

COMPARATIVE ANALYSIS OF MONOGRAPHS ON *PLANT SUBSTANCES* AND *SEMISYNTHETIC SUBSTANCES* INCLUDED IN THE EUROPEAN PHARMACOPOEIA (*PH. EUR. 8*)

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Abstract. A comparative analysis of the monographs on *Plant substances* and *Semisynthetic substances* included in the European Pharmacopoeia 8 (Ph. Eur. 8) was made regarding their chemical structure and the group of active substances to which they relate. The analysis shows a continuous increase in the number of monographs on these groups of substances (from 147 articles in Ph. Eur. 4 to 377 in Ph. Eur. 8). They constitute about 19.5 % of the total number of monographs in the Ph. Eur. 8. The total number of monographs on plant substances is 123, of which the largest is the number of alkaloids (46), followed by mono- and polysaccharides (29), terpenes (11) and organic acids (10). From the group of alkaloids are included 13 monographs on isoquinoline, 8 on indole, 7 on alkaloids with nitrogen atom in the side-chain, 6 on tropane and 5 articles on purine alkaloids. The total number of monographs on semisynthetic substances is 254. From them 58 are derivatives of various higher fatty acids, higher fatty alcohols and lipids; 57 are articles on derivatives of alkaloids; 44 monographs are on mono- and disaccharides (mainly derivatives of gluconic acid) and sugar alcohols (mainly sorbitans and polysorbates); 33 are on homopolysaccharides (mainly cellulose derivatives); 14 are on heteropolysaccharides; 22 are on phenolic compounds (mainly derivatives of hydroxybenzoic acid); and 16 articles on nonaromatic organic acids. There are 16 monographs on indole and ergoalkaloids, 13 on isoquinoline alkaloids (12 of these semisynthetic products are morphine alkaloids), 11 on tropane alkaloids, 6 on purine alkaloids and 5 are the articles on analogues of ephedrine.

Key Words: European Pharmacopoeia, Plant substances monographs, Semisynthetic substances monographs, Comparative analysis.

Introduction

Medicinal plants and their derivatives are an integral part of their use in pharmacy, traditional and official medicine for treatment of various diseases. They are also widely applied as excipients for fillings, binders, as corrigents and other products during the application of various medicinal forms.

The overview and comparative analysis of monographs in the European Pharmacopoeia (Ph. Eur. 8) [1] shows that it includes 170 monographs about *Herbal drugs* and 136 articles on *Herbal drug preparations*, of which 63 articles are about extracts, tinctures, homeopathic preparations, etc., 33 articles on essential oils and 40 articles on natural plant and fish fat oils and waxes. They account for 16% of the total number of articles included in Ph. Eur. 8 [2].

Apart from being offered in plant mono- and

combined teas and non-purified total forms such as extracts and tinctures, a large number of natural substances are applied in the medicine as pure substances. This is especially valid for natural chemical substances derived from highly active and poisonous drugs such as alkaloids, cardiac glycosides and some other substances of plant origin.

In many cases, other substances with more beneficial properties or effects can be derived from such natural pure substances via additional chemical, microbiological and other transformations of parts of the molecule. This leads to the creation of new, more effective and less toxic phytopreparations or the creation of such of changed effect or changed properties.

In all national and international pharmacopoeias, inclusive and Ph. Eur. 8, there are multiple articles on pure natural substances and their semisynthetic de-

rivatives having broad application as medicinal drugs and in the pharmaceutical production.

Purpose

The purpose of this research is to make a comparative analysis of pharmacopoeial articles about pure *Plant substances* and their semisynthetic derivatives (*Semisynthetic substances*), included in the European Pharmacopoeia 8 (Ph. Eur. 8) with regard to the chemical structure and the groups of active substances to which they relate.

The research does not include the monographs about other natural products of microbial and animal origin such as antibiotics, hormones, enzymes, amino acids, proteins and their semisynthetic substances, vaccines, serums, etc. which are seen by some authors as natural substances.

Results and discussion

The review of the individual editions of the European Pharmacopoeia shows continuous increase in the number of articles about pure natural drugs and their semisynthetic derivatives used for medicinal purposes or for application in the pharmaceutical industry. This is shown in Table 1.

The IVth edition of European Pharmacopoeia (Ph. Eur. 4, 2002) contains a total of 147 monographs on pure substances of plant origin and their semisynthetic products.

In the Vth edition of European Pharmacopoeia (Ph. Eur. 5, 2005), the number of monographs on plant substances is 98 whereas about semisynthetic plant products, there are articles on 171 substances.

In the VIth edition of European Pharmacopoeia (Ph. Eur. 6, 2008), there are monographs on 111 plant substances. The monographs on semisynthetic products from plant substances are totals 218.

The VIIth edition of European Pharmacopoeia (Ph. Eur. 7, 2011) includes monographs on 118 pure plant substances. The number of articles on semisynthetic substances of plant origin is 248.

In the VIIIth edition of the Ph. Eur., which is val-

id from the start of 2014 (Ph. Eur. 8, 2014) the total number of includes monographs for pure plant substances is 123. The number of articles on semisynthetic substances of plant origin is 254.

A comparative analysis of the monograph count included in the VIIIth edition of Ph. Eur. shows that the articles about herbal drugs, herbal drug preparations and fish oils (a total of 306) are around 16% of the total number of pharmacopoeial articles.

Comparative analysis of monographs on synthetic substances and the monographs on pure natural substances and semisynthetic substances from plant origin (a total of 377) shows that they account for 19,5% of the total number of articles on synthetic and natural substances described in the European Pharmacopoeia (Ph. Eur. 8).

Plant substances

They are derived from various plants, they require continuous processing and a special technology about their production and they are highly biologically active. They are obtained in a crystal or amorphous mode as standardised substances of accurately defined purity. In them, all concomitant substances must be fully removed to achieve purity of up to 99-100%.

The aspiration to isolate and introduce individual natural substances in medicine is due to a number of advantages which these substances have as compared to the complex mixtures from many substances. For them, the accurate structurally characterised and chemically defined formula is known; they are dosed much more easily and accurately; they have a well-known therapeutic and toxic dose; they allow for parenteral application; the mechanism of action, pharmacokinetics and pharmacodynamics, the method and time of elimination from the body are known; achievement of a certain medicinal effect with a much smaller quantity. These pure substances are included in extemporal medicinal forms prepared in the pharmacy or for ready medicinal forms prepared in plant conditions – drops, capsules, pills, tablets, injection forms, unguents, etc.

Table 1. Number of monographs on plant substances and semisynthetic substances in the different editions of Ph. Eur.

| Edition of Ph. Eur. | Plant substances | Semisynthetic substances |
|---------------------|------------------|--------------------------|
| Ph. Eur. 4, 2002 | | 147 |
| Ph. Eur. 5, 2005 | 98 | total |
| Ph. Eur. 6, 2008 | 111 | 171 |
| Ph. Eur. 7, 2011 | 118 | 218 |
| Ph. Eur. 8, 2014 | 123 | 248 |
| | | 254 |

Table 2. Plant substances by chemical groups included in Ph. Eur.8

| Plant substances by chemical groups | Number of monographs |
|---|----------------------|
| Monosaccharides | 7 |
| Disaccharides | 4 |
| Sugar alcohols | 8 |
| Homopolysaccharides (starches, cellulose) | 7 |
| Heteropolysaccharides | 3 |
| Total: | 29 |
| Higherfattyacids (HFA) | 5 |
| Higherfattyalcohols (HFAlc) | 4 |
| Total: | 9 |
| Organic acids | 10 |
| Total: | 10 |
| Phenolicalcoholsandaldehydes | 7 |
| Flavonoids | 3 |
| Tannins | 1 |
| Total: | 11 |
| Terpenes | 11 |
| Sterols | 2 |
| Cardiac glycosides | 5 |
| Total: | 18 |
| Alkaloids | 46 |
| Total: | 46 |
| Total: | 123 |

These pure plant substances by groups included in Ph. Eur. 8 are presented in Table 2.

Monographs are developed for the following sugars, sugar alcohols and polysaccharides (29 in total):

- The hexoses galactose, fructose, 4 forms of glucose and 1 for a pentose xylose;

- Disaccharides sucrose, 2 forms of lactose and trehalose;

- Sugar alcohols glycerol, mannitol, 4 forms of sorbitol (=glucitol), sorbic acid and xylitol;

- There are 7 pharmacopoeial articles on starches and cellulose (*Maydis amyllum*, *Oryzae amyllum*, *Solani amyllum*, *Tritici amyllum*, *Amylum pregelificatum*, *Pisi amyllum*, *Cellulosi pulvis*) and 3 articles on heteropolysaccharides (acarbose - from several stamps of the microorganism *Actinoplanes utahensis*, xanthan gum – high-molecular anion polysaccharides derived through fermentation of carbohydrates with *Xanthomonas campestris* and carrageenan – from red algae).

The articles on plant substances from higher fatty acids (HFA) are for the usual trivial acids which are

in the group of fatty acids' glycerides (oleic, palmitic, stearic, undecylenic and caprylic acid) whereas for higher fatty alcohols (HFAlc) which are in the group of waxes (cetyl, stearyl, oleyl alcohol and a mixture of cetyl and stearyl alcohol) (a total of 9 articles).

The number of plant organic acids is significant (10 in total) and alcohols (7 in total) for which there are pharmacopoeial monographs created. These are acids and alcohols which are found in a smaller or larger quantity in almost all plants and in some types of fruit and other organs they are accumulated in significant quantities. Due to the large needs, many of them now are obtained completely synthetically. Monographs have been developed for the following natural organic acids: citric acid – anhydrous and monohydrate, ascorbic, benzoic, lactic, fumaric, malic, nicotinic, tartaric and salicylic acid. Of the phenolic alcohols and aldehydes in Ph. Eur. are included benzyl alcohol, guaiacol, resorcinol, hexylresorcinol, phloroglucinol anhydrous, phloroglucinol dihydrate and vanillin.

All natural substances indicated and enumerated so far (sugars, polysaccharides, HFA, HFAlc, organic acids and alcohols) usually do not have medicinal action but are widely used in pharmaceutical practice in the preparation of various pharmaceutical forms, cosmetic preparations, toothpastes as fillings, binders, corrigents, as preservatives, etc.

Although the number of drugs and medicinal products containing flavonoids as active substances is very large (24 in total) [2], the pharmacopoeia includes articles about three flavonoids only (rutoside dihydrate, diosmin and neohesperidin dihydrochalcone), and the classical product tannin (*Acidum tannicum*) of tannins is included.

The same goes for the large number of articles on essential oil drugs and essential oils described in Ph. Eur. 8 (31 monographs on essential oil drugs and 33 monographs about essential oils) [2]. Although only 5 monographs are included about some of the main components from essential oils (eucalyptol, D-camphor, levomenthol, thymol, eugenol) and 6 articles about other terpenoid active substances (colophon, vitamin A, phytomenadione (vitamin K₁), alpha-tocopherol, squalane, β -caroten). There are monographs about 2 sterols (phytosterol and cholesterol). They are included in extemporaneous or finished pharmaceutical forms or are used as excipients.

Of the cardiac glycosides, articles about 5 compounds are included, of which 4 are cardenolides of digitalis type primarily from lanatoside C (β -

Table 3. *Plant substances from different groups of alkaloids included in Ph. Eur. 8*

| Group of alkaloids | Number of articles |
|--|--------------------|
| Alkaloids with nitrogen atom in the side chain | 7 |
| Pyridine and piperidine alkaloids | 2 |
| Tropane alkaloids | 6 |
| Quinoline alkaloids | 3 |
| Isoquinoline alkaloids | 13 |
| Indole alkaloids | 8 |
| Imidazole alkaloids | 2 |
| Purine alkaloids | 5 |
| Total: | 46 |

acetyldigoxin, deslanoside (Lanatoside C), digitoxin, digoxin) and just one glycoside of strophanthus type (ouabain).

The largest is the number of articles on individual compounds from alkaloids (46). According to its chemical structure they are distributed by groups as is indicated in Table 3.

As is clear from the table, the number of alkaloids of the isoquinoline group is the largest. They include 9 articles about alkaloids from opium (papaverine hydrochloride, noscapine and noscapine hydrochloride, morphine hydrochloride and morphine sulfate, 4 forms of codeine), 2 forms of emetine hydrochloride (pentahydrate and heptahydrate), galantamine hydrobromide and the dimeric alkaloid tubocurarine chloride.

Of the indole alkaloids, 8 monographs are included: 2 salts of eserin (salicylate and sulfate), reserpine, yohimbine hydrochloride, 2 antitumour alkaloids of *Cataranthus roseus* - vinblastine sulfate and vincristine sulfate, 2 ergoalkaloids of *Claviceps purpurea* - ergometrine maleate and ergotamine tartrate.

The next group by number of articles is alkaloids with nitrogen in the side chain which stand out with their diverse chemical composition and various origin (5 representatives and forms from ephedrine and pseudoephedrine, colchicine and paclitaxel).

There are 6 articles about tropane alkaloids of which 5 are from the tropine subgroup (hyosamine sulfate, racemic form of atropine, atropine sulfate, hyosine base and hyosine hydrobromide) and 1 of the ecgonine group (cocaine hydrochloride).

In the pharmacopoeia, 5 monographs are described about purine alkaloids (2 forms about caffeine, 2 forms about theophylline and 1 article about

theobromine), 2 forms from imidazole alkaloids (pilocarpine hydrochloride and pilocarpine nitrate), 3 forms from quinoline alkaloids (quinine hydrochloride, quinine sulphate, quinidine sulfate).

Of the pyridine alkaloids, there are only 2 alkaloids in Ph. Eur. 8 (lobeline hydrochloride and nicotine).

Semisynthetic products from plant substances

Of the isolated pure natural substances, semisynthetic derivatives of better effect, higher biological activity, lower toxicity, better solubility and other useful properties can be obtained through chemical transformations. This is one of the main dimensions in contemporary phytochemistry for obtaining phytopharmaceutical products. Such products are often included in medicinal preparations. The main lines in deriving semisynthetic substances are: enhancement of the main action; enhancement of other secondary actions; change in the main action; emergence of a new action which is not typical for the main substance; decrease of toxicity; change in the properties of the substance; models for complete synthesis of substances with the same action; sources of complex chemical structure for semisynthesis of substances with similar or another action; application in other areas.

The number of articles on semisynthetic substances in Ph. Eur. 8 obtained through chemical modification from natural substances are presented in Table 4.

The total number of monographs on semisynthetic substances from carbohydrates is 91. Of them 44 articles are about monosaccharides, disaccharides and sugar alcohols, of which 12 are about monosaccharides, 12 about disaccharides and 20 about sugar alcohols.

Of the monosaccharides, the largest number is of derivatives of gluconic acid (calcium gluconate, ferrous gluconate, magnesium gluconate, manganese gluconate, zinc gluconate, technetium gluconate, chlorhexidine digluconate) and such important pharmaceutical products as tribenoside (from glucose) and cytarabine (from arabinose).

Derivatives from disaccharides are primarily from sucrose (sucrose monopalmitate, sucrose stearate, sucralose, etc.), glucopyranosyl glucitol (maltitol and isomaltitol), the lactulose used as a laxative and other derivatives.

Semisynthetic products from sugar alcohols are primarily made of glycerol (glycerol trinitrate, glycerol triacetate, calcium glycerophosphate, magnesium glycerophosphate, manganese glycerophosphate hydrate, sodium glycerophosphate hydrate) and sorb-

Table 4. Semisynthetic substances by chemical groups included in Ph. Eur. 8

| Semisynthetic substances by chemical groups | Number of monographs |
|---|----------------------|
| Monosaccharides | 12 |
| Disaccharides | 12 |
| Sugar alcohols | 20 |
| Homopolysaccharides (starches, cellulose, dextrans) | 33 |
| Heteropolysaccharides (heparins, of plant and animal origin) | 14 |
| Total: | 91 |
| Higher fatty acids (HFA) | 26 |
| Higher fatty alcohols (HFAlc) | 10 |
| Esters of higher fatty acids (HFA) with higher fatty alcohols (HFAlc) | 3 |
| Lipids | 19 |
| Total: | 58 |
| Organic acids | 16 |
| Total: | 16 |
| Simple phenols (Monophenols) | 3 |
| Hydroxybenzoic acid | 14 |
| Lignans | 1 |
| Coumarins | 3 |
| Flavonoids | 1 |
| Total: | 22 |
| Terpenes | 8 |
| Saponins | 2 |
| Total: | 10 |
| Alkaloids | 57 |
| Total: | 57 |
| Total: | 254 |

itol (isosorbide mononitrate, isosorbide dinitrate, meglumine) which are used as medications. The largest is the number of monographs on esters of sorbitol and its derivatives with various fatty acids such as polysorbates (polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80) and sorbitans (sorbitan laurate, sorbitan oleate, sorbitan sesquioleate, sorbitan trioleate, sorbitan palmitate, sorbitan stearate) which are applied primarily in pharmaceutical production of medications as excipients.

In the pharmacopoeia, the largest number of articles about semisynthetic derivatives is for homopolysaccharides (33) and heteropolysaccharides (14).

Semisynthetic substances from homopolysaccharides by Ph. Eur. 8 are primarily from derivatives of the cellulose (17 articles about carmellose, carmellose calcium, cellulose acetate, cellulose acetate butyrate,

cellulose acetate phthalate, cellulose microcrystalline, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hypromellose, hypromellose phthalate, methylcellulose, methylhydroxyethylcellulose), derivatives from starch (7 monographs about carboxymethylamylum sodium A B, C, hydroxyethylamylum, hydroxypropylamylum, dextrine, maltodextrine), from dextrans (5 monographs about dextranomer, dextrane 1 about injections, dextrane 40 for injections, dextrane 60 for injections, dextrane 70 for injections) and oligomeric derivatives of glucose (4 articles about alphadex, betadex, hydroxypropylbetadex, carbomers).

Semisynthetic substances from heteropolysaccharides (a total of 14) are from plant origin (2 such as guar galactomannan and sodium alginate) and from animal origin (12 articles). Of them, the largest and of the largest medical significance are the derivatives of heparin (9, among which heparin sodium, heparin calcium, enoxaparin sodium, nadroparin calcium, parnaparin sodium, tinzaparin sodium, dalteparin sodium, danaparoid sodium) and 3 other animal products such as sodium hyaluronate, chitosan hydrochloride (heteropolysaccharide derived through partial deacetylation of chitin isolated from scallops shells, shrimps and crabs) and chondroitin sulfate sodium (natural copolymer from two disaccharides derived from a cartilage of marine and terrestrial animals).

In the pharmacopoeia, there are a total of 58 monographs about derivatives of various higher fatty acids, higher fatty alcohols, their esters and lipids. Of them, articles about higher fatty acids (HFA) are 26, about higher fatty alcohols – 10, about their esters – 3 and about lipids – 19.

Semisynthetic substances from higher fatty acids (HFA) are mainly salts from the caprylic, undecylenic, lauric, palmitic and stearic acids, esters of some of these acids with glycols (ethyleneglycol, diethyleneglycol, propyleneglycol), esters of the stearic and oleic acid with macrogols, etc.

Salts and esters of octyldodecanol, lauryl, cetyl, stearyl and oleyl alcohols and mixtures from them with sodium and various acids (sulphuric, fumaric), ethers of these alcohols with macrogols (macrogol lauryl ether, macrogol stearyl ether, macrogol cetostearyl ether, macrogol stearyl ether, macrogol cetostearyl ether, macrogol oleyl ether) refer to the semisynthetic substances from higher fatty alcohols (HFAlc).

Three articles about semisynthetic esters of higher fatty acids (HFA) with higher fatty alcohols (HFAlc) (cocoyl caprylocaprate, cetyl palmitate and cetostearyl isononanoate).

The articles about semisynthetic lipids refer to various artificially obtained mono-, di- and triesters of glycerol with various higher fatty acids and macrogols or mixtures thereof (glycerol monocaprylate, glycerol monocaprylocaprate, glycerol monostearate, glycerol distearate, glycerol monooleate, glycerol monolinoleate, glycerol dibehenate, macrogolglycerol laurate, macrogolglycerol stearate, macrogolglycerol oleate, macrogol glycerol linoleate, macrogolglycerol ricinoleate, etc.).

All semisynthetic substances from HFA, HFAlc and lipids do not have medicinal properties and are used primarily as excipients in the pharmaceutical, cosmetic industry and in other areas.

Of note is the relatively high number of articles about semisynthetic derivatives from organic acids (16 monographs). These are salts of the ascorbic acid (2 items, calcium and sodium ascorbate), lactic acid (6 articles, 4 forms of calcium lactate with various numbers of molecules of water, magnesium and sodium lactate), citric acid (6 articles, 3 forms of magnesium citrate, potassium citrate, sodium citrate, tributyl citrate) and 2 articles on derivatives of tartaric and nicotinic acids.

They are mainly applied as excipients, regulators of acidity, preservatives, flavour enhancers and for other purposes in the pharmaceutical industry, in the manufacture of food additives, foodstuffs, soft beverages and other lines.

The share of semisynthetic derivatives from natural phenolic compounds is relatively low (22 in total).

Of them, the largest is the number of semisynthetic products from aromatic acids (14 articles). These are primarily esters of the hydroxybenzoic acid (7 articles) such as benzyl benzoate, parabens methyl parahydroxybenzoate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate and their 3 sodium salts. Parabens are widely used in practice as preservatives of perishable products, liquid medicinal forms, food products, etc. Other articles are about semisynthetic products from gallic acid (4 in total) which is one of the most widely available in the plant world and is part of gallotannins. Monographs are for bismuth subgallate (dermatol), propyl gallate, octyl gallate and dodecyl gallate. They are mainly used as astringent and antiseptic agents. There are a total of 3 articles on semisynthetic derivatives of the salicylic acid (methyl salicylate, sodium salicylate and sodium aminosalicylate dihydrate) applied as analgetic and anti-inflammatory agents.

For the other groups of phenolic and polyphenolic compounds, there are very few articles about

semisynthetic derivatives included in the pharmacopoeia. These are 3 products from simple phenols (ichthammol, guaifenesin and menadione), 1 of lignans (etoposide), 1 of flavonoids (troxerutin) and 3 of coumarins (hymecromone, warfarin sodium and warfarin sodium clathrate). Of them, etoposide is a major anti-cancer product, troxerutin is a main substance in many venotonic and capillary enhancement medicinal agents whereas dicoumarol has served as a model system for full synthesis of a whole series of indirect anticoagulant agents such as warfarin, acenocoumarol, pelentan, etc.

The number of monographs on semisynthetic products from terpenes and terpenoids is very small (a total of 10). There are just 2 articles on terpenes (camphor racemic and menthol racemic) and 6 articles about esters (acetates and succinates) of various isomeric forms of diterpenoid tocopherol. Semisynthetic substances from saponins included in Ph. Eur. 8 are just 2 (ammonium glycyrrhizate and enoxolone (from oleanolic acid)).

The number of articles about semisynthetic derivatives from the most important from medical standpoint group of alkaloids (57 monographs) is the largest. According to its chemical composition they are distributed by groups as is indicated in Table 5.

As is clear from the table, the largest number of articles in the pharmacopoeia is on semisynthetic products from isoquinoline alkaloids (13). Primarily semisynthetic derivatives of alkaloids from opium fall into this group as well. This is performed through etherification of the phenolic group, oxydation of the alcoholic group at C₆ of the morphinan nucleus, dehydrogenating the double link at C₇ and C₈, introduction of a new hydroxyl group at C₁₄, replacement of the

Table 5. Semisynthetic substances from different groups of alkaloids included in Ph. Eur. 8

| Groups of semisynthetic alkaloids | Number of monographs |
|-----------------------------------|----------------------|
| Diterpene alkaloids | 2 |
| Ephedrine derivatives | 5 |
| Nicotine and nicotinic acid | 3 |
| Tropane alkaloids | 11 |
| Quinolizidine alkaloids | 1 |
| Isoquinoline alkaloids | 13 |
| Indole alkaloids | 7 |
| Ergot alkaloids | 9 |
| Purine alkaloids | 6 |
| Total: | 57 |

methyl group at the nitrogen atom on the 17th place with a longer aliphatic chain and other changes in the structure of morphin. The monographs included in the pharmacopoeia about semisynthetic products of morphine are about ethylmorphine hydrochloride, pholcodine, dihydrocodeine hydrogen tartrate, hydromorphone hydrochloride, hydrocodone hydrogen tartrate, oxycodone hydrochloride, dextromethorphan hydrobromide, naloxone hydrochloride dihydrate, naltrexone hydrochloride, buprenorphine, buprenorphine hydrochloride, apomorphine hydrochloride and the fully synthetic bisbenzylisoquinoline alkaloid with two quaternary nitrogen atoms of atracurium besylate.

In the second place, there are monographs about semisynthetic substances from tropane alkaloids. Eleven such products are included in the pharmacopoeia. They are derived mainly in three lines:

- through esterification of the hydroxyl group in the tropane nucleus with another acid: homatropine hydrobromide (an ester of tropine with mandelic acid), tropisetron hydrochloride (an ester of tropine with 1H-indol-3-carboxylic acid), depropine citrate (an ester of tropine with dibenzocycloheptadienol), tiotropium bromide monohydrate;

- through replacement of a hydrogen at the nitrogen atom and obtaining quaternary bases: methylatropine bromide (N-methylatropine), methylatropine nitrate, ipratropium bromide (N-isopropyl atropine), hyoscine butylbromide = scopolamine butylbromide (N-butyl hyoscine), oxitropium bromide (N-ethylhyoscine)

- through combined esterification of the hydroxyl group and replacement at the nitrogen atom: homatropine methylbromide (N-methylhomatropine), tropium chloride (ester of N-cyclobutyl tropine with hydroxydiphenylacetic acid).

Concerning indole alkaloids, a total of 16 articles about semisynthetic derivatives and synthetic analogues which can be divided into two subgroups: indole alkaloids from higher plants (7 in total) and ergot alkaloids from *Claviceps purpurea* (9 in total).

Some fully synthetic analogues of various natural alkaloids can be referred to the first group. For example, in practice some fully synthetic structural analogues of natural alkaloid eserine (physostigmine) are most frequently used. Of them, articles on neostigmine bromide, neostigmine methylsulfate and pyridostigmine bromide are included in the pharmacopoeia. Very important semisynthetic products of this group are vinpocetine (derived from the natural alkaloid vincamine of *Vinca minor*) with vasodila-

tion action and antiaggregation effect on platelets. The two new anticancer products vindesine sulphate (desacetyl vinblastine amide) and vinorelbine tartrate (vinblastine dehydrate) are derived from the natural dimeric alkaloid vinblastine which is contained in the leaves of *Catharanthus roseus*. There is also an article about a semisynthetic product (alcuronium chloride), an analogue of C₄₀ curare alkaloids (toxiferines) with myorelaxant action.

The second group consists of monographs on semisynthetic substances from the ergot alkaloids from *Claviceps purpurea*. This takes place through methylation of the alkaloid ergometrine (methylergometrine maleate) through hydrogenation of the double link at C₉-C₁₀ (dihydroergotamine mesilate, dihydroergotamine tartrate, dihydroergocristine mesilate, codergocrine mesilate (a mixture of dihydroergotoxin alkaloids dihydroergocornin, dihydroergocristine, α -dihydroergocryptine, β -dihydroergocryptine mesilates). Through bromination in the second place of the indole nucleus of ergocriptine, bromocriptine mesilate is obtained. The list of monographs is complemented by 1 article about a semisynthetic product from amide of the lysergic acid (cabergoline) and 2 monographs about derivatives of lysergol (nicergoline and pergolide mesylate).

The next group in terms of number of articles are semisynthetic substances from purine alkaloids (6 monographs). Of them, the largest number is dedicated to derivatives of theophylline. The pharmacopoeia describes monographs about theophylline-ethylenediamine anhydrous, theophylline-ethylenediamine hydrate, etofylline, proxiphylline, diprophylline and the one widely used in practice as medications pentoxifylline (a semisynthetic product of theobromine).

The pharmacopoeia includes 5 monographs on analogues of ephedrine. Due to their easy synthesis, they are usually derived not through modification of the structure of ephedrine but through full synthesis. These are the substances with adrenomimetic effect: amphetamine sulfate, ethylefrine hydrochloride, phenylephrine, phenylephrine hydrochloride and phenylpropanolamine hydrochloride (norephedrine).

Other monographs on semisynthetic products are: 2 articles about diterpenoid alkaloids, analogues of paclitaxel known for its anticancer action (docetaxel anhydrous and docetaxel trihydrate); 3 articles about semisynthetic substances from the pyridine alkaloid nicotine (nicotinamide, nicotine resinate and nicotine ditartrate dihydrate); one synthetic analogue of quinolizidine alkaloids (granisetron hydrochloride).

Conclusion

A comparative analysis of the monographs on *Plant substances* and *Semisynthetic substances* included in the European Pharmacopoeia 8 (Ph. Eur. 8) was made regarding their chemical structure and the group of active substances to which they relate. The analysis shows a continuous increase in the number of monographs on these groups of substances (from 147 articles in Ph. Eur. 4 to 377 in Ph. Eur. 8). They constitute about 19.5 % of the total number of monographs in the Ph. Eur. 8.

In Ph. Eur. 8 the total number of monographs on plant substances is 123, of which the largest is the number of alkaloids (46), followed by mono- and polysaccharides (29), terpenes (11) and organic acids (10). From the group of alkaloids are included 13 monographs on isoquinoline, 8 on indole, 7 on alkaloids with nitrogen atom in the side-chain, 6 on tropane and 5 articles on purine alkaloids.

The total number of monographs on semisynthetic substances is 254. From them 58 are derivatives of various higher fatty acids, higher fatty alcohols and lipids; 57 are articles on derivatives of alkaloids; 44 monographs are on mono- and disaccharides

(mainly derivatives of gluconic acid) and sugar alcohols (mainly sorbitans and polysorbates); 33 are on homopolysaccharides (mainly cellulose derivatives); 14 are on heteropolysaccharides; 22 are on phenolic compounds (mainly derivatives of hydroxybenzoic acid); and 16 articles on nonaromatic organic acids. There are 16 monographs on indole and ergoalkaloids, 13 on isoquinoline alkaloids (12 of these semisynthetic products are morphine alkaloids), 11 on tropane alkaloids, 6 on purine alkaloids and 5 are the articles on analogues of ephedrine.

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