosmetic, food and beverages industry. Moreover, such a discipline could be more atractive not only for students of pharmacy, but also for learners of veterinary medicine and namely veterinary hygiene, studying at other two faculties of our university. For such enlargement of the discipline, we will ask for a next grant from the Fund for Development of Universities of the Czech Republic.

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NOTES

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2. *Český lékopis 2005 [The Czech Pharmacopoeia 2005]*. Grada, Prague, 2005, p. 3629.

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4. ChemDat, the Merck chemical database: www.chemdat.info.

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