REVIEW ARTICLE

Oral mucosa and therapy of recurrent aphthous stomatitis

Orální mukóza a léčba rekurentní aftózní stomatitidy

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Received 27 November 2012 / Accepted 12 December 2012

Summary

Oral mucosa is one of the specific surfaces of the human body, which is permanently exposed to external factors related with food intake, breathing and speaking processes, which can lead to the onset of some problems. Disorders of the oral mucosa are a group of diseases, affecting, in the course of life, the majority of the population. Many of the oral mucosa ailments are manifested by lesions. Recurrent aphthous stomatitis (RAS) is the most common of these diseases. Despite much clinical and research attention, its causes remain poorly understood and treatment is only symptomatic. RAS is reported to affect up to 25% of the population worldwide. Topical or systemic therapy (corticosteroids, antiseptics, anti-inflamatory drugs, immunomodulating agents, etc.) can be used for treatment of RAS-associated symptoms. In general, topical therapy should be preferred due to the smaller drug load of the organism. In both cases, the active substance has to be in suitable dosage form. Recently, besides the conventional ways of application (rinses), the main disadvantage of which is the short time of resistance in the oral cavity, mucoadhesive dosage forms are used. The aim of this article is to give a theoretical overview of the oral mucosa topic and its most frequent disease – recurrent aphthous stomatitis in terms of various types of the disease classification, diagnosis and therapy, and in terms of the usage of various types of active substances and medical forms.

Keywords: oral mucosa • recurrent aphthous stomatitis • therapy • mucoadhesive dosage forms

Souhrn

Sliznice dutiny ústní je jedním ze specifických povrchů lidského těla. Je trvale vystavena působení vnějších faktorů spojených s příjmem potravy, dýcháním a mluvením, jejichž vliv může vést ke vzniku některých onemocnění. Choroby sliznice dutiny ústní v průběhu života postihují většinu populace. Velká část těchto onemocnění se manifestuje v podobě povrchových lézí. Rekurentní aftózní stomatitida (RAS) je nejčastější z těchto chorob. Přes značnou klinickou a výzkumnou pozornost zůstávají její příčiny stále nedostatečně vysvětleny a léčba je omezena na symptomatickou terapii nepříjemných projevů onemocnění. RAS se v průběhu života vyskytne až u 25 % celosvětové populace. Místní i systémová terapie (kortikosteroidy, antiseptika, protizánětlivá léčiva, imunomodulační přípravky atd.) může být použita pouze pro léčbu a mírnění symptomů spojených s propuknutím RAS. Obecně platí, že by měla být dávána přednost lokální léčbě z důvodu menší zátěže organismu léky. V každém případě je nedílnou součástí úspěšné terapie této choroby volba vhodné lékové formy. V poslední době se kromě tradičních způsobů aplikace (výplachy), jejichž nevýhodou je krátká doba působení v ústní dutině, začínají do praxe prosazovat moderní mukoadhezivní lékové formy. Cílem tohoto článku je podat teoretický přehled týkající se sliznice ústní dutiny a jejího nejčastějšího onemocnění – rekurentní aftózní stomatitidy z hlediska klasifikace jednotlivých typů onemocnění, diagnostiky a terapie, a to z pohledu použití různých léčivých látek a lékových forem.

Klíčová slova: sliznice dutiny ústní • rekurentní aftózní stomatitida • terapie • mukoadhezivní lékové formy

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Oral mucosa

The oral mucosa is formed from the outermost layer of stratified squamous epithelium. Below it, there are three further underlying layers – basement membrane, lamina propria and submucosa as the innermost layer. General similarities to stratified squamous epithelia from other parts of the body can be found, such as mitotically active basal cell layer supporting differentiating cell layers situated above it and an outer layer shedding cells from the epithelial surface[1]. In the case of buccal mucosa, the

epithelium consists of about 40–50 cell layers increasing in size and becoming flatter as they are situated closely to the surface, while the sublingual epithelium contains somewhat fewer layers[2].

The turnover time for the buccal epithelium has been estimated to 5–6 days[3]. The thickness of the oral mucosa is relatively variable: the thickness of the buccal mucosa ranges from 500–800 μm while the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae are only about 100–200 μm thick. The site in the oral cavity is another factor determining the epithelium composition. The mucosal areas exposed to mechanical stress (the gingivae, alveolar mucosa and hard palate) are keratinized (similarly to the epidermis) as opposed to the non-keratinized soft palate mucosa or sublingual and buccal regions[3]. The keratinized and non-keratinized epithelia also differ in water permeability and in the content of neutral lipids such as ceramides and acylceramides, which have been associated with the barrier function. These lipids can be predominantly found in water-impermeable keratinized epithelia, while only small amounts of ceramides and virtually no acylceramides are presented in the non-keratinized epithelia such as the floor of the mouth or the buccal epithelia[4–6]. Small amounts of neutral polar lipids (mainly cholesterol sulfate and glucosyl ceramides) were also identified in relatively water-permeable non-keratinized epithelia[3–5].

Properties of the oral mucosa can be generally set between those of the epidermis and of the intestinal mucosa. Permeability of the buccal mucosa is reported to be 4–4000 times greater than that of the skin[7]. This wide range reflects great differences between various types of the oral mucosae with respect to permeability, which is obviously related to their various functions and structures. The permeability of the sublingual mucosa is generally the highest, followed by the buccal, and the least permeable is then the palatal mucosa[3], which corresponds to the thickness and degree of keratinization of the tissues in question – the sublingual mucosa is non-keratinized and the thinnest, the buccal mucosa is thicker and non-keratinized, and although the thickness of the palatal mucosa is intermediate, its keratinization renders it the least permeable[2].

The permeability of the oral mucosa is also closely connected to an intercellular material derived from "membrane coating granules" (MCGs), organelles formed as a product of cell differentiation[8]. MCGs then fuse with the plasmatic membranes at the apical cell surfaces, which allow their content to be discharged into the intercellular space in the outermost 200 μm of the superficial layer of the epithelium. The non-keratinized epithelium contains non-lamellar MCGs (the main lipidic components are cholesterol esters, cholesterol, and glycosphingolipids) while lamellar lipid stacks (including sphingomyelin, glucosylceramides, ceramides, and other non-polar lipids) can be found in MCGs of keratinized epithelium. Some permeability resistance is also attributed to the basement membrane, however, as its structure is not dense enough to filter out even relatively large molecules, the outer epithelium is generally considered to play the main part in limiting permeability[4].

As indicative by the name "oral mucosa", the outermost layer is covered with *mucus* – predominantly a mixture of protein and carbohydrate complexes, which may be either attached to the cell surfaces, or freely suspended in the layer. The mucus is reported to play role in cell adhesion and at the same time to act as a lubricant allowing relative motion of the cells[9]. Its bioadhesive properties are also used in mucoadhesive drug delivery systems[10]. Due to the sialic acid and sulfate residues in the mucus, it carries a negative charge at the physiological pH, which influences its adhesive properties and allows it to form a gelatinous layer on the epithelial cell surface[1, 2].

Unlike in stratified squamous epithelia in other parts of the body where mucus is produced by specialized mucus secreting cells (e.g. the goblet cells), mucus in the oral mucosa is secreted as a part of the saliva by major and particularly (up to 70% of the total salivary mucin) minor salivary glands[9, 11].

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is the most common disease of the oral mucosa. Although it has been widely studied, the knowledge of the causes is still limited, and the treatment is only symptomatic. RAS is a common oral mucosal disease characterised by multiple recurrent small round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors, with first occurrence in childhood or adolescence. Up to 25% of the worldwide population is estimated to be affected by RAS[12, 13].

RAS is usually defined as recurrent bouts of one or several rounded, shallow ulcers at intervals of a few months to a few days, afflicting otherwise healthy people. Aphthous ulcers are usually extremely painful for the first 4–5 days and can interfere with eating and speaking during that period. Three main manifestations are referred to as *minor*, *major* or *herpetiform* ulcers[12–14].

About 80% of patients with RAS are affected by the *Minor RAS* (MiRAS), rendering it therefore the most common form of the disease. Ordinarily MiRAS are small (< 5 mm in diameter), round or oval shaped, with a grey-white pseudomembrane and an erythematous halo around. Non-keratinized surfaces, particularly the labial and buccal mucosa and floor of the mouth, are the most susceptible to MiRAS, whereas occurrence on the gingiva, palate, or dorsum of the tongue is uncommon. Within 10–14 days, the ulcers heal without scarring[12–14].

Major RAS (MaRAS), called also periadenitis mucosa necrotica recurrent, is a severe form of RAS, afflicting about 10% of patients with RAS. The ulcers of MaRAS, occurring often on the lips, soft palate and fauces, may exceed 1 cm in size, persist for up to 6 weeks and often heal with scarring. MaRAS is usually chronic and

persistent for up to 20 years with first manifestation after puberty[12–14].

The third form of RAS, *Herpetiform ulceration* (HU), occurs in 1–10% of patients suffering with RAS. Characteristic symptoms are multiple groups of recurrent small, painful ulcers (up to 100 ulcers at a time), which are typically 2–3 mm large, although their fusion into large irregular ulcers is not uncommon. Onset of HU is typically later than of the other two types and women are reported to be more susceptible to HU than men[12–14].

The exact etiology and pathophysiology of RAS is poorly understood, although a relationship between aphthous ulcers and a focal immune dysfunction, in which T-lymphocytes play a significant role, is generally accepted. Many etiologic, predisposing, and precipitating factors have been suggested including hypersensitivity to food and drugs, trauma, hormonal changes, haematological deficiencies (particularly serum iron, folate and vitamin B_{12}), cessation of smoking, immunological problems, environmental and psychological stresses, genetic factors, and viral infections[15–20].

Differential diagnosis

When recurrent oral ulcerations appear as previously described, multiple diagnoses must be considered, such as[21–23]:

- *Herpes simplex virus* (HSV) can be easily mistaken for aphthous ulcerations. HSV lesions however begin as a cluster of vesicles which then ulcerate, while RAS start directly in the ulcerous state. RAS will also appear in several locations while HSV tends to form a cluster in a single location (although it is true that the initial outbreak can involve the entire oral mucosa). HSV lesions are usually less than 3 mm in diameter while RAS lesions are typically larger. A vast majority of RAS ulcers are on labial or buccal mucosa, whereas HSV lesions appear more frequently on the mucosa attached to the underlying periosteum (i.e. gingival mucosa). When in doubt, the clinician can differentiate HSV using laboratory studies (antigen detection, serology, culture, PCR, or Tzanck smear).
- *Behçet's disease* can manifest with oral ulcerations similar to RAS, a complete physical examination will however reveal the correct diagnosis. Similarly to RAS, the cause of Behcet's disease is unknown. This vasculitis presents with oral, genital, and ocular lesions, of which the oral and genital lesions are ulcerative. In the eye, uveitis and iritis, which can lead to blindness, along with a hypopyon are the typical manifestations.
- *Coxsackievirus* A2, A4, A6, A8, and A10 can cause ulcerations similar to HSV, too. The primary location of these ulcers, which begin as vesicles, is the posterior oral cavity and oropharynx.
- *Hand-foot-and-mouth disease,* caused by Coxsackievirus A16, can be differentiated from RAS by the initial appearance of vesicles, similarly to the other *Coxsackievirus*es, however the main difference from RAS is the presence of lesions on the hands and feet.
- *Crohn's disease* and *systemic lupus erythematosus* can be accompanied with recurrent oral ulcerations, however these diseases will have extraoral manifestations as a rule.
- A painless ulcer ("chancre") of primary *syphilis* may occur in the oral cavity in patients engaging in oral sex.
- *Erythema multiforme* can lead to ulceration, it is however not a primary manifestation. It typically begins with a red plaque in the oral cavity followed by formation of a bulla which then ruptures, becomes secondarily infected, and only then develops ulceration. Also, most of erythema multiforme cases have the typical lesions on the skin.
- *Pemphigus* is a disease usually occurring in older patients with onset in the fifth decade. The ulcers develop after the rupture of the originally formed vesicles and bullae. Oral manifestations of pemphigoid follow the cutaneous lesions and immunofluorescence will show deposition of IgG and C3 in a linear pattern at the basement membrane. Bullous pemphigoid occurs in the elderly (generally those older than 60 years) and presents as tense bullae on the inner thighs and flexor surfaces of the forearms, axillae, groins, and abdomen.

Therapy

Three goals of the therapy can be generally outlined: to reduce the ulcer pain, to promote ulcer healing, and to prevent recurrence. However, as the causes of RAS are uncertain, a completely effective treatment or prevention is unknown[21]. The achievable maximum is suppressing the local immune response, reduction of the discomfort and preventing the secondary infection. If used with care, topical chlorhexidine, corticosteroids or amlexanox may be beneficial. Systemic steroids seem to be helpful in recalcitrant cases[13]. Removal of ulcers using traditional surgical methods is ineffective, however carbon dioxide laser therapy has recently been shown as helpful in RAS cases[24].

Topical therapy

Treatment with topical agents generally elicits fewer side-effects than systemic therapy and is therefore preferred. However, systemic immunomodulation may be necessary in serious RAS cases.

Anaesthetics

Local anaesthetics such as *lidocaine* or *dyclonine hydrochloride* are often used for short-term pain relief. Despite having no direct therapeutic effects, such treatment is extremely important particularly in the case of major ulcers. These ulcers may be so painful that the pain prevents the patient from eating. As their healing takes up to 6 weeks, reduced food intake for such a long time can result in a substantial weight loss in the patient[21].

Corticosteroids

Corticosteroids are the most frequently used drugs in RAS treatment and several have been found to be effective in acceleration of healing of the ulcers and generally reducing RAS symptoms. Despite this fact, there is only one systematic review of their use[25]. There are concerns about side-effects of long-term or repeated use of corticosteroids, particularly about the possible effects on adrenal glands; however, it has been reported that even some more potent steroids, such as *triamcinolon acetonide* 0.025% or *fluocinonide* 0.05% in adhesive paste, and *betamethasone* mouth rinse rarely cause this[12, 13, 26].

Antimicrobials and antiseptics

Antimicrobials may be used for RAS treatment, however it is generally accepted that their use is more connected with their anti-inflammatory and analgesic effects than with their antimicrobial functions.

Although there is no evidence of bacterial origin of RAS, several studies reported that some topical antimicrobials such as *chlorhexidine* (as a 0.2% w/w mouth rinse or a 1% gel) are able to accelerate healing of RAS ulcers and prolong the ulcer-free periods in RAS patients[13, 27–29].

Triclosan

A drug with antimicrobial, antiinflammatory, and analgesic effects, was also shown to elicit some effects including pain relief, reduction of the number of ulcers and shortening the ulcerative phase[25] when used as a mouth wash[30–32].

Anti-inflammatory agents

Studies with an over-the-counter anti-inflammatory drug *benzydamine hydrochloride* in the form of a mouthwash have reported transient relief of pain, however no effects on healing have been found[12, 33, 34].

Amlexanox

Another anti-allergic and anti-inflammatory drug reported to have beneficial effects in RAS treatment, although the exact mode of action is unknown. Application of amlexanox 5% paste 2–4 times daily considerably reduced the size of ulcers as well as pain, and speeded up healing. However, local application of bioerodible mucoadhesive patches containing 2 mg of amlexanox applied in the prodromal phase of RAS did not show any positive effects. Negative reactions to amlexanox are nevertheless rare and not serious (a transient mild stinging at the site of application)[12].

Others

Another possible treatment is a therapy using topical adhesives forming an impenetrable barrier protecting the ulcers from irritation and thus preventing the pain, to a certain extent, for several hours. One such adhesive is *Solcoseryl®* (a deproteinized extract of young calf blood, lauromacrogol 450). The only adverse effect is a severe burning sensation for several seconds after application[12, 13].

Systemic therapy

Immunomodulating systemic treatment may be needed in patients with particularly frequent or severe RAS.

Systemic *steroids* have been proved very effective against RAS, causing most ulcers to heal within a week. Their administration was also helpful in controlling severe outbreaks of RAS, however had no effect on recurrences. The systemic side effects of steroids are nevertheless a factor limiting their usefulness and they are therefore indicated only for persistent major ulcers.

Other drugs such as *thalidomide*, *5-aminosalicylic acid*, *sucralfate*, *colchicine*, *cromolyn, B-type vitamins*, *folic acid*, etc. were also reported to be effective[12, 16].

Contribution of dosage form to RAS therapy

All the above-mentioned drugs should be formulated into suitable dosage forms due to easy administration to the oral cavity and effective therapy.

Conventional dosage forms

Conventional oral dosage forms may be divided into liquid, semi-solid or solid dosage forms.

Semi-solid dosage forms for oral administration include hydrophilic gels, ointments and pastes. They are intended for local application in the oral cavity and its specific parts as gingivae[35]. In comparison to *liquid forms* the time of active pharmacotherapy is prolonged from seconds or at the most a few minutes to tens of minutes[36]. Hydrogels are usually homogenous, clear preparations consisting of a liquid phase (water, glycerol or propylene glycol) within a three-dimensional polymeric matrix of suitable gelling agents (cellulose derivatives, starch, tragacanth, carboxyvinyl polymers etc.)[35]. Evaporating of liquid phase causes typical cooling effect of hydrogels. They are applied to the mucous membranes for protective, therapeutic or prophylactic purpose[37]. Examples of registered oral gels used in the RAS therapy are Kamistad® Senzitiv gel (German chamomile fluid extract, lidocaine) or Mundisal® gel (choline salicylate). Pastes are homogenous, semi-solid preparations containing high concentrations of insoluble powdered substances (usually more than 25%) dispersed in a suitable base[35]. Pastes are usually less greasy, more absorptive and stiffer in consistency than ointments because of the large quantity of powdered ingredients present[37]. Commercially available paste is for example Solcoseryl® Oral paste (deproteinized extract of young calf blood, lauromacrogol 450).

Solid dosage forms contain one or more active ingredients and other excipients (fillers, binders, colouring, flavouring and sweetening agents, etc.). Conventional solid forms include buccal or sublingual tablets or capsules and lozenges[35]. Lozenges are usually

sweetened and flavoured and are intended to be slowly dissolved in the mouth, commonly are used for local therapy (containing antimicrobial agents or anaesthetics), but systemic action can be also reached by swallowing the saliva with dissolved drug[35]. More common dosage forms are erodible or chewable buccal or sublingual tablets and capsules. Due to involuntary swallowing of the dosage form itself or part of it and due to a continuous dilution of the suspended or dissolved drug by the saliva flow, there is a high risk that a major part of the drug of such dosage form may not be available for buccal absorption. Moreover, administration of conventional buccal and sublingual tablets and capsules does not correspond with drinking and eating and could be a handicap for speaking[38]. The examples of commercially available convenient solid dosage forms for use in the treatment of RAS are Orofar® (lozenges with lidocaine and benzoxonium chloride) or Hexoral® (oral pastilles with benzocaine and chlorhexidine).

Mucoadhesive dosage forms

The modern group of mucoadhesive dosage forms, formed on the basis of bioadhesive polymers can significantly prolong the contact time with various mucosal membranes. This ability to maintain a delivery system at a particular location for an extended time has a great appeal for both local disease treatment and systemic drug absorption[39].

Retentive mucoadhesive formulations may prove to be an alternative to the conventional oral dosage forms as they can be readily attached to the oral cavity, retained for prolonged period of time, and removed if necessary[40].

Several mucoadhesive dosage forms have been studied and reported by many researchers either for local or systemic actions[41]. They can be divided into three groups:

- liquid mucoadhesive dosage forms,
- semi-solid mucoadhesive dosage forms,
- solid mucoadhesive dosage forms.

Liquid mucoadhesive dosage forms

Viscous liquids may be used to coat the buccal surface of the oral cavity either as protectants or as vehicles for drug delivery to the mucosal surface[41]. The use of highly viscous solutions leads to an improvement in the retention on the mucosal surface and also to a reduction in the dosage frequency due to enhanced bioavailability. However, liquid mucoadhesive dosage forms are more commonly used as ocular delivery systems (e.g. for tropicamide, pilocarpine or ofloxacin) or as artificial tears[42].

Semi-solid mucoadhesive dosage forms

Semi-solid mucoadhesive dosage forms, such as gels, pastes and ointments, have many advantages, such as easy dispersion throughout the oral mucosa, ability to form intimate contact with the mucosal membrane and rapid release of drug, adherence for extended time period and patient acceptability. However, their main limitation is an inability to deliver a precise drug dose to the site, which excludes them from use for drugs with a narrow therapeutic window. The main application of adhesive gels is the local delivery of drugs for periodontitis treatment[41, 43]. Team of the Ege University, Turkey, recently developed a bioadhesive benzydamine hydrochloride containing gel formulation for the treatment of different oral painful conditions[44]. Commercially available semi-solid mucoadhesive forms for RAS treatment are e.g. Zilactin®-B gel (benzocaine) or Corsodyl® gel (chlorhexidine gluconate).

Solid mucoadhesive dosage forms

Tablets: To date, tablets have been the most commonly investigated dosage form for buccal delivery. Several bioadhesive tablet formulations have been developed in recent years either for local application or systemic delivery of drugs liable to decomposition in the gastrointestinal tract or fast metabolism in the liver. They are intended to be placed directly onto the mucosal surface and are retained in position until dissolution and/or release of drug is complete. The drug release can be either unidirectional, targeting buccal mucosa, or multidirectional into the saliva. Unlike conventional tablets, buccal mucoadhesive tablets allow drinking and speaking without significant discomfort. Other advantages are the high drug bioavailability, non-invasive way of administration, ability to deliver measured dose of drug or suitability for patients with swallowing disorders. On the other hand, there are limitations for buccal tablets, namely the size and possible local irritation[45–47]. Currently, there is no registered buccal adhesive tablet for RAS treatment, although mucoadhesive tablets are successfully used for treatment of some other disorders. Examples of commercially available buccal mucoadhesive tablets are Suscard® (glyceryl trinitrate), Loramyc® (miconazole), or Buccastem® (prochlorperazine).

Wafers: Mucoadhesive wafer is another adhesive and stable solid dosage form prepared usually by lyophilisation from gels. The rate of drug release from wafers is, due to its porous network, faster than release from the corresponding film[58]. High porosity of wafers leads to their fast disintegration. The downside to this is the lower mechanical resistance of wafers, which may cause problems during packaging and other processing[49].

Films/patches: Films or patches are the most recently developed dosage form for buccal administration. In the scientific literature it is possible to find equivalent terms "patches", "films" and also "discs". Some reviews include films (especially these forming *in situ*) into the semi-solid form[41]. Films are laminates usually consisting of two or three layers and, thanks to their flexibility and comfortable use, are preferred over adhesive tablets. Small thickness of the film with non-irritating properties and strong mucoadhesiveness of the polymer demand only minimal changes in the patients' normal activities such as eating, drinking or speaking. In addition, they can circumvent the relatively short residence time of oral

gels on the mucosa and provide a measured dose of drug to the application site. Moreover, they can also help protect the wound surface or cover mucosal defects of the oral cavity, which leads to pain reduction[43, 50–52]. Flexible patches of various sizes allow their adaptation to the morphology of the oral cavity and size of the defect.

Conflicts of interest: none.

This article was completed with support of a Ministry of Health of Czech Republic research project NT11396 and IGA VFU Brno, Czech Republic, research project No. 78/2012/FaF.

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ZPRÁVY

● 55 rokov Katedry farmaceutickej chémie FaF UK v Bratislave

Farmaceutická fakulta Univerzity Komenského (FaF UK) a Slovenská farmaceutická spoločnosť (SFS), o.z, SLS usporiadali 14.12.2012 na počesť 55. výročia založenia Katedry farmaceutickej chémie FaF UK v Bratislave slávnostný seminár.

Účastníkov semináru privítala E. Sedlárová, vedúca tejto katedry, ktorá stručne zhodnotila prínos L. Kňažka, J. Čižmárika, V. Matejekovej, J. Ďurindu a L. Beneša ako bývalých vedúcich tohto pracoviska v kontexte 60.výročia založenia samostatnej FaF UK.

Hlavný príspevok semináru na tému *Prínos katedry do farmaceutických vied* predniesol J. Čižmárik. Zdôraznil v ňom, že od roku 1957, kedy bola katedra založená, sa jej učitelia a vedeckí pracovníci podielali a prispeli k štúdiu hydrotrópie, solibilizácie liečiv, izolácie obsahových látok lišajníkov a propolisu, k príprave a štúdiu vzťahov medzi chemickou štruktúrou, fyzikálno chemickými vlastnosťami (molekulovými deskriptormi) a účinku v skupiny syntetických antituberkulotík, azachalkónov ako inhibítorov hormónov nadobličiek, lokálnych anestetík zo skupiny bázických anilidov, karbamátov, beta lytík zo skupiny aryloxyaminopropanolov a korelácii parametrov TLC, GC a HPLC s biologickým účinkom. Osobitnú pozornosť venoval pentakaínu, heptakaínu, karbizokaínu a látke H+B, ktoré sú originálnými potenciálnými liečivami vyvinutými na tomto pracovisku. V závere svojho vystúpenia vyzdvihol práce a výsledky zo štúdia termodynamických parametrov liečiv, chemometrie, kvantovej chémie, kvantovej mechaniky, vývoja liečiv s pomocou počítačov (CADD) a metód molekulového modelovania. Konštatoval, že práce katedry z oblasti predikcie, projekcie, prípravy, izolácie, identifikácie, analytických profilov liečiv, štúdia QSAR, lokálno anestetického, antiarytmického, antiinfekčného, antituberkulotického alebo antihypertenzívneho účinku sú adekvátne citované v chemickej a farmaceutickej odbornej literatúre.

V ďalšej časti semináru za dlhoročnú pedagogickú, vedecko-výskumnú a organizátorsku prácu boli V. Matejeková a S. Szucsová ocenené Striebornou medailou Galenosa FaF UK a Ľ. Búčiová Medailou PhMr. Vladimíra J. Žuffu SFS.

V časti príhovory hostí a priateľov vystúpili J. Kyselovič, R. Medvecký, F. Devínsky, J. Csollei, I. Tumová, I. Pavlíková a D. Uhríková.

Semináru sa zúčastnili nielen súčasní, ale i mnohí bývalí učitelia a pracovníci katedry, viacerí učitelia FaF UK, ale i spolupracovníci z viacerých fakúlt a akademických inštitúcii.

J. Čižmárik