Farmaceutska tehnologija i kozmetologija

Pharmaceutical Technology and Cosmetology

SADRŽAJ – CONTENTS

INOVACIJE U RAZVOJU ORALNOG DISPERZIBILNOG FILMA I SAVREMENI ZAHTEVI ZA KVALITET

Gordana Žigić, Ivana Džunić

Agencija za lekove i medicinska sredstva Srbije (Srbija)

Formulacije koje pokazuju veoma kratko vreme raspadanja, kao što su oralni disperzibilni filmovi (ODF), imaju sve veći značaj poslednjih godina jer su pogodne za pacijenta (naročito u stanjima otežanog gutanja), omogućavaju brzo oslobađanje aktivne supstance direktno u sistemsku cirkulaciju, odnosno brzo delovanje leka i imaju brojne prednosti u odnosu na klasične oralne čvrste farmaceutske oblike. Cilj rada je da se prikažu savremena saznanja koja se odnose na razvoj formulacije i zahteve za kvalitet ODF. Pregledom najnovije literature i važeće regulative dat je sažeti prikaz inovacija u oblasti razvoja formulacije, procesa proizvodnje i zahteva za kvalitet ODF.

Najveći izazov u razvoju ODF formulacije predstavlja evaluacija ekscipijenasa tako da se postigne izbalansiran odnos između vremena raspadljivosti, stabilnosti aktivne supstance, reoloških i organoleptičkih karakteristika proizvoda, uz korišćenje minimalnog broja ekcipijenasa. Izborom odgovarajućeg polimera za formiranje filma, u adekvatnoj koncentraciji, postiže se homogena distribucija hidrosolubilnih ili nerastvorljivih (mikro i nanočestice) aktivnih supstanci, malih ili velikih molekula, bez promene fizičkih morfoloških osobina supstance (veličina čestica, naelektrisanje, kristalni oblik). Inovacije u razvoju procesa proizvodnje ODF uključuju proizvodnju ODF primenom 3D tehnologije štampanja u cilju dobijanja personalizovanih lekova i primenu novog koncepta kontinuiranog procesa proizvodnje, naročito u postupku ekstruzije topljenjem.

Da bi se zadovoljili savremeni zahtevi kvaliteta, ODF mora da poseduje poroznu strukturu, ujednačenu debljinu, kratko vreme raspadanja, dobru stabilnost, adekvatnu mehaničku otpornost u cilju sprečavanja oštećenja u toku rukovanja, ujednačen i homogen sadržaj, odgovarajuće oslobađanje aktivne supstance, prijatan ukus i osećaj u ustima i dr. Zahtevani kvalitet ODF se potvrđuje primenom odgovarajućih testova. Očekuje se da će ODF imati sve veći značaj u budućnosti jer su mnoga istraživanja koja su u toku usmerena na ispitivanje potencijalne primene ODF u proizvodnji biomolekula (vakcina) i formulacija sa mikro i nanočesticama aktivnih supstanci BCS klase II i IV, omogućavajući na taj način prelazak sa parenteralnog na oralni farmaceutski oblik leka.

INNOVATIONS IN DEVELOPMENT OF ORAL DISPERSIBLE FILMS AND CURRENT QUALITY REQUIREMENTS

Gordana Žigić, Ivana Džunić

Medicines and Medical Devices Agency of Serbia (Serbia)

Fast disintegrating formulations, such as oral dispersible films (ODF), have increasing importance in recent years because they are convenient for patients (especially those who have difficulty in swallowing), allow fast dissolution of active substances directly to the systemic circulation providing rapid onset of action and have numerous advantages in comparison with conventional oral solid dosage forms. The aim of this study is to present the recent findings related to formulation development and quality requirements for ODF. Review of the novel literature data and current regulation, as well as recent innovations in the field of formulation and manufacturing process development and quality requirements for ODF is presented.

A major challenge in ODF formulation development is evaluation of excipients in order to achieve the right balance between disintegration time, stability of active substances, rheological and organoleptic product characteristics, while minimising the number of excipients. The proper selection of film forming polymers, at appropriate concentration, leads to homogeneous distribution of hydrosoluble or insoluble (micro and nanoparticles) active substances of small and large molecules without changing physical morphological properties of the substance (particle size, charge, crystal form). Innovations in manufacturing process development of ODF include manufacturing of ODF applying 3D printing technology in order to get personalised medicines and application of a new concept of continuous manufacturing, especially in hot melt extrusion process.

In order to fulfill current quality requirements, ODF must have porous structure, uniform thickness, fast disintegration, good stability, adequate mechanical strength to resist being damaged during handling, uniform and homogeneous content, appropriate dissolution, pleasant taste and mouth feel etc. Required quality of ODF is demonstrated by carrying out suitable tests. It is expected that ODF will have growing significance in the future because many ongoing studies are focused on potential application of ODF in manufacturing of biomolecules (vaccines) and formulations with micro and nanoparticles of BCS class II and IV active substances, thus enabling the switch from a parenteral dosage form to an oral one.

ISPITIVANJE UTICAJA RAZLIČITIH FORMULACIJA I NAČINA PROIZVODNJE NA BIOEKVIVALENTNOST FILM TABLETA DIKLOFENAK NATRIJUMA

Sanja Kecman[1], Svetlana Goločorbin Kon[2], Milan Jokanović[3], Ranko Škrbic[4], Momir Mikov[5]

[1]Hemofarm d.o.o, član Stada grupe, Banja Luka, Republika Srpska (Bosna i Hercegovina), [2]Katedra za farmaciju, Univerzitet u Novom Sadu - Medicinski fakultet (Srbija), [3]Katedra za farmaciju, Univerzitet u Nišu - Medicinski fakultet (Srbija), [4]Katedra za farmakologiju i toksikologiju, Univerzitet u Banjoj Luci - Medicinski fakultet, Republika Srpska (Bosna i Hercegovina), [5]Katedra za farmakologiju, toksikologiju i kliničku farmaciju, Univerzitet u Novom Sadu-Medicinski fakultet (Srbija)

Različiti tehnološki postupci proizvodnje i prisustvo različitih pomoćnih supstanci u preparatu ne moraju da znače odsustvo njihove bioekvivalentnosti. Ispitivanje bioekvivalentnosti u *in vitro* i *in vivo* uslovima su vršena za dva tehnološki različita farmaceutska proizvoda koja sadrže istu aktivnu supstancu, ali se razlikuju u izboru sredstva za oblaganje tabletnih jezgara. Istraživanje je imalo za cilj da ispita uticaje sredstva za oblaganje na profile oslobađanja i resorpciju lekovite supstance iz tableta koje sadrže diklofenak. Formulacija I je sadržala Eudragit L30, a Formulacija II Eudragit L100 kao sredstvo za oblaganje. Da bi se optimizirala stabilnost tableta, obje formulacije su sadržavale različite pomoćne sastojke. *In vitro* ispitivanja su obuhvatila ispitivanje variranja mase, dijametra, čvrstine i raspadljivosti tableta, kao i brzine rastvaranja diklofenaka iz tableta. U drugom dijelu istraživanja, nakon oralnog davanja diklofenak tableta zečevima, ispitivani su koncentracija lijeka u plazmi i farmakokinetički parametri. Podaci iz sprovedenih istraživanja u *in vitro* uslovima su pokazali da postoje razlike između ispitivanih formulacija I i II, dok su *in vivo* testovi pokazali njihovu ekvivalentnost. Prema rezultatima dobijenim u okviru *in vivo* ispitivanja, nije bilo značajnih razlika u farmakokinetičkim parametrima.

Istraživanje pokazuje da, i pored razlike u profilima oslobađanja diklofenaka *in vitro*, postoji bioekvivalentnost ispitivanih formulacija. Mogućnost uvođenja novog eksperimentalnog modela za poređenje farmakokinetike novog lijeka sa već registrovanim lijekom na kunićima bi, ukoliko se potvrdi bioekvivalentnost, omogućilo proizvođačima lekova da se sa većom sigurnošću odluče za ispitivanje na ljudima.

TESTING THE INFLUENCE OF DIFFERENT FORMULATIONS AND PRODUCTION METHODS ON DICLOFENAC SODIUM FILM TABLETS BIOEQUIVALENCE

Sanja Kecman[1], Svetlana Goločorbin Kon[2], Milan Jokanović[3], Ranko Škrbic[4], Momir Mikov[5]

[1]Hemofarm d.o.o, a Member of Stada Group, Banja Luka, Republic of Srpska (Bosnia and Herzegovina), [2]Department of Pharmacy, University of Novi Sad - Faculty of Medicine (Serbia), [3]Department of Pharmacy, University of Niš - Faculty of Medicine (Serbia), [4]Department of Pharmacology, University of Banja Luka - Faculty of Medicine, Republic of Srpska (Bosnia and Herzegovina), [5]Department of Pharmacology, Toxicology and Clinical Pharmacology, University of Novi Sad - Faculty of Medicine (Serbia)

Different technological production procedures and formulation composition do not necessarily mean the absence of drug products bioequivalence. *In vitro* and *in vivo* bioequivalence was tested for two pharmaceutical products containing the same API, but differing in the coating agents applied. The aim of the research was to investigate the impact of different formulations and production methods on dissolution profiles and *in vivo* absorption of diclofenac sodium from film coated tablets.

Formulation I contained Eudragit L30, while Formulation II contained Eudragit L100, as tablet coating agents. To optimise the tablet stability, both formulations contained different excipients. The tablets were tested *in vitro* with regards to their weight variation, hardness, diameter, mass uniformity, disintegration time, dissolution profiles and drug content. In the second part of the research, after administering diclofenac tablets to rabbits orally, the drug concentration in plasma and pharmacokinetic parameters were estimated. The data from performed *in vitro* tests showed the non-equivalence of the investigated formulations I and II, while *in vivo* tests showed products equivalence. According to the *in vivo* test results, there were no significant differences in the pharmacokinetic parameters observed.

The research shows that, although there was difference in diclofenac *in vitro* dissolution profiles, the bioequivalence of tested formulations has been observed *in vivo*. The possibility of introducing a new experimental model for comparison of pharmacokinetics of the new drug with already registered drug on rabbits would, if bioequivalence is confirmed, enable manufacturers to decide to conduct the testing on humans.

DEVELOPMENT AND CHARACTERIZATION OF NATURAL HONEY LOZENGES

Bojan Pavlović[1], Jelena Pešić[1], Katarina Jončić Savić[1], Hiroto Uchida[2]

[1]Phytonet d.o.o., Belgrade (Serbia), [2]Tomita Pharmaceutical Co. Ltd (Japan)

Honey is a natural product that has been widely used for its therapeutic effects. It is composed primarily of fructose and glucose but also contains fructo-oligosaccharides and many amino acids, vitamins, minerals and enzymes. Most of those compounds act together to provide a synergistic antioxidant effect. Application of raw honey in modern medicine has a limited use due to its specific physico-chemical properties, which made them extremely unsuitable for the formulation of stable, modern pharmaceutical forms. However, typically honey powder is a dehydrated form of natural honey and contains less than 2% of the natural liquid form of honey, usually pre-treated at high or extremely low temperatures. The aim of this study was to develop robust lozenge formulation that contains high concentration of natural raw honey. Unique Calcium Silicate (Florite®R, Tomita Pharmaceutical Co., Ltd.) withits high liquid adsorption ability was used for preparing Unique Honey Powder loaded with raw honey, ranging from 50 to 70% (w/w) by mixing only. Lozenges were formulated with Unique Honey Powder due to its high compressibility. The factorial design of experiments was employed to systematically optimise thephysical characteristics of lozenges containing Unique Honey Powder and filler, keeping compression force as constant. Lozenges were prepared by direct compression method. The compressed lozenges weree valuated for their hardness, thickness, weight variation, friability, appearance and taste. The optimum formulation was selected by desirability function. The experimental results have shown that the ratio of Unique Honey Powder per lozenge up to 60%(w/w) still provided physico-chemical properties in the acceptable limits. Furthermore,palatability and taste of the lozenges were found desirable.

The advantage of the developed lozenges is significantly higher contents of raw honey compared to existing products. The use of Florite®R provides simple application of liquid active materials for formulating different stable drypharmaceutical forms.

FORMULATION AND CHARACTERIZATION OF NANOSIZED CARRIERS AS POTENTIAL PLATFORMS FOR TOPICAL DELIVERY OF ANTIOXIDANTS

Elena Drakalska, Bistra Angelovska, Marija Sterjova, Aleksandar Cvetkovski

University „Goce Delchev", Shtip- Faculty of Medical Sciences (Macedonia)

Skin is protected from the harmful effects of free radicals by the presence of anendogenous antioxidant system. However, when exposed to ultraviolet (UV) radiation, there is an imbalance between pro-oxidants and antioxidants, leading to oxidative stress and photoaging of the skin. In order to prevent skin aging, use of topical antioxidants in different formulations is method of choice in pharmaceutical industry. However, many bioactive substances are unstable when exposed to light, lose activity during storage and possess low solubility and bioavailability. The aim of this study is to present the advantages of incorporation of antioxidants into nanocarriers such as niosomes, liposomes and nanoemulsions as an intriguing strategy to overcome listed limitations of antioxidants. We gathered the data needed for this study by searching relevant scientific and professional literature, made a comparison between antioxidant loaded nanosystems and free solutions, listed the advantages and disadvantages, discussed the results of clinical studies on various antioxidants incorporated into nanoparticles and listed the market's patented formulations by now. Obtained results showed significantly higher stability of antioxidants loaded nanocarriers compared with free drug, enhanced penetration into dermis and potentiation of antioxidant effect. From the collected and processed data we concluded that nanocarriers are potential platforms for antioxidants providing higher solubility, greater stability and enhanced bioavailability.

IN VITRO PROFILI BRZINE RASTVARANJA DVIJE FORMULACIJE DEKSKETOPROFEN FILM TABLETA: KOMPARATIVNA STUDIJA

Berina Pilipović, Maja Pašić-Kulenović, Larisa Alagić-Džambić, Vlado Mekinjić

Bosnalijek d.d., Sarajevo (Bosna i Hercegovina)

Ispitivanje brzine rastvaranja ljekovite supstance se obično koristi za procjenu kvaliteta ljekovitih preparata. U ovoj studiji upoređeni su *in vitro* profili brzine rastvaranja deksketoprofen trometamola iz dvije formulacije film tableta, kao i odgovarajućeg referentnog preparata. Pripremljene su dvije formulacije film tableta koje sadrže deksketoprofen trometamol metodom vlažne granulacije i sprovedeno uporedno ispitivanje brzine rastvaranja. Formulacije su se razlikovale po vrsti i količini sredstva za dezintegraciju. *In vitro* test brzine rastvaranja deksketoprofen 25 mg film tableta proveden je prema opštoj proceduri Ph. Eur. 2.9.3 (ili USP <711>) primenom aparature sa rotirajućom lopaticom. Kao medijum je korištena voda, 0,1 mol/l HCl, pH 4,5, pH 6,8 i pH 7,4 volumen 900 ml i 75 rpm. Uzorci su uzeti nakon 5, 10, 15, 20, 30 i 45 minuta.

U uporednim profilima brzine rastvaranja formulacija 01 (koja je sadržavala natrijum-skrobglikolat kao superdezintegrator) i referentnog lijeka, više od 85% aktivne supstance se rastvara u roku od 15 minuta, a profili brzine rastvaranja mogu biti prihvaćeni kao slični bez dalje matematičke obrade. U uporednim profilima brzine rastvaranja formulacija 02 i referentnog lijeka nema sličnosti (vrijednost f_2 <50). Može se zaključiti da postoji sličnost između deksketoprofen 25 mg filmom obloženih tableta formulacije 01 sa referentnim lijekom. Potvrđeno je da različiti pristupi formulaciji mogu dovesti do velikih razlika u profilima brzine rastvaranja među formulacijama. Formulacija 01 je odabrana za studiju bioekvivalencije, koja je dokazana u odnosu na referentni lijek.

IN VITRO DISSOLUTION PROFILES OF TWO DEXKETOPROFEN FILM COATED TABLET FORMULATIONS: A COMPARATIVE STUDY

Berina Pilipović, Maja Pašić-Kulenović, Larisa Alagić-Džambić, Vlado Mekinjić

Bosnalijek d.d., Sarajevo (Bosnia and Hercegovina)

Dissolution test is usually employed to evaluate the performance of drug products. In this study, we compared the *in vitro* dissolution profiles of two film coated tablet formulations containing dexketoprofen trometamol with the aim of evaluating the similarity with the reference product. Two formulations of film coated tablets containing dexketoprofen trometamol were evaluated and compared with reference drug. The formulations differed by type and amount of disintegration agent. *In vitro* dissolution testing of dexketoprofen 25 mg film coated tablets was performed according to the general procedure Ph. Eur. 2.9.3 (or USP <711>) using the rotating paddle apparatus. Evaluation has been carried out in water, 0.1 mol/l HCl, pH 4.5, pH 6.8 and pH 7.4, media volume 900 ml, with paddle rotation speed of 75 rpm. Media samples have been taken after 5, 10, 15, 20, 30 and 45 minutes.

Comparative dissolution profiles for dexketoprofen 25 mg film coated tablets formulation 01 (which contained sodium starch glycolate as superdisintegrant) and reference drug revealed that more than 85% of the drug is dissolved within 15 minutes, and dissolution profiles may be accepted as similar without further mathematical evaluation. Comparative dissolution profiles for dexketoprofen 25 mg film coated tablets formulation 02 and reference drug indicated absence of similarity (f_2 < 50). It can be concluded that there is similarity between dexketoprofen 25 mg film coated tablets formulation 01 with reference drug. It has been confirmed that different formulation strategies can lead to great differences in drug dissolution rates. Formulation 01 was selected for a bioequivalence study, which was demonstrated in relation to the reference drug.

APPLICATION OF MODERN STATISTICAL TOOLS FOR DESIGN AND OPTIMIZATION OF PHARMACEUTICAL TECHNOLOGICAL PROCESS OF WET GRANULATION

Dejan Kuneski[1], Marija Glavas Dodov[2], Packa Antovska[1], Sonja Ugarkovic[1]

[1]Research & Development, ALKALOID AD Skopje, [2]University „Ss Cyril and Methodius" Skopje - Faculty of Pharmacy, Skopje (Macedonia)

High-shear mixer granulation is complex process with many parameters for adjustment, optimization and, especially, interpretation of their influence on the physical characteristics of the obtained granulates. The aim of our study was to optimize the high-shear mixer granulation process during which the influence of the most critical process parameters such as: the volume of water as granulating solution, granulating solution addition rate and wet massing time on the physical characteristics of the obtained granulates (particle size distribution, porosity, compressibility index, flowability and filling of the tableting dies) will be determined with the use of modern statistical tool as Central Composite Design.

Granulates without active substance were produced on laboratory high-shear mixer granulator with excipients: lactose monohydrate as filler, starch, pregelatinized and povidone as fillers and binders, crospovidone as disintegrant and magnesium stearate as lubricant. Design-Expert® V8 was used as statistical software.

The particle size of the produced granulates was positively correlated with the process parameters. Porosity was positively correlated with quantity of the water and addition rate, but negatively correlated with wet massing time. Longer wet massing time decrease the air between the particles, which leads to decreased porosity or more dense granules.

The compressibility index was negatively correlated with the investigated process parameters. Smaller particles lead to smaller specific surface for cohesion and packaging which leads to bigger bulk density, lower tapped density and lower value of the compressibility index. Flowability was positively correlated with the amount of water. Bigger particles give better flowability. Negative correlation was detected between process parameters and the filling of the tableting dies. Detection of the nature of the influence of the process parameters and the cross-validation of the model gives us enough confidence for optimization of the high-shear wet granulation process in a direction of getting a desirable physical characteristics of the obtained granulates.

COMPARATIVE EVALUATION OF WET GRANULATION AND DIRECT COMPRESSION TECHNOLOGY DURING DEVELOPMENT OF LOW-DOSE IMMEDIATE RELEASE TABLET

Katerina Tnokovska, Bosilka Stefanova, Natasa Karalija, Packa Antovska, Sonja Ugarkovic

Research & Development, ALKALOID AD Skopje (Macedonia)

During development of low dose drug products, the main challenges are related to achieving and maintaining a homogeneous mix. Rationale selection of the technological process and excipients for the specific steps during formulation/process development are critical factors to be considered to develop a homogeneous and segregation-free low dose formulation. The aim of this study was comparison of two different technologies: wet granulation and dry mixing/direct compression during development of low-dose tablets (0.195% API) in regards to homogeneity of final blend, assay and drug dissolution. Two pilot batches have been produced using different technological processes: wet granulation and dry mixing/direct compression. Homogeneity testing of final blend was carried out on samples collected from six locations. Furthermore, the produced batches were evaluated on the following critical quality attributes (CQA) such as: dissolution and assay regarding the tablets originating from both technological processes.

The obtained results regarding the homogeneity of the final blend have shown that both technologies give results in pre-determined acceptance criteria. However, as one may notice from the results, the average value of the assay is closer to the target assay value in regards to the technology of wet granulation. It can be concluded from the results that both CQA regarding two technological processes are with-in the pre-determined acceptance criteria. However the results regarding the dissolution profile related to wet granulation technology is related with more complete dissolution of the API from the tablet in comparison to the direct compression technology. The presented results in this study clearly indicate that wet granulation is more prone to be a technology of choice for such a low dose formulation which would result in tablets with uniform distribution of the API in the final blend and complete release of the API from the designed tablets.

SCALE-UP OF A HIGH-SHEAR GRANULATION PROCESS

Krume Toshev[1], Vlatko Kantardzioski[2], Elizabeta Ristevska Bogoevska[1], Natasha Anevska Stojanovska[1], Sonja Ugarkovic[1]

[1]Research & Development, Alkaloid AD, Skopje, [2]Production of Solid Dosage Forms, Alkaloid AD, Skopje (Macedonia)

Scale-up of a high-shear wet granulation process can present many challenges. There are various approaches for scale-up described in the literature but it seems that one golden rule doesn't exist and often some modifications should be made in order to achieve similar characteristics of the granules on different production scales. The most common rules for scale-up of high-shear wet granulation are applying a constant Froude number and a constant impeller tip speed. The objective of our study was to perform a scale-up of the granulation process of a BCS class IV API on a geometrically similar equipment for high shear granulation and to compare the characteristics of the produced granules and tablets. The scaling was performed from granulator of volume 65L to 300L. The impeller speed on the larger scale equipment was adjusted so that the Froude number was kept constant on both scales. The granulation solution to powder mass ratio and the chopper speed were also kept constant. The wet granulation time was set so that similar increase in power consumption was reached.

The obtained wet granules were similar in appearance and had similar particle size distribution. Slightly higher particle density was observed for the granules on the larger scale because by keeping the Froude-number constant some over-mixing can exist as the impeller tip speed is higher on the larger mixer granulator. Obtained dry granules had similar bulk density, tapped density and flow rate. Slightly higher particle density and smaller particle size was observed for the granules on the larger scale which can be attributed to a higher attrition during the drying process. Physical and chemical characteristics of tablets were well-within acceptance criteria. The similarity of characteristics of granules and tablets on both scales confirm the successful scale-up of the process.

EVALUATION OF PROCESS ROBUSTNESS OF TABLET COMPRESSION BY EXPERIMENTAL DESIGN

Nadica Vanova, Dejan Kostovski, Ana Georgieva, Natasa Anevska Stojanovska, Sonja Ugarkovic

Institute for Research and Development, Alkaloid AD, Skopje (Macedonia)

The key step in process understanding and developing a product which meets its predetermined acceptance criteria while performing robust manufacturing process is to identify the potential critical process parameters (CPPs). Mechanistic understanding of material properties would be needed for highlighting the critical process parameters. The only way to evaluate the CPPs influence on critical quality attributes (CQAs) is to perform multiple experiments, where testing one factor at a time would be time consuming and not relevant for evaluation of eventual interaction between the critical factors. The aim is to test the influence of the most prominent tablet compression process parameters on the CQAs of a fixed combination product containing BCS class I and III active compounds.

2^4 full factorial design using MODDE Go® with four replicates in the center point was applied with varying four factors: turret speed (tablets/hour), main compression force (kN), pre-compression force (kN) and feed rate (rpm), adjusted to obtain low and high levels of the target range in order to provide flexibility in the process while still producing product which meets relevant quality criteria.

Evaluation of tablet compression process by factorial design showed that the tested factors within the tested range have no significant influence on the CQA of the final product. Each combination of the tested parameters within the tested range would produce product with acceptable quality.

The chosen method is appropriate for robustness testing of tablet compression process, considering the values for model validity and reproducibility where is demonstrated that the model is useful and reproducible with good control over the experimental error.

AN INVESTIGATION INTO THE EFFECT OF PRE-COMPRESSION AND COMPRESSION FORCES ON DRUG DISSOLUTION FROM IMMEDIATE RELEASE TABLETS

Oja Ali Memed, Sanja Simeonovska Gusic, Dejan Kostovski, Nikola Jovanovic, Ana Janevska, Packa Antovska, Sonja Ugarkovic

Institute for Research and Development, ALKALOID AD, Skopje (Macedonia)

Tableting process is one of the most important steps during development of immediate release tablets since relevant variables such as pre-compression force, compression force and others can have direct impact on the quality of the final product. The aim of our study was to evaluate the effects of different parameters of compression (pre-compression and compression force) on dissolution profile of the selected formulation containing highly potent model drug.

Final blend has been produced using wet granulation/direct compression technology. During the process of tableting compression forces were varied at three levels: 0.4/12.9kN, 1.3/13.1kN and 1.6/10.0kN (i.e. pre-compression/compression force, respectively). The samples prepared were characterized with respect to tablet hardness, thickness, diameter and disintegration time, as well as drug dissolution in different dissolution media (0.1M HCl, pH 1.2, pH 4.5, pH 6.8). Dissolution profiles obtained were compared based on the similarity factor values (f_2).

Pharmaceutical - technological characteristics of the samples prepared were within the pre-determined acceptance criteria. Tablets prepared with different pre-compression/compression forces were evaluated for *in-vitro* dissolution test in different media and obtained results were compared with the dissolution profiles of the referent product.

From the obtained results, the largest similarity of *in vitro* dissolution profiles compared with the referent product was noticed on tablets produced with pre-compression force/compression force 1.6kN/10.0kN. Increasing pre-compression force (varied from 0.4kN to 1.6kN) caused a decrease in dissolution rate but increase in similarity factor f_2. This was probably due to bonding of the softer granules into bigger granules with smaller specific area during the tableting process. From the obtained results we can conclude that compression forces are significant factors during tableting process which directly influence *in vitro* profile of the final product. Well-designed formulation and setting of critical parameters during product development provides repeatable/robust process that ensures production of tablets with desired quality.

UTICAJ PROIZVODNIH PARAMETARA PROCESA NA PROFILE BRZINE RASTVARANJA SULFAMETOKSAZOLA I TRIMETOPRIMA IZ TABLETA

Nermina Jahić, Midhat Vehabović, Maja Pašić-Kulenović, Larisa Alagić-Džambić, Ehlimana Osmanović Omerdić

Bosnalijek d.d., Sektor Razvoj i registracija, Sarajevo (Bosna i Hercegovina)

Kombinacija trimetoprima i sulfametoksazola u masenom odnosu 1:5 (80 mg trimetoprima i 400 mg sulfametoksazola) predstavlja antibiotik koji se koristi za lečenje različitih bakterijskih infekcija. Cilj ove studije je da se proceni efekat promena sile kompresije i visine cilindra u procesu tabletiranja i uporede profili brzine rastvaranja aktivnih supstanci iz uzoraka ispitivane serije (sa različitim tvrdoćama tableta) u odnosu na referentni lek.

Svi materijali korišteni u formulaciji se konvencionalno primenjuju u formulaciji čvrstih farmaceutskih oblika lekova. Oni su opisani u trenutno važećem izdanju Ph.Eur. i ispunjavaju odgovarajuće zahteve kvaliteta. Ispitivana serija je pripremljena za tabletiranje metodom vlažne granulacije u ultra brzom mikseru. Dobijeni granulat je komprimovan na rotacionoj tablet presi, na okruglim klipovima promera 12 mm i podeljen u pet podserija na osnovu primenjene različite sile kompresije i dobijene tvrdoće tableta. Za analizu *in vitro* profila brzine rastvaranja aktivnih supstanci korištena je USP aparatura 2 (tipa lopatice), brzina obrtaja 75 rpm, temperatura 37±0,5°C, 900 ml, tri medijuma za ispitivanje brzine rastvaranja (pH 1,2, 4,5; 6,8). Uzorci su uzorkovani nakon 10, 15, 30 i 45 minuta i analizirani HPLC metodom.

Dobijeni rezultati pokazuju da promene u proizvodnim parametrima procesa mogu dovesti do značajno različitih profila brzine rastvaranja aktivnih supstanci za istu formulaciju. Profili brzine rastvaranja trimetoprima i sulfametoksazola dobijeni analizom pokazali su da su tablete koje su proizvedene sa najvećom silom kompresije (2500 daN) na vrlo niskoj visini cilindra (2,25 mm) slični referentnom leku u sva tri medijuma za ispitivanje brzine rastvaranja različitih pH vrednosti. Vrednost faktora sličnosti (f_2) između 50 i 100 ukazuje na to da su dva profila rastvaranja aktivne supstance slična. Povećanje sile kompresije u procesu tabletiranja značajno je povećalo tvrdoću tableta i uticalo na profile brzine rastvaranja aktivnih supstanci.

INFLUENCE OF MANUFACTURING PROCESS PARAMETERS ON SULPHAMETHOXAZOL AND TRIMETHOPRIM TABLET DISSOLUTION

Nermina Jahić, Midhat Vehabović, Maja Pašić-Kulenović, Larisa Alagić-Džambić, Ehlimana Osmanović Omerdić

Bosnalijek d.d., Development and Registration Department, Sarajevo (Bosnia and Herzegovina)

Combination of trimethoprim and sulfamethoxazole in the 1:5 weight ratio (80 mg trimethoprim and 400 mg sulfamethoxazole) is widely used antibiotic for the treatment of a variety of bacterial infections. The aim of this study was to evaluate the effect of changes in compression force and tablet cylinder height during tableting process and compare dissolution profiles of the test batch (with different tablet hardness) versus reference brand product tablets. All materials used in formulation are conventionally applied in the formulation of solid dosage forms. They are described in the current Ph.Eur. and complied to the quality requirements. Test batch was prepared for tableting using high shear mixer granulator. The granules were compressed on 12 mm round shape punches on a rotary compression machine and divided in five sub-batches based on different compression pressure applied and obtained tablet hardness. *In vitro* dissolution testing was carried out using USP Apparatus 2 (paddle type), rotation speed 75 rpm, at 37±0.5°C, 900 ml in three dissolution media (pH 1.2; 4.5; 6.8). Samples were withdrawn at 10, 15, 30 and 45 minutes and analyzed by HPLC method.

Results indicated that changes in the manufacturing process parameters can lead to significantly different dissolution profiles for the same formulation. Dissolution profiles of trimethoprim and sulfametoxazole obtained in the analysis demonstrated that tablets which are produced with highest compression force (2500 daN) at very low cylinder height (2.25mm) are similar to the brand product in all three tested media with different pH. Similarity factor value, f_2 between 50 and 100 suggests that two dissolution profiles are similar. Increasing compression force in tableting process significantly enhanced tablet hardness and affected drug dissolution rate.

Arh.farm 2018;68: 585-586 ***FTK-P12***

UTICAJ RAZLIČITIH FAKTORA FORMULACIJE I POSTUPKA IZRADE NA FARMACEUTSKO-TEHNOLOŠKE KARAKTERISTIKE TABLETA SA BARIJUM SULFATOM

Branka Grujić[1], Nebojša Cvetković[1], Jelena Kondić[1], Đorđe Medarević[2], Svetlana Ibrić[2]

[1]Institut za istraživanje i razvoj Galenika a.d., Beograd, [2]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija)

U radu je ispitivan razvoj tableta sa barijum-sulfatom koje se ne raspadaju u digestivnom traktu, a koriste se kao kontrastno sredstvo za merenje tranzitnog vremena kroz kolon. Intaktnost tableta u digestivnom traktu postiže se primenom polimera - polimetil-metakrilata (PMMA) i Eudragit® RS PO, sinterovanih u pari organskog rastvarača - acetona ili izopropanola (IPA). Ispitano je više različitih formulacija u kojima je varirano: vrsta polimera (Eudragit® RS PO ili PMMA), postupak izrade (vlažna granulacija ili direktna kompresija), granulacija punioca kalcijum-hidrogenfosfat dihidrata (praškasti ili sitno granulisani) i vreme sinterovanja u pari acetona ili IPA. Sinterovanje u pari acetona ili IPA je vršeno u toku 7, 14, 21, 28 i 35h na 35ºC. Kao izlazni parametar praćeni su zatezna čvrstina, kao značajna karakteristika tableta za dalji proces sinterovanja i raspadljivost sinterovanih tableta.

U završnom procesu izrade - sinterovanju tableta korišćene su samo formulacije kod kojih je zatezna čvrstina tableta bila ≥20 MPa. Iz tog razloga tablete izrađene direktnom kompresijom, kao i tablete izrađene vlažnom granulacijom sa PMMA nisu sinterovane. Zatezne čvrstine tableta pre i posle sinterovanja ukazuju da se primenom IPA u postupku vlažne granulacije dobijaju granule koje se bolje kompaktiraju (dobijaju se tablete veće zatezne čvrstine), dok je aceton u procesu sinterovanja na 35°C efikasniji, što je i očekivano s obzirom na viši napon pare na toj temperaturi u odnosu na IPA.

Ispitivanja su pokazala da je najadekvatnija formulacija koja u svom sastavu ima kalcijum-hidrogenfosfat dihidrat, prašak, polimere Eudragit® RS PO i PMMA u masenom odnosu 1:1, izrađena postupkom vlažne granulacije gde se kao rastvarač, osim etanola i vode koristi IPA, a proces sinterovanja vrši u pari acetona na 35°C u toku 35 h. Kod navedene formulacije ispunjen je propisani kriterijum o neraspadanju tableta u vremenskom intervalu od 7 dana.

THE INFLUENCE OF DIFFERENT FORMULATION FACTORS AND METHOD OF PREPARATION ON PHARMACEUTICAL TECHNOLOGICAL CHARACTERISTICS OF BARIUM SULPHATE TABLETS

Branka Grujić[1], Nebojša Cvetković[1], Jelena Kondić[1], Đorđe Medarević[2], Svetlana Ibrić[2]

[1]Research and Development, Galenika a.d., Belgrade, [2]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade – Faculty of Pharmacy (Serbia)

This study investigates development of non-disintegrating tablets with barium sulphate which are used as a contrast agent for measuring of transit time through the colon. Tablet intactness is achieved using polymers - Poly(methyl methacrylate) (PMMA) and Eudragit® RS PO, sintered in the vapour of organic solvent - acetone or isopropyl alcohol (IPA). Different formulations were tested with variations of polymer type (Eudragit® RS PO or PMMA), method of preparation (wet granulation or direct compression), grade of diluent calcium hydrogenphosphate dihydrate (powdered or finely granulated grade) and duration of sintering in the vapour of acetone or IPA. Sintering in the vapour of acetone or IPA was performed during 7, 14, 21, 28 and 35 h at 35ºC. Tensile strength as an important tablet characteristic for further sintering as well as disintegration of sintered tablets were tested as outputs. Tablet formulations with tensile strength ≥20 MPa were only used for sintering. Due to this reason, tablets prepared by direct compression and tablets prepared by wet granulation with PMMA were not sintered. Tensile strength of tablets before and after sintering showed that using of IPA in wet granulation process gives granules with better compaction properties (tablets with higher tensile strength were obtained), while acetone is more efficient for sintering at 35°C, as expected due to higher vapour pressure at this temperature, compared to IPA. Performed testing showed the best properties of formulation containing calcium hydrogenphosphate dihydrate, powder, Eudragit® RS PO and PMMA in mass ratio 1:1, which was prepared by wet granulation using mixture of ethanol, water and IPA and sintered in the vapour of acetone during 35 h at 35ºC. This formulation fulfilled criteria of non-disintegration during 7 days.

LEKOVI ZA HUMANU UPOTREBU KOJI SADRŽE PŠENIČNI SKROB I USKLAĐIVANJE SA NOVOM REGULATIVOM KOJA SE ODNOSI NA INFORMACIJE O GLUTENU - ISKUSTVA SRBIJE

Sofija Vrcelj-Jovanović, Marija Čarapić, Ljiljana Vojvodić, Saša Jaćović

Agencija za lekove i medicinska sredstava Srbije (Srbija)

Gluten je protein ili smeša prolamin proteina koji se uglavnom mogu naći u pšenici, ali i u ječmu, raži i manje u ovsu. Poremećaji povezani sa intolerancijom na gluten su: celijačna bolest, alergija na pšenicu i necelijačna preosetljivost na gluten. Celiaklija je sistemska imuna bolest i čest je poremećaj u Evropi sa prevalencom od 1-2%. Srbija takođe ima visoku učestalost celijakije 1:100 (oko 70 000 ljudi). Skrob se često koristi kao sredstvo za dopunjavanje/vezivanje/raspadanje u čvrstim farmaceutskim oblicima lekova, ili u novim oblicima/sistemima za isporuku lekova na ciljanom mestu. Prema monografiji Ph.Eur., za pšenični skrob zahtev za ukupne proteine, uključujući i gluten, je najviše 0,3%. Nova EMA smernica definiše preciznije podatke za gluten koje se moraju navesti na pakovanju i u Uputstvu za lek. Zbog čestih pitanja upućenih Agenciji za lekove koja se odnose na prisustvo glutena u lekovima, izvršena je evaluacija prisustva skroba u svim lekovima za humanu upotrebu, sa fokusom na pšenični skrob. Pregled baze podataka ALIMS-a i statistička analiza rezultata izvršeni su zaključno sa 30.09.2017.

Čvrsti farmaceutski oblici sadrže različite vrste skroba: kukuruzni, krompirov, pšenični, pirinčani, skrob preželatinizovan, natrijum-skrobglikolat, alumijnum-skroboktenilsukcinat, hidroksietil skrob. Utvrđeno je da u poslednjih pet godina nije uočeno značajno povećanje broja lekova koji sadrže pšenični skrob i da samo njih oko 1% sadrži ovaj skrob, što je manje od odobrenih u UK prema EMA/CHMP/704219/2013. Potrebno je definisati poreklo skroba prilikom dobijanja dozvole za lek, kako bi se utvrdilo prisustvo/odsustvo glutena, izbeći unakrsne kontaminacije sa proizvodima koji sadrže gluten i uskladiti informacije o leku sa EMA smernicom u vezi sa upozorenjem koje se odnosi na pšenični skrob (gluten). Pored SmPC-a i PIL-a koji su dostupni na internet stranici ALIMS, omogućiti da spisak lekova koji sadrže pšenični skrob bude dostupan javnosti.

HUMAN MEDICINES CONTAINING WHEAT STARCH AND HARMONIZATION WITH NEW REGULATION ON GLUTEN INFORMATION - EXPERIENCE OF SERBIA

Sofija Vrcelj-Jovanović, Marija Čarapić, Ljiljana Vojvodić, Saša Jaćović

Medicines and Medical Devices Agency of Serbia (Serbia)

Gluten is a protein or a mixture of prolamine protein found mainly in wheat, but also in barley, rye and less in oat. Human disorders related to gluten intolerance are celiac disease, allergy to wheat and non-celiac gluten sensitivity. CD is frequent disorder in Europe with a prevalence of 1-2%. Serbia also has a high incidence of CD: 1:100 (approximately 70000 people). Starch is commonly used as a filler, binder, disintegrant in solid dosage forms or within novel drug delivery systems. The Ph. Eur. Wheat starch monograph sets requirements for total protein (including gluten protein), with maximum limit of 0.3%. The new EMA guidance defines with more precision the statements in the PIL and packaging. Numerous questions were addressed to ALIMS in relation to the possible presence of gluten in medicines. The presence of starch in all human medicines was evaluated, with focus on the wheat starch. Search was performed by reviewing ALIMS database and by analyzing the results in order to detect medicines which contain different types of starch (closed on 30. September 2017).

Solid dosage forms contain starch originating from maize, potato, wheat, rice, as well as pregelatinized starch, sodium starch glycolate aluminum starch octenylsuccinate, calcium-carbonate starch mixture, hydroxyethyl starch. It was found that the increase in the number of medicines containing wheat starch was low in past five years. A small number, approximately 1% of human medicines, contain wheat starch, which is lower in comparison to UK results according to EMA/CHMP/704219/2013. Vegetable origin of starch should be defined in marketing authorization application in order to justify the presence/absence of gluten. Also the cross-contamination with products containing gluten should be avoided. Harmonization of product information with the updated EMA guidance is necessary concerning wheat starch safety warnings. A special list of human medicines containing wheat starch should be made publicly available.

Arh.farm 2018;68: 589-590 ***FTK-P14***

PREPARATI PARACETAMOLA ZA ORALNU PRIMENU U PEDIJATRIJSKOJ POPULACIJI: PREGLED EKSCIPIJENASA

Božana Nikolić

Univerzitet u Novom Sadu - Medicinski fakultet, Dom zdravlja Novi Sad (Srbija)

Neželjene reakcije na lekove mogu biti u vezi ne samo sa aktivnim supstancama nego i sa ekscipijensima. U ovom kontekstu, pedijatrijski pacijenti se razmatraju kao posebno vulnerabilna populacija. U okviru ovog pregleda fokus je na preparatima parcetamola s obzirom na rasprostranjenu upotrebu istih u pedijatrijskoj populaciji. Cilj istraživanja je bio da se identifikuju ekscipijensi prisutni u preparatima paracetamola za oralnu primenu kod dece, i da se razmotri njihov bezbednosni profil. Sažeci karakteristika leka za selektovane lekove (n=12) su preuzeti sa veb-sajta Agencije za lekove i medicinska sredstva Srbije; i iskazi od značaja su ekstrahovani iz odeljka 2 (*Kvalitativni i kvantitativni sastav*) i subodeljka 6.1 (*Lista pomoćnih supstanci*).

Deset ekscipijenasa (parabeni, natrijum-benzoat, boje, etanol, propilenglikol, saharoza, sorbitol, saharin, aspartam, maltitol) sa potencijalnim uticajem na bezbednosni profil je identifikovano. Konzervansi, boje i korastvarači su bili prisutni u 5, 3 i 3 preparata, sledstveno. U proseku, po dva zaslađivača je bilo prisutno u tečnim preparatima; a saharoza, sorbitol i saharin su bili najzastupljeniji. U vezi sa bezbednosnim profilom identifikovanih ekscipijenasa, boje i parabeni mogu prouzorkovati alergijske reakcije, i u slučaju parabena one su često odloženog tipa. Korastvarači (etanol, propilenglikol) su farmakološki aktivne supstance i ako se unesu u neuobičajeno velikim volumenima (npr, od 0,2 do 1,8 mL etanola nedeljno (1 ml ≈ 0,8 g) kod preterminske novorođenčadi, ili > 0,4 ml/kg etanola kod dece; ili, 60 ml propilenglikola bilo kao pojedinačna doza ili podeljeno u više doza tokom perioda od 24 časa ili 8 dana) mogu precipitirati simptome intoksikacije, posebno kod male dece zbog ograničenog metaboličkog i renalnog klirensa. Zaslađivači maskiraju neprijatan ukus leka i presudni su za adherencu kod pedijatrijskih pacijenata; međutim, saharoza i polioli (sorbitol i maltitol) nisu dobar izbor ekscipijensa kod dece sa intolerancijom na fruktozu; a saharin bi trebalo izbeći kod dece sa alergijom na sulfonamide.

U selekciji najprikladnijeg paracetamol preparata od značaja je razmotriti bezbednosni profil ekscipijenasa, posebno kod male dece i one sa istorijom reakcija hipersenzitivnosti ili retkih genetski prenosivih poremećaja metaboličkog porekla.

PARACETAMOL PREPARATIONS FOR ORAL USE IN PEDIATRIC POPULATION: A REVIEW OF EXCIPIENTS

Božana Nikolić

University of Novi Sad - Faculty of Medicine, Health Center Novi Sad (Serbia)

Adverse drug effects can be related not only to active substances but also to excipients. In this context, pediatric patients are considered as particulary vulnerable population. In this review, a focus is on paracetamol preparations with respect to their widespread use in pediatric population. The aim of the study was to identify excipients present in paracetamol preparations for oral use in children, and to consider their safety profile. Summary of Product Characteristics for the selected preparations (n=12) were retrieved from the Medicines and Medical Devices Agency of Serbia website; and statements of interest were extracted from section 2 *(Qualitative and quantitative composition)* and subsection 6.1 *(List of excipents)*.

Ten excipients (parabens, sodium benzoate, coloring agents, ethanol, propylene glycol, sucrose, sorbitol, saccharin, aspartame, maltitol) with potential impact on safety profile were identified. Preservatives, colorings and cosolvents were presented in 5, 3 and 3 preparations, respectively. On average, two sweeteners were present in liquid preparations; and sucrose, sorbitol and saccharin were the most common. In association with the safety profile of the identified excipients, parabens and colorings can cause allergic reactions, and in case of parabens they are commonly of delayed type. Cosolvents (ethanol, propylene glycol) are pharmacologically active substances and if they are ingested in unusually large volumes (eg, from 0.2 to 1.8 ml/week of ethanol (1 ml ≈ 0.8 g) in preterm neonates, or > 0.4 ml/kg of ethanol in children; or, 60 ml of propylene glycol either as a single dose or divided doses over a 24 hour period or a 8 day one) may precipitate symptoms of intoxication, especially in young children due to limited renal and metabolic clearance. Sweeteners mask the unpleasant taste of medicines and they are crucial for adherence in pediatric patients; however, sucrose and polyols (sorbitol, maltitol) are not a good choice of excipient in children with fructose intolerance; and saccharin should be avoided in children with sulfonamide allergy.

In the selection of the most appropriate paracetamol preparation is important to consider safety profile of excipients, especially in young children and those with history of hypersensitivity reactions or rare genetically-transmitted disorders of metabolic origin.

ALTERNATIVE STATISTICAL METHODS FOR DISSOLUTION SIMILARITY ASSESSMENT

Ivana Mitrevska[1], Ljupco Pejov[2], Ema Kikovska-Stojanovska[1], Suzan Memed-Sejfulah[1], Marija Jovanovska[1], Aneta Dimitrovska[3], Sonja Ugarkovic[1]

[1]Alkaloid AD Skopje, [2]Institute of Chemistry, 'Ss. Cyril and Methodius" University - Faculty of Natural Sciences and Mathematics, Skopje, [3]Institute of Applied Chemistry and Pharmaceutical Analysis, 'Ss. Cyril and Methodius" University - Faculty of Pharmacy, Skopje (Macedonia)

In vitro dissolution testing plays a critical role in the life cycle of a generic drug product. In developing a dissolution test for a generic product intended to be marketed, the dissolution method should be „sufficiently rugged and reproducible for daily operations, capable of being transferred between laboratories and adequately discriminating to distinguish any changes that could affect the product's *in vivo* performance". Thus, dissolution studies may be related to the bioavailability of the drugs in the body.

Similarity of dissolution is assessed by comparison of the dissolution profiles (usually % drug dissolved vs time) based on the similarity factor value (f_2) as described in the relevant EMA and FDA guidelines.

In cases when the f_2 statistics is not applicable, the guideline addresses the possibility for using alternative statistical tools, using model-dependent or model-independent methods. In relation to this, herein we present a case study of generic immediate release drug product - conventional tablets (further referred to as test product) that have been evaluated for comparative dissolution performance versus a reference drug product in a case when the f_2 statistics was not applicable.

From a regulatory point of view, the FDA guideline on Dissolution testing provides more detailed approach on the particulars in employing the alternative statistical methodologies for dissolution profiles comparison. This concept has been further elaborated in few studies, yet not many publications demonstrate real case studies on using alternative statistical methodologies for comparative dissolution analysis, hence it would be highly beneficial to further elaborate this concept and present a detailed regulatory approved approach.

The test product evaluated contains BCS 1 drug (high solubility, high permeability) and comparative dissolution analysis with the reference product was performed. f_2 statistics was not applicable since the requirement 'Not more than one mean value of > 85% dissolved for any of the formulations' was not fulfilled. Therefore, alternative statistical methodologies were employed: model-independent and model-dependent.

POBOLJŠANJE BRZINE RASTVARANJA KLOPIDOGREL-BISULFATA PRIMENOM ČVRSTIH DISPERZIJA

Ehlimana Osmanović Omerdić[1], Larisa Alagić-Džambić[1], Maja Pašić-Kulenović[1], Nermina Jahić[1], Dragana Vasiljević[2]

[1]Bosnalijek d.d., Sektor za razvoj i registraciju, Sarajevo (Bosna i Hercegovina),
[2] Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu–Farmaceutski fakultet (Srbija)

Klopidogrel-bisulfat (CB) je antiagregacioni lek, koji pripada klasi II BSK. Čvrste disperzije (SD) su disperzije ljekovite supstance u inertnom hidrofilnom nosaču. Cilj rada je bio ispitivanje uticaja vrste i koncentracije hidrofilnog polimera na brzinu rastvaranja klopidogrel bisulfata iz čvrstih disperzija. SD su izrađene metodom rastvaranja, korišćenjem četiri različita hidrofilna polimera: makrogol 6000 (Polyglycol 6000 S), povidon (Kollidon® 30), kopovidon (Kollidon® VA 64) i poloksamer 407 (Kolliphor™ P 407) i četiri masena odnosa CB-polimer (1:1, 1:3, 1:5, 1:9). Uzorci SD i prašak CB su punjeni u kapsule, tako da sadrže 75 mg CB (terapijska doza). *In vitro* ispitivanje brzine rastvaranja je izvršeno na USP aparaturi 1, u fosfatnom puferu pH 6,8, kao medijumu. Koncentracija CB je određivana nakon 15, 30, 45 i 60 minuta, HPLC metodom sa UV detektorom. Profili brzine oslobađanja CB iz SD su poređeni sa profilom brzine oslobađanja čiste supstance.

SD izrađene sa hidrofilnim polimerima su pokazale poboljšanje brzine rastvaranja CB, u poređenju sa čistom aktivnom supstancom, gdje je koncentracija rastvorenog CB bila 32%, nakon 60 minuta. Sa povećanjem udjela polimera u čvrstim disperzijama dolazi do povećanja brzine rastvaranja CB. Ovo povećanje brzine rastvaranja aktivne supstance može se objasniti smanjenjem veličine čestica i povećanjem efektivne površine aktivne supstance. Nakon 60 minuta, za udio polimera 1:1, najviše se CB oslobodilo iz SD sa kopovidonom (54%), za udio polimera 1:3 iz SD sa kopovidonom i makrogolom (po 63%), za udio polimera 1:5 iz SD sa makrogolom (93%) i za udio polimera 1:9 iz SD sa poloksamerom 407 (96%).

Čvrste disperzije sa ispitivanim polimerima su omogućile poboljšanje brzine rastvaranja CB, u poređenju sa čistom aktivnom supstancom. Najveći procenat CB se oslobodio iz SD sa poloksamerom 407 (1:9) - 96% za 60 minuta. Ovi rezultati su pokazali da pravilan izbor vrste i koncentracije polimera igra važnu ulogu u povećanju brzine rastvaranja CB.

DISSOLUTION RATE IMPROVEMENT OF CLOPIDOGREL BISULPHATE BY SOLID DISPERSION METHOD

Ehlimana Osmanović Omerdić[1], Larisa Alagić-Džambić[1], Maja Pašić-Kulenović[1], Nermina Jahić[1], Dragana Vasiljević[2]

[1]Bosnalijek d.d., Development and Registration Department, Sarajevo (Bosnia and Herzegovina), [2]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Clopidogrel bisulfate (CB) is a potent antiplatelet drug, which belongs to BCS II class drugs. Solid dispersion (SD) is a dispersion of active ingredient in hydrophilic inert carrier matrix. The aim of this study was to assess influence of SD formation on the CB dissolution rate. Four different hydrophilic polymers: macrogol 6000 (Polyglycol 6000 S), povidone (Kollidon® 30), copovidone (Kollidon® VA 64) and poloxamer 407 (Kolliphor™ P 407), and four CB-polymer ratios (1:1, 1:3, 1:5, 1:9) were used to formulate SD using solvent evaporation method. All SD and pure CB samples were filled in capsules in order to contain 75 mg of CB (therapeutic dose). *In vitro* dissolution testing was performed in USP apparatus 1, in phosphate buffer pH 6.8, as a medium. Concentration of CB was determined by HPLC-UV method after 15, 30, 45 and 60 minutes. Dissolution profiles were compared to dissolution profile of CB pure drug.

SD prepared with hydrophyllic polymers showed improved dissolution compared to pure drug where 32% of CB was released after 60 min. It was observed that the increase in amount of polymers increased dissolution rate. This improvement could be due particle size reduction and an increase in the effective surface area. Results suggest that the best efficiency after 60 min for 1:1 weight ratio showed SD with copovidone (54%), for 1:3 ratio SD with macrogol 6000 and copovidone (63%), for 1:5 ratio SD with macrogol 6000 (93%) and for 1:9 ratio SD with poloxamer 407 (96%).

Preparation of binary SD with investigated polymers improved the drug dissolution rate compared to pure CB. SD with poloxamer 407 (1:9) was the most effective, providing 96% of drug released after 60 min. This study has shown that the proper selection of type and concentration of polymer plays important role in increasing the dissolution rate of CB.

ISPITIVANJE MOGUĆNOSTI PRIMENE GLICERIL-DIBEHENATA I POLIETILENGLIKOLA ZA KOPROCESOVANJE LAKTOZE POSTUPKOM GRANULACIJE TOPLJENJEM

Jelena Mudrić[1],Vladimir Dobričić[2], Svetlana Ibrić[1], Jelena Đuriš[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za farmaceutsku hemiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Koprocesovani ekscipijensi (KPE) predstavljaju kombinaciju dva ili više ekscipijenasa koji su obrađeni odgovarajućim postupkom i imaju unapređena svojstva u odnosu na fizičku smešu istog sastava. Posebno je značajan razvoj KPE koji se koriste pri direktnoj kompresiji. U ovoj studiji ispitana je mogućnost koprocesovanja laktoze sa gliceril-dibehenatom (GDB) ili polietilenglikolom (PEG) postupkom granulacije topljenjem.

KPE su imali sledeći sastav – laktoza, monohidrat (70%); kalcijum-hidrogen fosfat (15%); natrijum-skrobglikolat (5%) i vezivno sredstvo (10 %), pri čemu je KPEA sadržao PEG 4000, dok je KPEB sadržao GDB (Compritol® 888 ATO). Koprocesovanje je vršeno granulacijom topljenjem, a KPE su poređeni sa fizičkim smešama istog sastava. Potencijalne hemijske interakcije između ekscipijenasa ispitivane su infracrvenom spektroskopijom (FTIR). Komprimati su izrađivani na simulatoru kompresije (Gamlen Instruments, Velika Britanija) pri pritiscima u opsegu 80-130 MPa. Karakteristike materijala procenjene su ispitivanjem protočnosti, gustine, otpornosti komprimata na lomljenje, raspadljivosti i izračunavanjem *Carr*-ovog indeksa, *Hausner*-ovog odnosa i zatezne čvrstoće komprimata.

FTIR spektroskopijom je utvrđeno da pri koprocesovanju nije došlo do hemijskih promena ekscipijenasa. Oba koprocesovana ekscipijensa imaju unapređenu protočnost u odnosu na fizičke smeše. KPEA ima unapređenu tabletabilnost u odnosu na fizičku smešu (zatezna čvrstoća pri pritisku od 130 MPa iznosila je 2 MPa za KPEA u poređenju sa 1,5 MPa za komprimovanu fizičku smešu). Komprimati sa KPEB posedovali su nešto nižu zateznu čvrstoću u odnosu na fizičku smešu. Duže vreme bilo je potrebno da se raspadnu komprimati sa KPEA (52 s), u odnosu na komprimate sa KPEB (31 s). Komprimati fizičkih smeša su se raspali za isto vreme kao i odgovarajući KPE.

Koprocesovani ekscipijens, koji je kao vezivno sredstvo sadržao PEG poseduje bolju protočnost i mehaničke karakteristike u poređenju sa onim koji je sadržao GDB. U slučaju oba KPE nije potrebno koristiti lubrikans pri izradi tableta, što predstavlja dodatnu prednost koprocesovanih ekscipijenasa.

EXAMINATION OF THE POTENTIAL OF GLYCERYL-DIBEHENATE AND POLYETHYLENE GLYCOL APPLICATION FOR CO-PROCESSING OF LACTOSE BY THE MELT GRANULATION TECHNIQUE

Jelena Mudrić[1],Vladimir Dobričić[2], Svetlana Ibrić[1], Jelena Đuriš[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department of Pharmaceutical Chemistry, University of Belgrade - Faculty of Pharmacy (Serbia)

Co-processed excipients (CPEs) are combinations of two or more excipients,obtained by the appropriate procedure, that possess superior properties compared to the physical mixtures of the same combination of excipients. Development of CPEs for direct compression is especially important. This study has investigated the possibility of co-processing of lactose with glyceryl dibehenate (GDB) or polyethylene glycol 4000 (PEG) by the melt granulation technique.

CPEs were composed of lactose monohydrate (70%), calcium-hydrogen phosphate (15%), sodium starch glycolate (5%) and 10% of the meltable binder (PEG 4000 or Compritol® 888 ATO for co-processed excipient A or B, respectively). CPEs were made by the melt granulation technique and compared to the physical mixtures of the same composition. Infrared spectroscopy (FTIR) has been applied to analyze the potential for chemical interactions between excipients. The comprimates were made by powder compaction under the pressure in the range of 80-130 MPa. Properties of materials were estimated by determination of flowability, density, hardness, desintegration and by calculating Carr's index, Hausner's ratio and tensile strength of comprimates.

FTIR spectroscopy revealed no chemical changes upon co-procesinssing of excipients. Both CPEs had improved flowability in comparison to the physical mixtures. CPEA has enhanced tabletability (tensile strength under the compaction pressure of 130 was 2 MPa for CPEA in comparison to 1.5 MPa forcomprimates ofthe physical mixture). Compacts with CPEB possessed slightly lower tensile strength compared to the physical mixture. Disintegration time for tablets with CPEA (52 s) was longer in comparison toCPEB comprimates (31 s). Comprimates of physical mixtures had almost the same disintegration time as CPEs.

Excipient co-processed with PEG has superior mechanical properties and flowability in comparison to CPE with GDB. In the case of both CPEs there is no need for additional lubrication, which is adventage of co-processed excipients.

POREĐENJE FUNKCIONALNIH SVOJSTAVA POLIETILENOKSIDNOG POLIMERA U FORMULACIJI MUKOADHEZIVNIH FARMACEUTSKIH OBLIKA

Ivana Kurćubić, Svetlana Ibrić, Jelena Đuriš

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Hidrofilni polimeri nalaze veliku primenu u razvoju farmaceutskih preparata. Polietilenoksidni polimeri, kao nejonski polimeri sa pH nezavisnim bubrenjem, imaju svojstvo da modifikuju brzinu oslobađanja lekovite supstance, a sve više se ispituju i njihova bioadhezivna svojstva kao posledica interakcije između polimernih lanaca i makromolekula sa površine sluzokoža. Cilj ovog rada je bilo ispitivanje osnovnih funkcionalnih svojstva odabranog polietilenoksidnog polimera u formulaciji mukadhezivnih farmaceutskih oblika.

Hidrofilne matriks tablete izrađene su postupkom direktne kompresije na ekscenter tablet mašini (EK0 *single press punch, Korsch*, Nemačka) sa polietilenoksidnim polimerom (PEO) molekulske mase 600 000 sa udelom od 20 i 60%, dok su postupkom istiskivanja pripremljeni ekstrudati u obliku diska koji su potom podvrgnuti sušenju mikrotalasima. Ekstrudati su sadržali isti polimer sa udelomod 30%. Sprovedeno je ispitivanje stepena bubrenja i erozije tableta i ekstrudata kao i *in vitro* ispitivanje mukoadhezivnosti uz korišćenje modifikovane vage sa tasovima i 10% disperzije mucina.

Analizom stepena bubrenja uočeno je da ekstrudati apsorbuju najveću količinu vode (~ 330% nakon 2 sata), dok su tablete sa većim udelom polimera vezale veću količinu vode (~ 180 %) i znatno sporije erodirale u odnosu na tablete sa manjim udelom polimera. Ekstrudati su takođe pokazali i najveći stepen mukoadhezivnosti (~ 660 N/m^2), zatim slede tablete sa 60% (~ 500 N/m^2) i na kraju tablete sa 20% polimera (~ 300 N/m^2).

Ispitivanjem mukoadhezivnog svojstva PEO polimera utvrđeno je da i udeo ovog hidrofilnog polimera i vrsta farmaceutskog oblika utiču na silu vezivanja (polimer – mucin). Ekstrudate i tablete sa većim udelom polimera odlikuje visok stepen mukoadhezije, dobra sposobnost apsorbovanja vode i sporija erozija. Ova saznanja predstavljaju dobru osnovu za dalji razvoj mukoadhezivnih sistema za isporuku lekovitih supstanci.

COMPARISON OF THE FUNCTIONAL PROPERTIES OF POLYETHYLENEOXIDE POLYMER IN FORMULATION OF MUCOADHESIVE DOSAGE FORMS

Ivana Kurćubić, Svetlana Ibrić, Jelena Đuriš

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Hydrophilic polymers are broadly used in the development of pharmaceutical preparations. Polyethylene oxide polymers (PEO), as pH-independent nonionic polymers, have the ability to modify the release rate of the drug. Their bioadhesive properties, resulting from the interaction between polymer chains and macromolecules of the mucous membranes, are of great interest. The aim of this study was to examine the basic functional properties of the selected polyethylene oxide polymer in the formulation of mucodhesive pharmaceutical dosage forms.

The hydrophilic matrix tablets were directly compressed with a PEO polymer of 600,000 molecular weight,in the amount of 20 and 60%, while extrudates in the form of disk were prepared and subsequently exposed to microwaves. The concentration of polymer in films was 30%. Degree of swelling and erosion of tablets and extrudates was tested, as well as *in vitro* mucoadhesive strength, which was measured on the modified weight scale by using 10% porcine gastric mucin dispersion. Analysis of the swelling rate demonstrated that the extrudates absorbed the highest amount of water (~ 330% of the initial tablet weight after 2 hours), while tablets with a higher proportion of the polymer bounded higher amounts of water (~ 180%) and eroded significantly slower compared to tablets with a smaller proportion of polymer. Extrudates also had the highest degree of mucoadhesion (~ 660 N/m^2), followed by tablets with 60% (~ 500 N/m^2) and finally tablets with 20% of polymer (~ 290 N/m^2).

Obtained results revealed that the hydrophilic polymer amount, as well as the dosage form, have influenceon the degree of mucoadhesion. Extrudates and tablets with the higher amount of polymer have high degree of mucoadhesion, good water absorption capacity and erode slowly. These findings are a good basis for the further development of mucoadhesive delivery systems.

PRIMENA NOVOG KOPROCESOVANOG EKSCIPIJENSA RETALAC® ZA IZRADU TABLETA ZA PRODUŽENIM OSLOBAĐANJEM LEKOVITE SUPSTANCE POSTUPKOM DIREKTNE KOMPRESIJE

Biljana Gatarić[1], Nebojša Mandić-Kovačević[2], Ivana Vasiljević[2], Jelena Đuriš[2], Jelena Parojčić[2]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Banjoj Luci – Medicinski fakultet (Bosna i Hercegovina), [2]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Koprocesovani ekscipijensi su razvijeni da bi se prevazišla ograničena protočnost i kompresibilnosti koje mogu da se jave prilikom formulacije tableta. Novi koprocesovani ekscipijens, RetaLac®,dobijen je koprocesovanjem hipromeloze i laktoze, a dizajniran je tako da omogućava izradu tableta sa produženim oslobađanjem lekovite supstance postupkom direktne kompresije. Cilj ovog rada bio je procena mogućnosti primene RetaLac®-a u formulaciju tableta sa produženim oslobađanjem, kao i ispitivanje uticaja masenog odnosa RetaLac®/lekovita supstanca na brzinu oslobađanja različitih model lekovitih supstanci. Ispitivane formulacije su sadržale RetaLac®-a i odabranu model supstancu (karbamazepin, acetilsalicilna kiselina, paracetamol i kofein) u odnosu 1:1, odnosno 3:1. Smeše za tabletiranje su pripremljene pomoću mešalice za praškove (Farmalabor Tech powder mixer, Farmalabor, Italija) i komprimovane pomoću ekscentar tablet mašine (EK0 single press punch, Korsch, Nemačka). Izrađene tablete su okarakterisane u pogledu mehaničkih osobina i brzine oslobađanja lekovite supstance.

Primenom RetaLac® koprocesovanog ekscipijensa omogućena je direktna kompresija svih pripremljenih smeša, bez obzira na udeo lekovite supstance i protočnost smeše praškova. Ispitivani uzorci pokazali su zadovoljavajuću zateznu čvrstoću (0,5-2 MPa), izuzev tableta izrađenih sa većim udelom kofeina i paracetamola. Mehanizam oslobađanja lekovite supstance za sve uzorke je bio anomalni transport usled bubrenja i relaksacije polimera u ispitivanom medijumu.

Direktna kompresija smeše RetaLac®/lekovita supstanca je bila moguća bez obzira na udeo lekovite supstance i protočnost smeše. Produženo oslobađanje je postignuto u svim ispitivanim uzorcima, a mehanizam oslobađanja je bio anomalni transport. Studija je pokazala da je RetaLac® pogodan ekscipijens za izradu tableta sa produženim oslobađanjem sa relativno visokim udelom lekovitih supstanci različitih karakteristika, postupkom direktne kompresije.

INVESTIGATION INTO SUITABILITY OF NOVEL CO-PROCESSED EXCIPIENT RETALAC®FOR PREPARATION OF SUSTAINED RELEASE TABLETS BY DIRECT COMPRESSION

Biljana Gatarić[1], Nebojša Mandić-Kovačević[2], Ivana Vasiljević[2], Jelena Đuriš[2], Jelena Parojčić[2]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Banja Luka – Faculty of Medicine (Bosnia and Hercegovina), [2]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade – Faculty of Pharmacy (Serbia)

Co-processed excipients have been developed to overcome flowability and compressibility issues related to different tablet formulations. RetaLac® is hypromellose/lactose based, novel coprocessed excipient designed as direct compression aid for obtaining sustained drug release. The aim of the present work was to estimate RetaLac® suitability for tablet formulation and evaluate the effect of RetaLac®/drug ratio on the release rate of different model drugs. The investigated samples were composed of RetaLac® and selected model drug (carbamazepine, acetylsalicylic acid, paracetamol and caffeine) in the 1:1 and 3:1 weight ratio. Tablet ingredients were mixed using powder mixer (Farmalabor tech powder mixer, Farmalabor, Italy,) and compressed using a single punch-tablet machine (EK0 single punch press, Korsch, Germany). Prepared samples have been characterized with respect to their mechanical properties and drug release.

RetaLac® enabled direct compression of all the mixtures prepared, irrespective of the drug load and mixture flowability. The investigated samples exhibited desirable tensile strength (0.5-2 MPa), except the samples prepared with higher drug load of caffeine and paracetamol. Drug release mechanism for all the samples was anomalous, non-Fickian diffusion. This was likely due to swelling and relaxation of the polymer in the dissolution media.

Compression of RetaLac®/drug mixtures into compacts with satisfying characteristics was possible regardless of the drug load and mixture flowability. Sustained drug release was obtained for all the investigated samples. Drug release mechanism was anomalous, non-Fickian diffusion. The study has shown that RetaLac® can be used as controlled release agent for preparation of modified release tablets with relatively high drug content using direct compression as the method of choice.

ISPITIVANJE MEHANIČKIH SVOJSTAVA PELETA PRIPREMLJENIH METODOM EKSTRUZIJE/SFERONIZACIJE KORIŠĆENJEM RAZLIČITIH SMEŠA POLIMERA

Ivana Vasiljević[1], Erna Turković[1], Michael Piller[2], Andreas Zimmer[3], Jelena Parojčić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija), [2]Istraživački centar za farmaceutsko inženjerstvo, Grac (Austrija), [3]Institut farmaceutskih nauka, Katedra za farmaceutsku tehnologiju i biofarmaciju, Univerzitet u Gracu (Austrija)

Mehanička svojstva višečestičnih sistema su značajna za procenu pogodnosti za pakovanje i transport, kao i ponašanje prilikom kompresije. Sastav formulacije, posebno priroda i udeo polimera, značajno utiče na čvrstinu i elastičnost peleta. Cilj ovog rada bio je ispitivanje uticaja polimera na mehanička svojstva peleta pripremljenih esktruzijom/sferonizacijom, korišćenjem različitih smeša polimera.

Pelete sa 5, 7,5 ili 10% poli(etilen)oksida (PEO WSR303) ili karbomera (Carbopol 974P), 50% kofeina i mikrokristalnom celulozom pripremljene su vlažnom ekstruzijom/sferonizacijom, korišćenjem sita promera 0,8 mm (uzorci P1-3 i C1-3, redom). Pripremljeni uzorci ispitani su u pogledu sadržaja vlage, raspodele veličina čestica, odnosa dimenzija i prave gustine. Čvrstina peleta ispitana je pomoću reometra sa ploča-ploča sistemom bez rotacije, izračunate su zatezna čvrstina i Jungov modul.

Svi uzorci su pripremljeni uspešno, osim uzorka P3 sa 10% PEO, usled niskog prinosa. Sadržaj vlage peleta bio je manji od 3%, medijana veličine 834,21 μm (P2) do 915,17 μm (C3), a prava gustina 1,4573 g/cm^3 (C3) do 1,4800 g/cm^3 (C1). Veći udeo polimera doveo je do smanjenja prave gustine. Svi uzorci pokazali su zadovoljavajući odnos dimenzija.Ispitivanjem čvrstine peleta utvrđeno je da uzorci sa PEO pokazuju plastična svojstva, a pelete sa karbomerom krti lom. Pelete sa karbomerom imale su značajno veće vrednosti zatezne čvrstine (27,75 MPa za C1, do 33,25 MPa za C3) u poređenju sa PEO uzorcima (7,18 MPa za P1, 7,80 MPa, za P2), kao i vrednosti Jangovog modula. Ovo ukazuje na veću krutost i manju elastičnost peleta sa karbomerom. Povećanje udela polimera u okviru ispitivanog raspona neznatno je uticalo na mehanička svojstva peleta: zatezna čvrstina je bila veća, a vrednosti Jungovog modula smanjene.

Dobijeni rezultati ukazuju da polimer u formulaciji utiče na procesabilnost vlažne mase, kao i na mehanička svojstva peleta dobijenih ekstruzijom/sferonizacijom. Povećanje udela polimera povećalo je vrednosti zatezne čvrstine, ali su prinos i sfernost pripremljenih peleta bili niži.

INVESTIGATION INTO MECHANICAL PROPERTIES OF PELLETS PREPARED BY EXTRUSION/SPHERONIZATION USING DIFFERENT POLYMER BLENDS

Ivana Vasiljević[1], Erna Turković[1], Michael Piller[2], Andreas Zimmer[3], Jelena Parojčić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia), [2]Research Center Pharmaceutical Engineering GmbH, Graz (Austria), [3]Institute of Pharmaceutical Sciences, Department of Pharmaceutical Technology and Biopharmacy, University of Graz (Austria)

Multiparticulates mechanical properties are important for assessing suitability for packaging and transport, as well as their compression behavior. Formulation composition, especially polymer nature and concentration, affects pellet hardness and elasticity. The aim of this study was to investigate polymer effect on the mechanical properties of pellets prepared by extrusion/spheronization using different polymer blends.

Pellets containing 5, 7.5 or 10% poly(ethylene)oxide(PEO WSR303) or carbomer (Carbopol 974P), 50% caffeine and microcrystalline cellulose were prepared by wet extrusion/spheronization using the sieve aperture 0.8 mm (samples P1-3 and C1-3, respectively). The samples prepared were characterized with respect to moisture content, particle size distribution, aspect ratio and true density. Pellet hardness was determined by rheometer with a plate-plate system in non-rotational mode, tensile strength and Young's modulus were calculated subsequently.

All samples were successfully prepared, apart from P3 (containing 10% PEO), whose yield was low. Pellet moisture content was less than 3%; median pellet size 834.21 μm (P2) to 915.17 μm (C3), while their true density was 1.4573 g/cm^3 (C3) to 1.4800 g/cm^3 (C1). All the investigated samples showed satisfying aspect ratio for pharmaceutical application. Hardness testing results revealed ductile properties of PEO pellets, while carbomer pellets exhibited brittle fracture. Carbomer pellets had significantly higher tensile strength (27.75 MPa for C1, to 33.25 MPa for C3) compared with PEO samples (7.18 MPa for P1, 7.80 MPa for P2), as well as Young's modulus. This indicates that carbomer pellets were stiffer and less elastic. Increase in polymer content within the investigated experimental range slightly affected pellet hardness: tensile strength increased, while Young's modulus was lower.

The results obtained indicate that polymers employed can influence wet mass processability and mechanical properties of pellets obtained by extrusion spheronisation. Increase in polymer content resulted in slightly increased tensile strength, but led to reduced yield and aspect ratio of the pellets obtained.

OPTIMIZACIJA PROCESNIH PARAMETARA 3D ŠTAMPANJA ZA PROIZVODNJU PRINTLETA SLA TEHNOLOGIJOM

Mirjana Krkobabić, Marijana Madžarević, Svetlana Ibrić

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, (Srbija)

Stereolitografija (SLA) se zasniva na dejstvu lasera koji dovodi do očvršćavanja prethodno pripremljenog fotopolimerizujućeg rastvora u kome se nalazi lekovita supstanca, polimer i fotoinicijator. Najznačajniji parametri kod ove vrste štampanja su snaga izvora svetlosti, vreme izlaganja laseru i količine primenjenih polimera i fotoinicijatora. Cilj rada bio je da se ispita uticaj sadržaja vode u formulaciji na potrebno vreme izlaganja pripremljenih rezina dejstvu lasera kako bi se postiglo uspešno štampanje printleta. Dobijenim printletama su ispitane mehaničke karakteristike.

Pripremljeni su rezini koje sadrže polietilenglikol diakrilat (PEGDA), polietilenglikol 400 (PEG 400), ibuprofen, vodu i riboflavin. U svakoj formulaciji sadržaj ibuprofena bio je 5%, a sadržaj vode je variran od 5 do 30%. Model printleta je napravljen u programu 3D Builder i preveden je u .stl dokument, a parametri su optimizovani u Creation Workshop X programu. Printlete su štampane na SLA štampaču Duplicator 7, Wanhao. Debljina svakog sloja u toku štampanja bila je 100 μm. Sa 5% vode uspešno su štampane printlete uz vreme izloženosti laserskim zracima 100000 ms. Štampanja sa manjim vremenom izloženosti rezina bila su neuspešna jer usled nedovoljne izloženosti laseru nije došlo do očvršćavanja formulacija. Povećanje sadržaja vode na 10,1% zahtevalo je da vreme izloženosti bude najmanje 400000 ms, a sa 30% vode u formulaciji štampanje printleta bilo je moguće pri vremenu ekspozicije od 800000 ms. Mehaničke karakteristike ispitivanih printleta bile su ujednačene. Najveću čvrstinu pokazale su printlete sa 10,1% vode (60,30±20,20N).

Sadržaj vode utiče na vreme izloženosti laserskim zracima tako da je sa povećanjem sadržaja vode u formulaciji potrebno duže vreme izlaganja. Preporuke za vreme izloženosti laserskim zracima ne postoje, pa je zbog toga potrebno optimizovati ovaj parametar za svaku formulaciju pojedinačno da bi se omogućilo uspešno štampanje printleta.

OPTIMIZATION OF PRINTING PROCESS PARAMETERS FOR PRINTLETS FABRICATED BY SLA PRINTING

Mirjana Krkobabić, Marijana Madžarević, Svetlana Ibrić

Department of Pharmaceutical Technology and Cosmetology,
University of Belgrade - Faculty of Pharmacy (Serbia)

Stereolithography (SLA) is based on the solidification of a liquid resin by photopolymerization. Resin should contain drug, polymer and photoinitiator. The most important parameters for this technology are the power of the light source, the exposure time, and the amount of polymers and photoinitiator. The aim of the study was to evaluate the influence of the water content in the formulation on the exposure time in order to successfully fabricate printlets. The obtained printlets were tested for mechanical properties.

Resins are prepared of polyethyleneglycol diacrylate (PEGDA), polyethyleneglycol 400 (PEG 400), ibuprofen, water, and riboflavin. In each formulation, ibuprofen content was 5% and the water content was varied from 5 to 30%. The templates used to print the printlets were designed with 3D Builder software and exported as a stereolithography file (.stl) into software Creation Workshop X where parameters are set. Printlets were fabricated with SLA printer Duplicator 7, Wanhao. The layer thickness was 100 μm. With 5% of water, printlets were successfully fabricated with exposure time of 100000 ms. There was no solidification of the resins with a lower exposure time. The increase in water content up to 10.1% required the exposure time to be at least 400000 ms, and with 30% of water in the formulation printing was possible at exposure time of 800000 ms. The mechanical characteristics of the printlets were uniform. The highest strength was shown by printlets with 10.1% water (60.30 ± 20.20N).

The water content affects the exposure time to the laser beams. With the increase in the water content in the formulation, a longer exposure time is required. The guideline for exposure time does not exist, so it is necessary to optimize this parameter for each formulation individually to successfully fabricate printlets.

PREDLOG METODA ZA ISPITIVANJE FUNKCIONALNIH SVOJSTAVA ORALNIH FILMOVA

Marko Krstić[1], Ana-Marija Meglić[2], Nikola Jakovljević[2], Jovana Talić[2], Sandra Cvijić[2]

[1]ZUA Julija Pharm, [2]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija)

Mukoadhezivni oralni filmovi predstavljaju novi pristup u formulaciji farmaceutskih preparata koji pokazuje određene prednosti u odnosu na konvencionalne preparate za oralnu primenu. Međutim, farmakopeje i regulatorni vodiči ne navode uslove i kriterijume za ispitivanje ovih farmaceutskih oblika. Cilj istraživanja je bio da se proceni uticaj sastava formulacije i načina izrade na mehaničke i adhezivne osobine oralnih filmova baziranih na hidroksipropilmetilcelulozi (HPMC).

Ispitivani filmovi su se sastojali iz polimera (HPMC), plastifikatora (makrogol 400) i piroksikama kao aktivne supstance. Kao rastvarači za izradu disperzija korišćeni su apsolutni etanol i prečišćena voda. Ispitivanja su obuhvatila određivanje mehaničkih karakteristika, variranja mase i debljine filmova, raspadljivosti, vremena kvašenja, brzine apsorpcije medijuma, mukoadhezivnosti na bukalnoj svinjskoj sluzokoži, sadržaja piroksikama i pH vrednost disperzija za izradu filmova. Rezultati su ukazali na uniformnost debljine i mase izrađenih filmova. Sadržaj piroksikama bio je 97,55-103,83% a pH vrednost disperzije 4,09-4,70 što je posledica blago kisele prirode piroksikama. Deblji filmovi su pokazali veću mehaničku čvrstinu u odnosu na tanje filmove istog sastava, dok su se oni sa dodatkom plastifikatora odlikovali većom fleksibilnošću i procentom istezanja. Takođe, pokazano je da tanji filmovi brže upijaju veštačku salivu od debljih filmova istog sastava. Povećanje debljine filma i udela polimera produžilo je vreme raspadanja filmova. *In vitro* ispitivanje sa bukalnom svinjskom sluzokožom u uravnoteženom sistemu za procenu adhezivnosti pokazalo je da sa porastom udela polimera raste mukoadhezivnost, dok dodatak plastifikatora negativno utiče na jačinu adhezije.

Prilikom razvoja oralnih filmova važno je izvršiti opsežna istraživanja kako bi se identifikovala optimalna formulacija koja zadovoljava unapred određene karakteristike kvaliteta. Ovakav farmaceutski oblik bi usled jednostavnog načina primene znatno poboljšao komplijansu pacijenata. Predlozi načina i uslova ispitivanja izneti u ovoj studiji predstavljaju doprinos u tom smeru.

A CONTRIBUTION ON THE METHODS TO DETERMINE FUNCTIONAL CHARACTERISTICS OF BUCCAL PATCHES

Marko Krstić[1], Ana-Marija Meglić[2], Nikola Jakovljević[2], Jovana Talić[2], Sandra Cvijić[2]

[1]ZUA Julija Pharm, [2]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Mucoadhesive buccal patches represent a new approach in drug formulation with certain advantages in comparison to conventional oral dosage forms. However, pharmacopoeias and regulatory guidances do not propose experimental conditions nor requirements for the assessment of these dosage forms. The aim of the study was to evaluate the influence of formulation composition and method of preparation on mechanical and adhesive properties of hydroxypropylmethylcellulose (HPMC)-based buccal patches.

The investigated patches consisted of polymer (HPMC), plasticizer (macrogol 400), and piroxicam as the model drug. Absolute ethanol and purified water were used as solvents. The investigation of patches included determination of: mechanical characteristics, variation in mass and thickness, disintegration time, wetting time and saliva uptake, mucoadhesivity on porcine buccal mucosa, drug content and pH value of the dispersions for patches preparation.

The obtained results indicated uniformity of thickness and mass of the patches. Piroxicam content was 97.55-103.83%, and pH value of the dispersions was 4.09-4.70 due to slightly acidic nature of piroxicam. Thicker patches had higher mechanical strenght compared to thinner patches of the same composition, while patches with the addition of macrogol showed greater flexibility and percent of elongation. Saliva uptake was faster for thinner patches in comparison to thicker patches of the same composition. Disintegration time was influenced by thickness of the patches and amount of HPMC. *In vitro* testing on porcine buccal mucosa revealed that increase in the amount of HPMC lead to stronger mucoadhesion, while the addition of plasticizer had negative effect on the adhesion strength of the patches.

Development of buccal patches requires extensive research in order to identify the optimal formulation that meets predefined quality characteristics. Such oral dosage form would significantly increase patients adherence. Recommendations on the methods and conditions to assess the characteristics of buccal patches, provided in this study, represents a contribution in this direction.

IN VITRO/IN SILICO PRISTUP ZA PROCENU DEPOZICIJE I APSORPCIJE INHALACIONO PRIMENJENIH LEKOVA KOD PACOVA: STUDIJA SLUČAJA

Jelisaveta Ignjatović[1], Meihua Han[2], Dongmei Cun[2], Mingshi Yang[2,3], Jelena Đuriš[1], Jelena Parojčić[1], Sandra Cvijić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija), [2]Wuya College of Innovation, Shenyang Pharmaceutical University (Kina), [3]Odsek za farmaciju, Univerzitet u Kopenhagenu - Fakultet zdravstvenih i medicinskih nauka (Danska)

Fiziološki zasnovani *in silico* modeli za predviđanje depozicije i apsorpcije inhalaciono primenjenih lekova se odnedavno koriste za biofarmaceutsku karakterizaciju ovih lekova. Međutim, nepotpuno poznavanje određenih fizioloških procesa i ponašanja leka u plućima neke su od prepreka koje ograničavaju primenu pomenutih modela. Cilj studije bio je da se analizira strategija razvoja *in silico* modela za predviđanje depozicije i apsorpcije inhalaciono primenjenih lekova, koristeći budesonid kao model supstancu.

MPPD model (v. 3.04, ARA Inc, USA) korišćen je za predviđanje depozicije budesonida u plućima pacova, a GastroPlus™ program (v. 9.0.0007, Simulation Plus Inc, USA) za predviđanje apsorpcije budesonida. Podaci o depoziciji leka po regionima pluća i koncentraciji u plazmi dobijeni su u *in vivo* studiji na *Sprague-Dawley* pacovima (težine 180-220 g). Farmakokinetički parametri generisani su pomoću GastroPlus™ PKPlus modula. Rezultati *in vivo* ispitivanja su pokazali da je frakcija deponovanog leka (u obliku mikročestica) u alveolama (61%) znatno veća u odnosu na *in silico* predviđenu vrednost (4,37%), dok je odstupanje između *in vivo* određene (36,80%) i predviđene (56,15%) vrednosti nešto manje u slučaju inhaliranih nanočestica leka. PKPlus analiza je pokazala da se farmakokinetika budesonida najbolje može opisati troprostornim modelom, mada neke ranije objavljene studije predlažu primenu jedno- ili dvoprostornih modela. *In silico* rezultati su pokazali da se primenom troprostornog farmakokinetičkog modela u kombinaciji sa *in vivo* podacima o depoziciji leka u plućima uspešnije predviđa koncentracija budesonida u plazmi u odnosu na podatke dobijene korišćenjem jedno- ili dvoprostornog farmakokinetičkog modela i *in silico* predviđenih vrednosti za regionalni profil depozicije.

Depozicija leka jedan je od ključnih faktora koji utiču na apsorpciju leka u plućima. Međutim, pokazano je da MPPD model ne simulira adekvatno depoziciju leka u plućima pacova. Takođe, kako farmakokinetički parametri u velikoj meri utiču na profil koncentracije leka u plazmi, neophodno je adekvatno dizajnirati *in vivo* studije na pacovima i obraditi dobijene rezultate.

IN VITRO/IN SILICO APPROACH TO ASSESS AN INHALED DRUG DEPOSITION AND ABSORPTION IN RATS: CASE STUDY

Jelisaveta Ignjatović[1], Meihua Han[2], Dongmei Cun[2], Mingshi Yang[2,3], Jelena Đuriš[1], Jelena Parojčić[1], Sandra Cvijić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade – Faculty of Pharmacy (Serbia), [2]Wuya College of Innovation, Shenyang Pharmaceutical University (China), [3]Department of Pharmacy, University of Copenhagen - Faculty of Health and Medical Sciences(Denmark)

Physiologically based *in silico* models for the prediction of inhaled drugs deposition and absorption recently emerged as advantageous biopharmaceutical assessment tool. However, lack of knowledge on certain physiological processes and drug performance in the lungs are some of the obstacles that hinder wider use of these models. The aim of this study was to analyze the strategy for generating an *in silico* model for the prediction of inhaled drug deposition and absorption using budesonide as a model drug.

MPPD model (v. 3.04, ARA Inc, USA) was used to predict budesonide deposition in rats, and Gastroplus™ software (v. 9.0.0007, Simulation Plus Inc, USA) was used to estimate the drug absorption profile. *In vivo* data on lung regional deposition and plasma concentration profiles were collected using Sprague-Dawley rats (180-220 g body weight). Drug pharmacokinetic parameters were obtained using GastroPlus™ PKPlus module. *In vivo* results showed that the deposited drug fraction in alveoli (61%) was much higher than the predicted value (4.37%) for the inhaled microparticles, while the difference between observed (36.80%) and predicted (56.15%) values for inhaled nanocrystals was less pronounced. PKPlus analysis indicated that budesonide pharmacokinetics is best described by three compartmental model although some previously published studies suggested one or two compartmental model. Modeling results indicated that three compartmental pharmacokinetic model coupled with *in vivo* deposition data gave better prediction of drug plasma concentration profile in comparison to one or two compartmental pharmacokinetic model and *in silico* deposition data.

Drug deposition is one of the key factors affecting pulmonary drug absorption. However, available MPPD model does not seem to accurately predict drug deposition in rats. In addition, since pharmacokinetic parameters inevitably affect drug plasma concentration profile, it is of paramount importance to properly design *in vivo* studies in rats and analyze the obtained results.

AERODINAMIČKO ODREĐIVANJE FRAKCIJE SITNIH ČESTICA PRAŠKOVA ZA INHALACIJU FORMULISANIH U OBLIKU LIPIDNIH MIKROČESTICA

Jelisaveta Ignjatović[1], Sandra Cvijić[1], Vladimir Dobričić[2], Svetlana Ibrić[1], Jelena Đuriš[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet,[2]Katedra za farmaceutsku hemiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija)

Lipidne mikročestice izrađene od biokompatibilnih i biodegradabilnih ekscipijenasa imaju veliki potencijal za primenu u obliku praškova za inhalaciju. Cilj rada bio je da se ispita veza između geometrijske i aerodinamičke veličine lipidnih mikročestica, i da se utvrdi uticaj brzine protoka vazduha na frakciju sitnih čestica.

U studiji su korišćene dve formulacije lipidnih mikročestica, F1 i F2, izrađene metodom emulgovanja topljenjem, pri čemu je za izradu formulacije F1 kao lipidna komponenta korišćen glicerildibehenat, a stearilalkohol za F2. Geometrijska raspodela veličine čestica određena je metodom laserske difrakcije (Mastersizer, Malvern UK). Aerodinamičko određivanje frakcije sitnih čestica vršeno je u staklenom impindžeru (Aparatura A, Ph. Eur. 9.0), primenom dve brzine protoka vazduha, 60±5 i 100±5 L/min. Sadržaj aktivne supstance, salbutamol-sulfata određen je metodom tečne hromatografije u kombinaciji sa masenom spekrometrijom (TSQ Quantum Access MAX, USA). Rezultati su pokazali nešto manji geometrijski prečnik čestica formulacije F2 (d_{50}= 11,00 μm) u odnosu na F1 (d_{50}= 13,45 μm) i veću frakciju sitnih čestica, manjih od 5 μm (21,36% za F2 i 17,11% za F1). Međutim, rezultati aerodinamičkog određivanja sitnih čestica pokazali su znatno manju frakciju sitnih čestica (2,76-5,77% za obe formulacije). Ovakve razlike su najverovatnije uslovljene oblikom čestica koje nisu sferne, kao i nešto većom gustinom čestica (> 1 g/cm^3). Takođe, pokazano je da ne postoji značajna razlika u udelu sitnih čestica pri promeni brzine protoka vazduha, kao ni pri primeni kapsula napunjenih praškom u odnosu na direktno punjenje inhalatora praškom. Ovaj podatak ukazuje da zanemarljiva količina praška zaostaje na omotaču kapsule, te je rizik od neujednačenog doziranja smanjen.

Dobijeni rezultati pokazuju da je za isporuku efektivne doze salbutamol-sulfata u pluća neophodno razviti formulacije sa manjim geometrijskim i aerodinamičkim prečnikom čestica i, posledično, većom frakcijom sitnih čestica.

AERODYNAMIC ASSESMENT OF FINE PARTICLES FRACTION FOR INHALATION POWDERS FORMULATED AS LIPID MICROPARTICLES

Jelisaveta Ignjatović[1], Sandra Cvijić[1], Vladimir Dobričić[2], Svetlana Ibrić[1], Jelena Đuriš[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade – Faculty of Pharmacy,[2]Department of Pharmaceutical Chemistry, University of Belgrade – Faculty of Pharmacy (Serbia)

Lipid microparticles composed of biocompatible and biodegradable excipients have been recognized as potentially useful deliver systems for inhaled drugs. The aim of this study was to determine the relationship between geometric and aerodynamic particle size of lipid microparticles, and to determine the effect of different airflows on fine particle fraction.

Two lipid microparticle formulations, F1 and F2, were tested in this study. Both formulations were prepared by melt emulsification method; F1 was made of glyceryl dibehenate and F2 of stearyl alcohol. Geometric particle size distribution was determined by laser diffraction (Mastersizer, Malvern UK). Glass impinger (apparatus A, Ph. Eur. 9.0) was used for aerodynamic assessment of fine particles fraction, using two air flows, 60±5 and 100±5 L/min. Salbutamol-sulphate content was determined by liquid chromatography tandem mass spectrometry. The results indicated smaller geometric particle diameter for F2 (d_{50}= 11.00 μm) compared to F1 microparticles (d_{50}= 13.45 μm), and higher fraction of particles smaller than 5 μm (21.36% for F2 and 17.11% for F1). However, the results of aerodynamic assesment showed significantly smaller fine particles fraction (2.76-5.77% for both formulations). These differencies probably result from the lack of particle sphericity or higher particle density (>1 g/cm^3). In addition, there was no significant difference of fine particles fraction under different air flows, nor between testing with capsules filled with powder and testing with powder directly filled in the inhaler. These data indicate that negligible amount of powder adheres to the capsule shell, and therefore the risk of inconsistent dosing is decreased.

The results suggest that improvement of the formulations in order to decrease geometric and aerodynamic diameter, and increase fine particles fraction, are necessary to deliver the effective salbutamol-sulphate dose to the lung.

STUDY ON PHYSICAL AND CHEMICAL BEHAVIOR OF β – CYCLODEXTRIN AND ITS INCLUSION COMPLEX WITH CAPTOPRIL

Adina Musuc[1], Irina Atkinson[1], Mirela Mitu[2], Oana Karampelas[2], Emma Cretu[2]

[1]Romanian Academy, „Ilie Murgulescu" Institute of Physical Chemistry, Bucharest, [2]University of Medicine and Pharmacy „Carol Davila" Bucharest, Faculty of Pharmacy (Romania)

Captopril (CAP), (2*S*)-1-[(2*S*)-2-methyl-3-sulfanylpropanoyl] pyrrolidine – 2 - carboxylic acid is a suitable candidate to be formulated in sublingual tablets, the best emergency pharmaceutical form to be used by the patient himself. CAP is included in class III of Biopharmaceutics Classification System; that means it has a low membrane permeability which decreases its absorption and in order to provide this drug in a more accessible and patient compliant form, its bitter taste must be masked. Also, CAP undergoes oxidative dimerization to the major degradation product captopril disulphide in aqueous solutions. By its formulation as an inclusion complex with β – cyclodextrin we are trying to adjust these inconvenients, and to obtain a stable and easy to use solid sublingual pharmaceutical form with an increased bioavailability. The aim of the current study is to evaluate the ability of β - cyclodextrin to include captopril.

The pasta method of complexation in solid state was used to obtain the inclusion complexes. For comparison was prepared a simple physical mixture. Physical and chemical characterization of raw materials, physical mixture and the inclusion complex were made using Fourier transform – infrared spectroscopy, X-ray diffraction, scanning electron microscopy and simultaneous thermal analysis. The results obtained using all these analytical techniques, proved that captopril forms stable complexes with β-cyclodextrin in 1:2 molar ratio, and the complexation was almost complete. The results of the present studies prove that CAP-β-CD inclusion complex can be embedded as an active ingredient of sublingual tablets that can be successfully used in therapeutic practice.

SAMOEMULGUJUĆI SISTEMI ZA ISPORUKU SIMVASTATINA: UTICAJ VRSTE KOSURFAKTANTA NA VELIČINU KAPI I OSLOBAĐANJE LEKOVITE SUPSTANCE

Zora Ćetković[1], Sandra Cvijić[2], Dragana Vasiljević[2]

[1] Klinički centar Srbije, [2]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu-Farmaceutski fakultet (Srbija)

Samoemulgujući sistemi su napredni sistemi za isporuku slabo rastvorljivih lekovitih supstanci, kao što je simvastatin. U njihov sastav mogu da uđu različite pomoćne supstance, a izbor zavisi od željenih karakteristika ovih sistema. Cilj studije je bio da se ispita uticaj različitih kosurfaktanata na veličinu emulgovanih kapi i brzinu oslobađanja simvastatina, kao model supstance.

Samoemulgujući sistemi su izrađeni korišćenjem oleil makrogol-6 glicerida (Labrafil®) (10,0%) kao uljane faze, kaprilokaproil makrogol-8 glicerida (Labrasol®) (67,5%) kao surfaktanta i četiri različita kosurfaktanta (22,5%): polisorbata 80, makrogol-15 hidroksistearata (Kolliphor® HS15), saharoze palmitata (D-1616) ili saharoze stearata (D-1816). Sadržaj simvastatina bio je 5% u svim formulacijama. Karakterizacija izrađenih sistema obuhvatila je procenu sposobnosti samoemulgovanja, kao i određivanja veličine emulgovanih kapi, indeksa polidisperziteta i brzine oslobađanja simvastatina. Vreme samoemulgovanja svih uzoraka bilo je veoma kratko (manje od 1 min). Tečni samoemulgujući sistemi, izrađeni sa polisorbatom 80 ili Kolliphor®-om HS15 kao kosurfaktantom, imali su malu prosečnu veličinu kapi (14,36±0,07 i 17,53±0,17 nm) i nizak indeks polidisperziteta (0,181±0,006 i 0,085±0,011). Polučvrsti samoemulgujući sistemi, izrađeni sa šećernim estrima (saharoza palmitatom ili saharoza stearatom), kao kosurfaktantima prirodnog porekla, imali su veću prosečnu veličinu kapi (251,4±0,64 i 277,0±1,65 nm) i veći indeks polidisperziteta (0,237±0,041 i 0,392±0,005). Iako je uočena razlika u veličini kapi između uzoraka koji sadrže sintetičke ili prirodne kosurfaktante, nije bilo razlike u brzini oslobađanja simvastatina između ovih samoemulgujućih sistema. Lekovita supstanca se potpuno oslobodila iz svih formulacija nakon prvih 5 minuta ispitivanja. Osim toga, polučvrsti samoemulgujući sistemi su pokazali bolja svojstva u pogledu lakoće punjenja u tvrde kapsule.

Ova ispitivanja su pokazala da se korišćenjem šećernih estara, kao kosurfaktanata, mogu dobiti polučvrsti samoemulgujući sistemi, kao potencijalni novi nosači lekovitih supstanci. Opisani sistemi obezbeđuju odgovarajuću brzinu oslobađanja inkorporirane teško rastvorljive lekovite supstance, a dodatna prednost u odnosu na tečne sisteme im je lakše punjenje u tvrde kapsule.

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS) OF SIMVASTATIN: THE INFLUENCE OF COSURFACTANT TYPE ON DROPLET SIZE AND DRUG RELEASE

Zora Ćetković[1], Sandra Cvijić[2], Dragana Vasiljević[2]

[1]Clinical Center of Serbia, [2]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy (Serbia)

Self-emulsifying drug delivery systems (SEDDS) are promising delivery systems for poorly water-soluble drugs like simvastatin. A number of excipients may be used to formulate these systems, and the choice of composition depends on the desired characteristics of the resulting SEDDS. The aim of this study was to investigate the influence of different cosurfactants on droplet size of SEDDS and release rate of simvastatin as a model drug.

SEDDS were formulated using oleoyl macrogol-6 glycerides (Labrafil®) (10.0%) as oil phase, caprylocaproyl macrogol-8 glycerides (Labrasol®) (67.5%) as surfactant and four different cosurfactants (22.5%): polisorbate 80, macrogol-15-hydroxystearate (Kolliphor® HS15), sucrose palmitate (D-1616) or sucrose stearate (D-1816). Simvastatin content was 5% (w/w) in all formulations. Prepared formulations were evaluated for self-emulsifying ability, droplet size, polydispersity index (PDI), and drug release rate. All formulations showed very short emulsification time of less than 1 min. The liquid SEDDS, containing polisorbate 80 or Kolliphor® HS15 as cosurfactants, had small mean droplet size (14.36±0.07 and 17.53±0.17 nm), and low PDI values (0.181±0.006 and 0.085±0.011). Semi-solid SEDDS, incorporating natural sugar-based excipients (sucrose palmitate or sucrose stearate) as cosurfactants, had larger mean droplet size (251.4±0.64 and 277.0±1.65 nm), and PDI values (0.237±0.041 and 0.392±0.005). Although there was a notable difference in droplet size between formulations containing synthetic and natural cosurfactants, there was no difference in simvastatin release rate between these SEDDS. A complete drug release occurred from all formulations within the first 5 minutes. In addition, semi-solid SEDDS were favorable in terms of ease capsule filling.

This study revealed that inclusion of natural excipients, sucrose esters, in SEDDS results in the formation of semi-solid systems. These novel SEDDS provide an appropriate release rate of incorporated poorly water-soluble drug. Additionally, their consistency is more appropriate for filling into hard capsules.

ISPITIVANJE UTICAJA HIDROGELA TIPA POLIELEKTROLITNOG KOMPLEKSA HITOZAN/KSANTAN NA *IN VITRO* KINETIKU OSLOBAĐANJA IBUPROFENA

Ana Ćirić, Ljiljana Đekić

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Ibuprofen je jedan od najčešće korišćenih nesteroidnih antiinflamatornih analgetika. Zbog kratkog poluvremena eliminacije ($t_{1/2}$~2h) neophodna je česta primena farmaceutskih preparata sa trenutnim oslobađanjem. Radi smanjenja učestalosti doziranja razmatraju se formulacije sa produženim oslobađanjem. Biokompatibilni i biodegradabilni kompleksi hitozana sa anjonskim polimerima mogu potencijalno uticati na kinetiku oslobađanja peroralno primenjenih lekova. Cilj rada bio je ispitivanje uticaja hidrogelova tipa polielektrolitnog kompleksa hitozan/ksantan na *in vitro* kinetiku oslobađanja slabo rastvorljivog ibuprofena.

Pripremljeni su hidrogelovi mešanjem vodenih disperzija hitozana 0,65% (pH 5,6; 0,1M HCl i 0,2M NaOH) i ksantana 0,65%, na sobnoj temperaturi. Nakon uklanjanja viška vode, ispiranja i sušenja dobijeni suvi ostatak (hidrogel) je usitnjen, prosejan (sito 600 μm) i upotrebljen za pripremu fizičkih smeša sa ibuprofenom u masenom odnosu 1:1 i 1:2. Smeše su napunjene u kapsule veličine 0 i ispitivan je *in vitro* profil oslobađanja u aparaturi sa lopaticom (50 rpm) (Erweka DT70, Nemačka), uz korišćenje 900 ml akceptorskog medijuma (fosfatni pufer pH 7,2) na 37±1°C. Dobijeni hidrogel u hidratisanom obliku bio je opalescentan, a suvi ostatak bledožute boje. Zahtev Američke farmakopeje (USP) za *in vitro* ispitivanje brzine rastvaranja ibuprofena iz konvencionalnih čvrstih farmaceutskih oblika (tableta) je da se najmanje 80% lekovite supstance oslobodi nakon 60 min. Kod ispitivane formulacije sa odnosom hidrogel:ibuprofen 1:1 nakon 60 min oslobođeno je 16,20% lekovite supstance, a kod formulacije sa odnosom hidrogel:ibuprofen 1:2 utvrđeno je da se nakon 60 min rastvorilo 9,78% ibuprofena. Dobijeni profili oslobađanja ibuprofena bili su u skladu sa kinetikom nultog reda (r^2> 0,95), a brzina rastvaranja iznosila je 0,416 mg/min (maseni odnos 1:1) i 0,396 mg/min (maseni odnos 1:2).

Na osnovu dobijenih rezultata može se zaključiti da se korišćenjem hidrogela tipa polielektrolitnog kompleksa hitozan/ksantan može postići produženo oslobađanje ibuprofena, pri čemu je ispitivani maseni odnos hidrogela i ibuprofena značajno uticao na brzinu rastvaranja aktivne supstance.

INVESTIGATION OF THE INFLUENCE OF POLYELECTROLYTE COMPLEX CHITOSAN/XANTHAN HYDROGELS ON THE IN VITRO RELEASE KINETICS OF IBUPROFEN

Ana Ćirić, Ljiljana Đekić

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Ibuprofen is one of the most frequently used non-steroidal anti-inflammatory analgesics. Due to its short half-life ($t_{1/2}$~2h), frequent administration of immediate release dosage forms is necessary. To reduce the frequency of dosing, prolonged release formulations are considered. Biocompatible and biodegradable chitosan complexes with anionic polymers can potentially influence the release kinetics of orally administered drugs. The aim of this paper was to investigate the influence of polyelectrolyte complex chitosan/xanthan hydrogels on *in vitro* release kinetics of poorly soluble ibuprofen.

Hydrogels were prepared by mixing aqueous dispersions of chitosan 0.65% (pH 5.6, 0.1M HCl and 0.2M NaOH) and xanthan 0.65% at room temperature. After removing excess water, rinsing and drying, resulting dried residue is crushed, sieved (sieve 600 μm) and used to prepare physical mixtures with ibuprofen in mass ratio 1:1 and 1:2. The mixtures were filled into capsules size 0 and *in vitro* release profile in the paddle apparatus (50 rpm) (Erweka DT70, Germany) was performed using 900 ml of acceptor medium (phosphate buffer pH 7.2) at 37±1°C.

The resulting hydrogel in hydrated form was opalescent, and dried residue pale yellow. The US Pharmacopoeia requirement for *in vitro* dissolution testing of ibuprofen from tablets is that at least 80% of ibuprofen is released after 60 min. In the investigated formulation with mass ratio hydrogel:ibuprofen 1:1, after 60 min 16.20% of ibuprofen was released, and in the formulation with mass ratio hydrogel:ibuprofen 1:2, after 60 min 9.78% of ibuprofen was released. Resulting ibuprofen release profiles were in accordance with zero order kinetics (r^2 >0.95) and dissolution rate was 0.416 mg/min (mass ratio 1:1) and 0.396 mg/min (mass ratio 1:2).

It can be concluded that prolonged release of ibuprofen can be achieved by using polyelectrolyte complex chitosan/xanthan hydrogels, where in investigated mass ratio hydrogel:ibuprofen significantly influence the dissolution rate.

UTICAJ MOLEKULSKE MASE HITOZANA NA FUNKCIONALNOST HITOZAN-HALOJZIT NANOKOMPOZITNIH FILMOVA ZA LOKALNU ISPORUKU ANTIBIOTIKA

Bojan Čalija[1], Danina Krajišnik[1], Aleksandra Daković[2], Kata Trifković[3], Nikola Milašinović[4], Jela Milić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Institut za tehnologiju nuklearnih i drugih mineralnih sirovina, [3]Katedra za hemijsko inženjerstvo, Univerzitet u Beogradu – Tehnološko-metalurški fakultet, [4]Katedra forenzike, Kriminalističko-policijska akademija (Srbija)

Dodatkom glina, poput halojzita, moguće je unaprediti funkcionalnost hitozanskih filmova, poboljšanjem termičke stabilnosti, mehaničkih i optičkih karakteristika. Karakteristike hitozan-halojzit kompozita zavise od svojstava i odnosa konstituenata i načina/postupka izrade. Molekulska masa hitozana prepoznata je kao ključna funkcionalna karakteristika ovog polimera kada se koristi za izradu nosača lekovitih supstanci. Cilj studije je ispitivanje uticaja molekulske mase hitozana na funkcionalnost hitozan-halojzit nanokompozitnih filmova kao potencijalnih nosača za lokalnu isporuku antibiotika.

Filmovi su izrađeni postupkom izlivanja 0,5% (m/m) disperzije halojzita u rastvoru 1,5% (m/m) hitozana i 0,5% (m/m) tetraciklin-hidrohlorida u akrilne kalupe. Za izradu disperzija korišćeni su visokodeacetilovani nisko- (253,7 kDa), srednje (417,7 kDa) i visokomolekularni (547,3 kDa) hitozan. Nakon sušenja, filmovi su podvrgnuti određivanju mase i debljine, mehaničkoj, strukturnoj i termičkoj karakterizaciji i ispitivanju brzine oslobađanja tetraciklin-hidrohlorida u fosfatnom puferu pH vrednosti 5,8. Nanokompozitni filmovi su opalescentni i žuti, usled prisustva halojzita i tetraciklin-hidrohlorida. Masa i debljina filmova su opadale od 76,77±3,29 do 63,18±1,84 mg, odnosno od 89,12±6,83 do 77,7±2,3 μm, redom, sa porastom molekulske mase hitozana. Porast molekulske mase hitozana dovodio je i do smanjenja izduženja pri kidanju (od 60,94±5,05 do 23,42±1,31%), a porasta napona pri kidanju (od 24,66±2,56 do 230,04±33,44 MPa) i modula elastičnosti (od 40,45±2,16 do 491,64±62,94 MPa). FT-IR i termičkom analizom potvrđene su hitozan-halojzit interakcije i poboljšana termička stabilnost nanokompozitnih filmova u odnosu na hitozanske, ali nije uočen uticaj molekulske mase hitozana na strukturu i termičke osobine filmova. Tetraciklin-hidrohlorid se usporeno oslobađao iz nanokompozitnih filmova, a posebno iz filmova izrađenih od niskomolekularnog hitozana ($t_{50\%}$≈5,5 h; $t_{90\%}$>8 h). Dobijeni rezultati ukazuju da molekulska masa hitozana ima značajan uticaj na masu, debljinu i mehaničke karakteristike hitozan-halojzit nanokompozitnih filmova, kao i na brzinu oslobađanja tetraciklin-hidrohlorida, ali ne i na njihovu strukturu i termička svojstva.

INFLUENCE OF CHITOSAN MOLECULAR WEIGHT ON FUNCTIONALITY OF NANOCOMPOSITE CHITOSAN-HALLOYSITE FILMS FOR LOCAL DELIVERY OF ANTIBIOTICS

Bojan Čalija[1], Danina Krajišnik[1], Aleksandra Daković[2], Kata Trifković[3], Nikola Milašinović[4], Jela Milić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Institute for the Technology of Nuclear and Other Mineral Raw Materials, [3]Department of Chemical Engineering, University of Belgrade - Faculty of Technology and Metallurgy, [4]Department of Forensics, Academy of Criminalistic and Police Studies (Serbia)

Addition of clays, such as halloysite, may improve functionality of chitosan films by improving their thermal stability, mechanical and optical characteristics. Characteristics of chitosan-halloysite composites depend on characteristics and ratio of individual constituents, and preparation procedure. Molecular weight is identified as one of the key functionality-related characteristics of this polymer, as excipients for drug delivery devices. This study was aimed to investigate influence of chitosan molecular weight on functionality of chitosan-halloysite nanocomposite films as potential carriers for sustained delivery of antibiotics.

The films were prepared by casting 0.5% (w/w) halloysite dispersion in 1.5% (w/w) chitosan and 0.5% (w/w) tetracycline hydrochloride solution into acrylic molds. Highly deacetylated chitosans having average molecular weight of 253.7, 417.7 i 547.3 kDa, labelled as low-, medium- and high molecular weight chitosan, respectively, were used for preparation of the dispersions. Upon drying films were subjected to mass and thickness determination, mechanical, structural and thermal characterization and drug release studies in phosphate buffer solution pH 5.8. Nanocomposite films were opalescent and yellow-colored due to presence of halloysite and tetracycline hydrochloride. Films mass and thickness decreased from 76.77±3.29 mg to 63.18±1.84 and from 89.12±6.83 to 77.7±2.3 μm, respectively, following the increase in the chitosan molecular weight. Increase in chitosan molecular weight also led to decrease in elongation at break (from 60.94±5.05 to 23.42±1.31%), and increase in tensile strength (from 24.66±2.56 to 230.04±33.44 MPa) and elastic modulus (from 40.45±2.16 to 491.64±62.94 MPa). FT-IR and thermal analysis confirmed chitosan-halloysite interactions and improved thermal stability of nanocomposite films in comparison to chitosan films, but did not reveal influence of chitosan molecular weight on structure and thermal properties of the films. Tetracycline hydrochloride release from films was sustained, particularly from the films consisted of low molecular weight chitosan ($t_{50\%}$≈5.5 h; $t_{90\%}$>8 h).

Obtained results revealed significant influence of chitosan molecular weight on mass, thickness, mechanical and drug release properties of nanocomposite chitosan-halloysite films, but not on their structure and thermal properties.

CHARACTERIZATION OF RISPERIDONE LOADED NANOSTRUCTURED LIPID FOR DRUG DELIVERY TO THE BRAIN

Hristina Litovin[1], Blagorodna Koprivica[1], Monika Stojanovska[2], Gjorgji Petrusevski[2], Maja Simonoska Crcarevska[1], Marija Glavas Dodov[1]

[1]Institute of Pharmaceutical Technology, Ss. Cyril & Methodius University-Faculty of Pharmacy, Skopje, [2]Institute for Research and Development, Alkaloid AD, Skopje (Macedonia)

Drug delivery to the CNS poses a formidable challenge. The BBB and the blood-cerebrospinal fluid barrier can hamper effective transport of drugs into the brain. The main objective of the study was to formulate and characterize risperidone (RISP) loaded nanostructured lipid carriers (NLC's) as a parenteral delivery carrier with prolonged circulatory time which favors interaction and penetration into brain endothelial cells.

Different formulations of NLC's loaded with RISP were prepared by phase inversion temperature (PIT) method. Particle size and particle size distribution, zeta potential encapsulation efficiency (EE), drug loading (DL), drug release, and thermal behavior of the prepared samples were determined. Optimized NLC's were surface-modified with Tween 80, PEG 400 and Solutol HS 15 (3.5 – 4.5%) to assess whether they show reduction of total protein adsorption thus leading to site-specific accumulation (targeting) into the brain.

By using 19.96% lipid matrix constituents (56% cetyl palmitate and 44% Miglyol 812 as oil), 5% RISP, 1.5% phospholipid, 17% Solutol HS 15 as hydrophilic emulsifier, nanoparticles with an average diameter of 133 nm (PdI~0.4) with unimodal narrow size distribution were prepared, zeta potential -13.8 mV, EE (89.24%), DL (31.3 mg/g) and gradual drug release after 96 h up to 81.87%. DSC scans and calculated recrystallization index showed that the lipid phase in formulated NLC`s remained in crystalline state with RISP solubilized in lipid matrix. Optimized NLC's formulation showed BSA adsorption of 0.75 mg/g lipid.

Present study reveals potential of RISP loaded NLC's as drug delivery system for parenteral administration with prolonged blood circulation time, thus favoring site-specific brain delivery.

INFLUENCE OF THE RELEASE PROPERTIES OF NANOLIPOSOMES ON THE ANTIOXIDANT CAPACITY OF ENCAPSULATED ROSEMARY EXTRACT

Ljubica Mihailova[1], Dushko Shalabalija[1], Ivana Cvetkovikj Karanfilova[2], Maja Simonoska Crcarevska[1], Marija Glavas Dodov[1]

[1]Institute of Pharmaceutical Technology, Ss. Cyril & Methodius University - Faculty of Pharmacy, Skopje [2]Institute of Pharmacognosy, Ss. Cyril & Methodius University - Faculty of Pharmacy, Skopje (Macedonia)

Free radicals induce lipid peroxidation in cell membranes and initiate neuronal dysfunction and death. Therefore, oxidative stress is a cardinal hallmark of neurodegenerative disorders such as Alzheimer's disease (AD). In addition to the numerous effects, Rosemary extract (RE) exhibits an antioxidant activity, considered as a possible source for AD prevention. Within this framework RE loaded NLs were prepared and the correlation between *in vitro* drug release properties and antioxidant potential was examined.

RE loaded NLs (lechitin:cholesterol:PEG = 8.7:1:1.7 and 9:1:0.17 for S1 and S2, respectively) were prepared by modified lipid film hydration technique. RE loading was determined and *in vitro* release from NLs was carried out in phosphate buffer pH 7.4 by previously validated HPLC method. Antioxidant capacity of RE loaded NLs and RE was determined using Oxygen Radical Antioxidant Capacity (ORAC) assay based on the oxidation of a fluorescent probe by peroxyl radicals from 2,2'-Azobis (2-amidinopropane) dihydrochloride. Fluorescence was measured every 30 min (VICTOR, Perkin Elmer, USA) during the examination period of 120 min. All experiments were conducted in triplicate and statistical analysis was done using ANOVA. RE loading, expressed through rosmarinic acid (RA), in NLs was 4.10 - 4.28 mg/100 mg lipid. Obtained drug release profiles pointed that prepared NLs were characterized with controlled release properties (0.55 and 0.99 mg RA released within 120 min for S1 and S2, respectively). RE loaded NLs showed statistically significant higher antioxidant activity (95.03±0.69% and 96.40±0.73% of the initial fluorescence) compared to native RE (90.04±2.51%), probably due to the presence of lecithin in the formulations and their controlled release properties. In this study an efficient *in vitro* antioxidant capacity of RE loaded NLs was confirmed, which may serve as a promising strategy for AD prevention.

PHYTOPHARMACEUTICALS FOR ALZHEIMER'S DISEASE TREATMENT: SALVIA OFF. LOADED NANOSTRUCTURED LIPID CARRIERS

Ljubica Mihailova, Monika Kostovska, Elena Markova, Lea Taneska, Dushko Shalabalija, Marija Glavas Dodov, Maja Simonoska Crcarevska

Institute of Pharmaceutical Technology, Center of Pharmaceutical Nanotechnology, Ss. Cyril & Methodius University - Faculty of Pharmacy, Skopje (Macedonia)

Combining the current knowledge of phytotherapy and pharmaceutics, nanostructured lipid particles (NLC) loaded with freeze dried *Salvia off. L* methanolic extract (FSE) for efficient Alzheimer's disease treatment could be engineered. The aim of the study was to determine the influence of quantity of hydrophilic surfactant upon NLC-FSE physico-chemical and biopharmaceutical properties and their possible correlation with antioxidant activity.

Four samples (S5-S8) of NLC-FSE were prepared by solvent evaporation method. Lipid phase consisted of phospolipon 90H (kindly donated by Phospholipid, Germany) as solid lipid and oleic acid as liquid lipid in ratio of 2.3:1. Total lipids along with FSE were dissolved in ethanol as organic solvent (1:0.11:20, respectively). Aqueous phase was composed of mixed water solution of 0.5% Poloxamer 407 and 1.1% (S5), 2% (S6), 2.8% (S7) and 3.4% (S8) of Tween 80. Ratio of lipid to aqueous phase was 1:2. Physico-chemical and biopharmaceutical properties were determined, as well as antioxidant activity.

Surface morphology, particle size and size distribution, zeta potential and protein-binding properties were discussed elsewhere. Increased quantity of Tween 80 resulted with decreased encapsulation efficiency (79.74%, 62.17%, 48.94% and 47.9% for S5, S6, S7 and S8, accordingly) probably due to the smaller particle size, as well as higher solubilisation of FSE thus promoting its partitioning into the outer water phase. *In vitro* dissolution studies indicated prolonged FSE release for 24 h - 44.98%; 24.17%, 20.52% and 18.77% for S5, S6, S7 and S8, respectively. Comparing the values of correlation coefficient of different kinetics models, the best fit was established for the Peppas and Sahlin model, where values of k1 and k2 indicated dominance of Fickian diffusion and insignificant effect of case II transport. Results of modified ORAC assay indicated that highest antioxidant activity was associated with fastest FSE release.

AMINO-MODIFIED SILICA NANOPARTICLES AS CARRIERS FOR 5-FLUOROURACIL: INFLUENCE OF PREPARATION PROCESS PARAMETERS ON PHYSICO-CHEMICAL PROPERTIES AND DRUG RELEASE

Beti Djurdjic[1], Katerina Goracinova[2,3], Nikola Geskovski[2], Boban Mugosa[4]

[1]Department of Pharmacy, University of Montenegro - Faculty of Medicine (Montenegro), [2]University Ss Cyril and Methodius - Faculty of Pharmacy, Skopje (Macedonia), [3]Qatar University - College of Pharmacy, Doha (Qatar), [4]Institute of Public Health, Podgorica (Montenegro)

The aim of this study was to synthesize amino-functionalized silica nanoparticles as systems for controlled release of 5-fluorouracil (5-FU) as well as to investigate the effects of the process parameters upon the particle size, drug encapsulation efficacy and drug release.

Silica nanoparticles were synthesized by sol-gel method at room (samples S1 and S2) and elevated temperature (45°C) (S3 and S4). The molar ratio (mmol) of the silica sol components was tetraethyl-orthosilicate: 3-aminopropyltriethoxysilane : ethanol : water : acetic acid= 4.433 : 0.0427 : 428 : 611 : 8.735. 5-Fluorouracil was added to the silica sol at the start of hydrolysis process (S1 and S3) and during the synthesis of polymeric matrix (S2 and S4). Prepared samples were characterized in terms of mean particle size and drug loading efficiency. In vitro drug release studies at different pH values (pH 1.2 and 7.4) were performed.

The mean particle size of nanoparticles was 418, 652, 144 and 207 nm for S1, S2, S3 and S4, respectively. Encapsulation efficacy and drug content of samples were 24.57% and 1.08 (S1), 29.70% and 1.50 (S2), 56.68% and 3.89 (S3) and 44.10% and 2.04 μg 5-FU/mg nanoparticles (S4). The experimental results suggest that the temperature increase during the synthesis will result in production of smaller particles with higher drug loading efficiency. Also, higher 5-FU loading was observed when the active substance was added at the start of hydrolysis process. Dissolution studies revealed similar pH dependent drug release behavior (faster release rate at pH 7.4) in all prepared formulations, starting with an initial burst release phase which was followed by controlled release of the encapsulated drug. The investigated sol-gel process parameters can affect the critical formulation attributes and should be considered as significant factors in further optimization studies.

COMPARATIVE DRUG RELEASE STUDIES OF OXALIPLATIN LOADED ORMOSIL NANOPARTICLES

Beti Djurdjic[1], Katerina Goracinova[2,3], Nikola Geskovski[2], Boban Mugosa[4]

[1]Department of Pharmacy, University of Montenegro - Faculty of Medicine (Montenegro), [2]University Ss Cyril and Methodius - Faculty of Pharmacy, Skopje (Macedonia), [3]Qatar University - College of Pharmacy, Doha (Qatar), [4]Institute of Public Health, Podgorica (Montenegro)

The main purpose of this research was to prepare oxaliplatin-loaded ORMOSIL nanoparticles with two different methods, and investigate their influence on the drug release behavior.

ORMOSIL nanoparticles were prepared at elevated temperature by one-step acid-catalyzed hydrolysis using two different approaches: the addition of tetraethyl-orthosilicate and 3-aminopropyltriethoxysilane together at the beginning of the hydrolysis process (co-condensation method) (formulation F1) or with post-modification (adding 3-aminopropyltriethoxysilane in hydrolised silica sol) (formulation F2). Nanoparticles size and drug loading were determined and drug release studies under different pH conditions (0.1M HCl pH 1.2 and phosphate buffer pH 7.4) were performed. Kinetic parameters were obtained by mathematical processing of the drug release data with DDSolver using different models (zero-order, first-order, Higuchi, Korsmeyer-Peppas).

The particle size distribution of the prepared nanoparticles appeared as unimodal with average particle sizes 151 nm (F1) and 163 nm (F2). The content of oxaliplatin was 1.53 μg/mg (35.78 EE%) for F1 and 3.42 μg/mg nanoparticles (53.17 EE%) for F2. The different methods of organic modification resulted in production of nanoparticles with different matrix structure, hydrophilicity and porosity. The formulation prepared with co-condensation method presented lower encapsulation efficiency and faster release rate of oxaliplatin, relative to the formulation produced using post-modification method. The drug release data showed the best fit to Korsmeyer-Peppas equation: r^2 were 0.9932 and 0.9892 (F1) and 0.9865 and 0.9870 (F2) at pH 1.2 and pH 7.4, respectively. Obtained n values for samples F1 (0.291 and 0.230) and samples F2 (0.249 and 0.076) at pH 1.2 and 7.4, respectively pointed to diffusion governed drug release from porous material. Our study demonstrated that the preparation method could affect the internal structure of the ORMOSIL nanoparticles resulting in significant differences in the encapsulation efficiency and release rate of oxaliplatin.

PRELIMINARNO PRAĆENJE FIZIČKE STABILNOSTI NANOSUSPENZIJA KURKUMINA DOBIJENIH *TOP-DOWN* METODOM

Milica Todorović, Ines Nikolić, Jelena Đoković, Snežana Savić

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Uprkos brojnim prednostima nanosuspenzija, nanometarska veličina čestica dovodi do povećanja slobodne površinske energije, koje je izvor inheretne fizičke nestabilnosti sistema. Kako bi se ovo preveniralo, koriste se različiti stabilizatori (polimeri, surfaktanti ili njihove kombinacije). Međutim, upotreba surfaktanata se povezuje sa brojnim problemima (narušavanje kristalne rešetke, kompatibilnost sa predviđenim putem primene…). Stoga je cilj ovog rada preliminarno ispitivanje stabilizacionog potencijala odabranih ekscipijenasa u formulaciji nanosuspenzija sa kurkuminom (CUR) kao model aktivnom supstancom (niska rastvorljivost i permeabilnost).

Primarna disperzija je dobijena dispergovanjem kurkumina i stabilizatora (polisorbat 80 i Poloksamer 188 (1:1 m/m) ili PVP K25 ili PVP K30) u visokoprečišćenoj vodi uz pomoć rotor-stator homogenizatora (*Ultra-Turrax T25*). Gruba disperzija je potom preneta u mikrotube sa kuglicama cirkonijum-oksida (medijum za usitnjavanje). Dalje smanjenje veličine čestica je postignuto uz pomoć ćelijskog disraptora (*Disruptor Genie*). Veličina i polidisperzni indeks (PDI) čestica su određeni metodom foton korelacione spektroskopije (*Zetasizer Nano ZS90*), pri čemu su merenja vršena 24 h, 7 i 30 dana nakon izrade nanosuspenzije.

Nakon celokupnog perioda praćenja, nanosuspenzije sa odnosom CUR i stabilizatora 2,5:1 (m/m) nisu pokazale statistički značajno povećanje veličine čestica i promenu PDI (*Repeated measures ANOVA, IBM SPSS statistics 23*). Dobijeni opseg veličina čestica se kreće od 129,5 do 191,3 nm, a PDI između 0,155 i 0,263. U kombinaciji polisorbata 80 i Poloksamera 188 su dobijene čestice najmanje veličine (129,5 – 148,6 nm), dok su kod nanosuspenzija stabilizovanih povidonima dobijene znatno veće čestice (162 – 171,9 nm, PVP K30, odnosno 177,6 – 191,3 nm PVP K25) uz niže vrednosti PDI (0,15 - 0,25) pri identičnim uslovima mlevenja (broj i dužina trajanja ciklusa).

Pored odnosa CUR/stabilizator i uticaja mehaničkog stresa, pokazano je da na veličinu i distribuciju veličine čestica utiče i tip stabilizatora. Dalja ispitivanja će pokazati da li je došlo do izmena u kristalnoj strukturi tokom mlevenja i eventualni uticaj polimera na takve pojave.

PRELIMINARY MONITORING OF CURCUMIN NANOSUSPENSION PHYSICAL STABILITY PRODUCED BY TOP-DOWN METHOD

Milica Todorović, Ines Nikolić, Jelena Đoković, Snežana Savić

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Despite the advantages of nanosuspensions, particle nanonisation leads to significant increase of free superficial energy, which is intrinsic source of system instability. To prevent this, different stabilizers are used. However, the use of surfactants is related to various issues (crystal structure deterioration, route of administration compatibility…). The aim of this paper is preliminary stability screening of curcumin (CUR, low solubility and permeability) nanosuspensions formulated with different excipients.

The primary dispersion was obtained by dispersing curcumin and stabilizers (polysorbate 80 and Poloxamer 188 (1:1 m/m) or PVP K25 or PVP K30) in highly purified water by using rotor-stator homogenizer (Ultra-Turrax T25). The coarse dispersion was transferred into microtubes with zirconia-oxide beads (milling medium). The further diminution of particles was accomplished by cell disruptor (Disruptor Genie). Size and PDI were determined by photon correlation spectroscopy (Zetasizer Nano ZS90) 24h, seven and thirty days after nanosuspension preparation.

Throughout the whole monitoring period, nanosuspensions with CUR to stabilizer ratio 2.5:1 (m/m) did not show the statistically significant increase in particle size and changes in PDI (Repeated measures ANOVA, IBM SPSS statistics 23). Obtained particle size range was from 129.5 to 191.3 nm, with PDI between 0.155 and 0.263. Nanosuspension with a mixture of Polysorbate 80 and Poloxamer 188 as a stabilizer showed the smallest particle size (129.5 – 148.6 nm) in comparison with other nanosuspensions. PVP K30 and PVP K25 showed significantly larger particle size (162 – 171.9 nm and 177.6 – 191.3 nm, respectively), but with smaller PDI values (0.15-0.25) under identical grinding conditions (number/duration of the cycles).

Besides CUR/stabilizer ratio and mechanical stress, these results may indicate that particle size and distribution may be affected by stabilizer type. Further studies will show whether there have been changes in the crystalline structure during grinding and the possible impact of the stabilizer on such occurrences.

NANOSTRUKTURIRANE LIPIDNE NANOČESTICE KAO POTENCIJALNI NOSAČI DK-I-60-3: PREFORMULACIONA I FORMULACIONA ISTRAŽIVANJA

Jelena Mitrović[1], Jelena Đoković[1], Vladimir Dobričić[2], Bojan Čalija[1], Predrag Vulić[3], Miroslav Savić[4], Snežana Savić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za farmaceutsku hemiju, Univerzitet u Beogradu – Farmaceutski fakultet, [3]Katedra za mineralogiju, Univerzitet u Beogradu – Rudarsko-geološki fakultet, [4]Katedra za farmakologiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija)

Pirazolohinoloni, ligandi za GABAa receptore, proučavaju se za terapiju neuropsihijatrijskih oboljenja. Za isporuku u mozak slabo rastvorljivih lekovitih supstanci intenzivno se razvijaju lipidne nanočestice. Cilj istraživanja je ispitivanje rastvorljivosti DK-I-60-3 u tečnim i čvrstim lipidima i izrada nanostrukturiranih lipidnih nosača (NLC) homogenizacijom pod visokim pritiskom.

Rastvorljivost DK-I-60-3 u uljima određivana je *shake-flask* metodom i analizirana LC-MS/MS metodom. Smeše Softisan 154 i triglicerida srednje dužine lanca (MCT) (1:4, 2:3, 1:1, 3:2, 3:7, 4:1) i Softisan 154, MCT i DK-I-60-3 sa različitim odnosima čvrstog i tečnog lipida (3:2, 3:7) i udelom DK-I-60-3 (1%, 5%) analizirane su diferencijalnom skenirajućom kalorimetrijom (DSC) i difrakcijom X-zraka. Formulacije NLC sa 10% lipidne faze (čvrst:tečan lipid 1:1, 3:2, 3:7) stabilizovane polisorbatom 80 (2%) izrađene su homogenizacijom pod visokim pritiskom (60°C, 10 ciklusa). Uzorkovanja su vršena nakon svakog ciklusa homogenizacije. Nakon izrade određivani su veličina čestica (Z-ave) i indeks polidisperznosti (PDI). U cilju ispitivanja uticaja procesnih parametara na Z-ave i PDI varirani su pritisak homogenizacije (500 i 800 bar) i hlađenje nakon homogenizacije (sobna temperatura i ledeno kupatilo).

DK-I-60-3 je slabo rastvorljiv u uljima (MCT 0,046 mg/ml, sojino ulje 0,048 mg/ml, ricinusovo ulje 1,244 mg/ml). Ipak, DSC rezultati ukazuju na delimičnu solubilizaciju DK-I-60-3 u smešama lipida, dok su temperature topljenja svih ispitivanih smeša ostale iznad 40°C. Izrađene NLC su bile tečne, mlečno bele, sa plavičastim odsjajem. Formulacije izrađene pod višim pritiskom i hlađene na sobnoj temperaturi imale su niže Z-ave. Veličina čestica se povećavala sa povećanjem udela ulja u lipidnom matriksu. Nakon 5 ciklusa homogenizacije sve formulacije su imale Z-ave 180-210 nm i PDI 0,100-0,161, a daljom homogenizacijom nisu se značajno menjali ovi parametri.

NLC se mogu proučavati kao nosači DK-I-60-3 i homogenizacijom pod visokim pritiskom (60°C, 800 bar, 5 ciklusa) mogu se dobiti NLC zadovoljavajućih fizičkohemijskih karakteristika.

NANOSTRUCTURED LIPID NANOPARTICLES AS POTENTIAL CARRIERS FOR DK-I-60-3: PREFORMULATION AND FORMULATION STUDIES

Jelena Mitrović[1], Jelena Đoković[1], Vladimir Dobričić[2], Bojan Čalija[1], Predrag Vulić[3], Miroslav Savić[4], Snežana Savić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department of Pharmaceutical Chemistry, University of Beograde – Faculty of Pharmacy, [3]Chair of Mineralogy, University of Beograde – Faculty of Mining and Geology, [4]Department of Pharmacology, University of Beograde – Faculty of Pharmacy (Serbia)

Pyrazoloquinolinones, GABAa receptor ligands, are investigated for neuropsychiatric disorders treatment. For brain delivery of poorly soluble actives, lipid nanoparticles are intensively developed. The aim was DK-I-60-3 solubility testing in liquid and solid lipids and nanostructured lipid carriers (NLC) preparation by high pressure homogenization.

DK-I-60-3 solubility in oils was investigated by shake-flask method and analyzed by LC-MS/MS method. Mixtures of Softisan 154 and medium chain triglycerides (MCT) (1:4, 2:3, 1:1, 3:2, 3:7, 4:1) and Softisan 154, MCT and DK-I-60-3 with different solid:liquid lipid ratio (3:2, 3:7) and DK-I-60-3 content (1%, 5%) were analyzed by differential scanning calorimetry (DSC) and X-ray diffraction. NLC with 10% lipid phase (solid:liquid lipid ratio 1:1, 3:2 i 3:7), stabilized by polysorbate 80 (2%) were prepared by high pressure homogenization (60°C, 10 cycles). Samples were taken after every homogenization cycle. Afterwards particle size (Z-ave) and polydispersity index (PDI) were determined. In order to investigate process parameters influence on Z-ave and PDI, homogenization pressure (500 and 800 bar) and cooling after homogenization (room temperature and ice bath) were varied.

DK-I-60-3 is poorly soluble in oils (MCT 0.046 mg/ml, Soybean oil 0.048 mg/ml, Castor oil 1.244 mg/ml). However, DSC results indicate partial solubilization of DK-I-60-3 in lipid mixtures, while melting temperature of all investigated mixtures remained above 40°C. After preparation, NLC were liquid, milky-white, with bluish reflection. Formulations prepared under higher pressure and cooled at room temperature had lower Z-ave. Particle size was increased by increasing the oil content in lipid matrix. After 5 homogenization cycles, all formulations had Z-ave 180-210 nm and PDI 0.100-0.161, further homogenization didn't significantly change these parameters.

NLC could be investigated as carriers for DK-I-60-3 and by high pressure homogenization (60°C, 800 bar, 5 cycles) NLC with satisfying physicochemical characteristics could be obtained.

PEG-ILOVANE NANOEMULZIJE: UTICAJ INKORPORACIJE KURKUMINA I IZBORA PROCESA STERILIZACIJE NA FIZIČKO-HEMIJSKE PERFORMANSE

Jelena Đoković[1], Sanela Savić[2], Jelena Mitrović[1], Dorota Watrobska-Swietlikowska[3], Snežana Savić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]DCP Hemigal, Leskovac (Srbija), [3]Katedra za farmaceutsku tehnologiju, Medicinski Univerzitet u Gdanjsku (Poljska)

U cilju povećanja rastvorljivosti i biološke raspoloživosti kurkumina (K), razvijene su nanoemulzije sa kurkuminom (KNE). PEG-ilovani fosfolipidi (PEG-FL) su dodati radi produženja vremena cirkulacije nanoemulzionih (NE) kapi. Cilj ove studije je procena uticaja dodavanja kurkumina u formulaciju i procesa sterilizacije - autoklaviranja ili aseptične filtracije na fizičkohemijske karakteristike (veličinu kapi i zeta potencijal) NE, PEG-ilovanih i ne-PEG-ilovanih.

NE su pripremljene metodom homogenizacije pod visokim pritiskom na 50°C. Masna faza (sojino ulje, benzil alkohol, trigliceridi srednje dužine lanca, lecitin soje i butilhidroksitoluen) je dodata u vodenu fazu (glicerol, polisorbat 80, natrijum oleat i visoko prečišćena voda) i homogenizovana na homogenizatoru pod visokim pritiskom 10 ciklusa na 800 bara (EmulsiFlex-C3, Avestin Inc., Canada). PEG-FL: PEG2000-DSPE/PEG5000-DPPE, su dodati u masnu ili u vodenu fazu u koncentraciji od 0,1%/0,3%. Kod KNE, K je prvo rastvoren u benzil alkoholu, a potom dodat u masnu fazu. Nakon izrade sve NE su bile filtrirane kroz membranski filter dimenzija pora 0,22 μm, a placebo nanoemulzije (bez kurkumina) su bile autoklavirane (121°C; 15 min). Izmerena je veličina kapi (Z-Ave, d10, d50, d100), indeks polidisperznosti (PDI) i zeta potencijal.

Veličina kapi (Z-Ave) svih nanoemulzija je bila od 101 do 108 nm, što je potvrđeno laserskom difrakcijom- vrednost d50 za sve formulacije se nalazila u opsegu od 105 do 113 nm. Nije uočeno prisustvo većih kapi. PDI je bio manji od 0,15, a zeta potencijal niži od -40 mV, što dokazuje da su sve razvijene NE pogodne za parenteralnu primenu.

Merenja veličine kapi i zeta potencijala su pokazala da ne postoji značajna razlika između PEG-ilovanih i ne PEG-ilovanih NE bilo da sadrže kurkumin ili ne, da li su autoklavirane, filtrirane ili nesterilisane, što znači da PEG-ilovane nanoemulzije mogu da budu sterilisane ili/i im se može dodati kurkumin bez narušavanja fizičko-hemijske stabilnosti sistema.

PEG-YLATED NANOEMULSIONS: CURCUMIN LOADING AND STERILIZATION PROCESS IMPACT ON PHYSICOCHEMICAL PERFORMANCE

Jelena Đoković[1], Sanela Savić[2], Jelena Mitrović[1], Dorota Watrobska-Swietlikowska[3], Snežana Savić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]DCP Hemigal, Leskovac (Serbia), [3]Department of Pharmaceutical Technology, Medical University of Gdansk (Poland)

In order to increase solubility and bioavaibility of curcumin (C), C-loaded nanoemulsions (CNEs) were developed. PEG-ylated phospholipids (PEG-PLs) were added to prolong the circulation time of nanoemulsion (NE) droplets. The aim of this study was to assess the impact of C-loading and sterilization process - autoclaving or aseptic filtration on the NEs physicochemical characteristics (droplet size and zeta potential), both PEG-ylated and non-PEG-ylated.

NEs were prepared by high pressure homogenization method at 50°C. Oil phase (soybean oil, benzyl alcohol, medium chain triglycerides, soybean lecithin and butylhydroxytoluene) was added to water phase (glycerol, polysorbate 80, sodium oleate and highly purified water) and homogenized with high-pressure homogenizer (EmulsiFlex-C3, Avestin Inc., Canada) for 10 cycles at 800 bar. PEG-PLs – PEG2000-DSPE/PEG5000-DPPE, were added to the oil or water phase at 0,1%/0,3% concentration. For CNEs, C was first dissolved in benzyl alcohol, and then added into oil phase. After preparation, all NEs were filtered through 0,22 μm membrane filter and placebo nanoemulsions – without curcumin were autoclaved (121°C; 15 min). NE droplet size (Z-Ave, d10, d50, d100), polydispersity index (PDI) and zeta potential were measured.

Mean droplet size (Z-Ave) of all NEs (C-loaded and placebo, non-sterilized, autoclaved and filtered) was in the range of 101–108 nm, confirmed by laser diffraction measurements - d50 values for all formulations was between 105 and 113 nm. No larger droplets were detected. PDI was below 0.15 and ZP below - 40 mV, suggesting that all developed NEs were suitable for parenteral use.

Droplets size/PDI and zeta potential measurements showed no significant difference between PEG-ylated and non-PEG-ylated NEs, both with and without curcumin, autoclaved, filtered or non-sterilized, which means that PEG-ylated NEs can be sterilized and/or curcumin loaded without compromising physicochemical stability of the system.

ISPITIVANJE UTICAJA LEVANA NA LIBERACIONE I SENZORNE PROFILE LEKOVA ZA PRIMENU NA KOŽI

Ivana Pantelić[1], Milica Lukić[1], Gordana Gojgić-Cvijović[2], Snežana Savić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Centar za hemiju, IHTM, Univerzitet u Beogradu (Srbija)

Od savremenih farmaceutskih ekscipijenasa sve češće se očekuje da daju i izvestan doprinos poboljšanju adherence. Egzopolisaharidi poput levana predstavljaju obećavajuću grupu materijala prirodnog porekla, sa brojnim anticipiranim ulogama od kojih se najčešće ističe stvaranje kontinuiranog filma na mestu nanošenja, koji bi omogućio manje čestu primenu leka, pa sledstveno i bolju adherencu. Ipak, uticaj ovog složenog fruktana na senzorne karakteristike lekova još uvek nije razmatran.

Primenom imerzionih ćelija ispitan je uticaj dodatka levana velike molekulske mase na profile oslobađanja ketoprofena i diklofenak-dietilamina, kao model lekova različitih karakteristika (rastvorljivost, amfifilnost, termodinamička aktivnost). Dodatak levana u emulzione sisteme variran je na 4 nivoa (0/0,2/1/3% m/m), uz istovremenu varijaciju vrste primarnog stabilizatora sistema (nejonski/anjonski). Uz to sprovedena je i preliminarna senzorna analiza uzoraka sa 0,2% levana u poređenju sa uzorcima bez levana i uzorcima u kojima je levan zamenjen ksantan gumom.

Preliminarni skrining fizičko-hemijskih osobina levana potvrdio je neutralnu prirodu ovog biopolimera, koga ne odlikuje sposobnost bubrenja prilikom obrazovanja veoma tankog filma na površini kože. Izračunavanje saturacionih koncentracija model lekova u ispitivanim uzorcima pokazalo je da je inicijalna koncentracija leka u filmu mnogo veća od njegove rastvorljivosti u podlozi. Na taj način potvrđeni su osnovni preduslovi za primenu Higučijeve jednačine kao prihvaćenog pokazatelja kontrolisane isporuke lekovitih supstanci iz polučvrstih preparata za primenu na koži. Uporedna analiza vrednosti fluksa i kumulativne količine oslobođenog leka ukazala je na različite optimalne koncentracije levana shodno prirodi osnovnog stabilizatora sistema: 1% levana u slučaju anjonskog, a 0,2% u slučaju nejonskog mešanog emulgatora. Osim blagog uticaja na boju uzoraka, dodatak levana nije značajno uticao na njihov inicijalni senzorni profil. Od posebnog značaja je izostanak uticaja levana na lepljivost uzorka, što je poznat nedostatak primene ksantan gume.

Dobijeni rezultati ukazuju na potencijal primene levana kao multifunkcionalnog ekscipijensa sa direktnim uticajem na poboljšanje adherence kod lekova za primenu na koži.

INVESTIGATION OF LEVAN'S INFLUENCE ON RELEASE AND SENSORY PROFILES OF TOPICAL DRUGS

Ivana Pantelić[1], Milica Lukić[1], Gordana Gojgić-Cvijović[2], Snežana Savić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department of Chemistry, IHTM, University of Belgrade (Serbia)

Apart from their basic function(s), novel pharmaceutical excipients should preferably also improve adherence. Exopolysaccharides such as levan represent a promising group of natural-origin materials, with numerous anticipated functions. Among those, their film-forming capacity is usually stressed, since it could enable less frequent drug application and, hence, better adherence. However, the influence of this complex fructan on sensory characteristics of topical drugs has not been addressed yet.

Immersion cells were used to assess the influence of high-molecular levan on ketoprofen and diclofenac-diethylamine release profiles, being model drugs of diverse properties (solubility, amphiphilicity, thermodynamic activity). The addition of levan to emulsion systems was varied in 4 levels (0/0.2/1/3% m/m), with alteration of the primary system stabilizer type (non-ionic/anionic). Additionally, a preliminary sensory study of samples with and without 0.2% levan was performed, and compared to corresponding xanthan gum samples.

Preliminary screening of levan's physicochemical properties confirmed the neutral nature of this biopolymer, with no swelling phase while generating a very thin film. Saturation concentrations of the model drugs in the investigated samples showed that the initial drug concentration in the film is much higher than drug solubility in the base. Thus, fundamental prerequisites for the application of the Higuchi equation were met, allowing for the quantification of the controlled drug release. Comparative analysis of flux and cumulative amounts of drug released indicated different optimal levan concentrations relative to the nature of the primary system stabilizer: 1% levan for anionic, and 0.2% for non-ionic mixed emulsifier. Apart from a slight influence on the samples' colour, the addition of levan did not significantly change their initial sensory profile. The absence of levan's contribution to sample stickiness was of special importance, since this is a known drawback of xanthan gum.The obtained results reveal the potential use of levan as a multifunctional excipient with direct influence on improving adherence to topical drugs.

ISPITIVANJE UTICAJA LEVANA KAO POTENCIJALNOG MULTIFUNKCIONALNOG EKSCIPIJENSA NA PROFIL OSLOBAĐANJA SALICILNE KISELINE IZ EMULZIONOG SISTEMA TIPA KREMA

Milica Lukić, Ines Nikolić, Ivana Pantelić, Snežana Savić

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

U skladu sa aktuelnim ispitivanjima mogućnosti primene sirovina prirodnog porekla kao multifunkcionalnih sastojaka u razvoju farmaceutskih i kozmetičkih nosača, posebnu pažnju brojnih istraživača privlači levan. Ovaj biopolisaharid interesantan je i kao aktivna supstanca i kao funkcionalni ekscipijens/kozmetički sastojak. Sa ciljem da se upotpune naša prethodna istraživanja, u ovoj studiji ispitivali smo uticaj prisustva levana na profile oslobađanja salicilne kiseline (SK) iz kremova koji su stabilizovani tečno-kristalnim lamelarnim fazama.

Izrađena su 4 uzorka krema: placebo, krem sa 1% levana, krem sa 2% SK i krem sa 2% SK i 1% levana. Pored inicijalne fizičko-hemijske karakterizacije primenom polarizacione mikroskopije i merenja pH, provodljivosti i kontinualnog reološkog ponašanja, sprovedeno je i in vitro ispitivanje liberacionih profila SK, primenom dva tipa difuzionih ćelija: Franz-ova i VanKel-ova imerziona ćelija.

Dodatak levana i SK nije uticao na specifičnu strukturu krema. Sam levan nije značajno uticao na promenu pH vrednosti i provodljivosti ni placeba ni krema sa SK, ali je povećao njihove viskozitete i histerezne površine. Liberacioni profili kremova sa SK nezavisno od prisustva levana prate Higuchi-evu kinetiku oslobađanja, ali se SK u prisustvu levana otpušta postepeno, beležeći manje vrednosti permeacionog koeficijenta (189 g/cm^2/h i 201 g/cm^2/h). Iako je činjenica da ugušćivanje sistema za posledicu ima sporije oslobađanje aktivne supstance, za tačno razumevanje uticaja prisutnog levana na brzinu oslobađanja neophodna su dodatna istraživanja vezana za njegov doprinos specifičnoj strukturi.

Kroz sprovedeni set eksperimenata pokazano je da levan ne samo da utiče na stabilizaciju i aplikativna svojstva razvijenih kremova, već može modifikovati kinetiku oslobađanja model supstance. To ga zajedno sa njegovim prirodnim poreklom i biodegradabilnošću čini atraktivnim multifunkcionalnim ekscipijensom.

LEVAN AS MULTIFUNCTIONAL INGREDIENT AND ITS INFLUENCE ON LIBERATION PROFILE OF SALICYLIC ACID FROM EMULSION SYSTEM OF CREAM TYPE

Milica Lukić, Ines Nikolić, Ivana Pantelić, Snežana Savić

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

In accordance with the actual investigations related to the use of substances with natural origin as multifunctional ingredients in development of pharmaceutical or cosmetic vehicles, levan is gaining special attention. This biopolysaccharide is interesting as an active substance as well as the functional excipient/cosmetic ingredient. In this study we have investigated the influence of levan on liberation profiles of salicylic acid (SA) which was incorporated in creams stabilized with the specific liquid-crystalline lamellar phases.

Four cream samples were prepared: placebo sample, cream with 1% of levan, cream with 2% of SA and cream with 2% of SA and 1% of levan. Beside the physical-chemical characterization performed using polarization microscopy, pH and conductivity measurements and continual rheology, in vitro screening of model drugs liberation profiles was performed with the use of two types of diffusion cells: Franz and VanKel immersion cell.

Addition of levan and SA did not alter the specific structure of placebo sample. Although levan did not significantly influence the pH and conductivity values of placebo and cream with SA, it did induce an increase in viscosity and hysteresis areas of both creams. Liberation profiles of creams with SA, regardless to the levan presence, follow the Higuchi liberation kinetics. But, with the levan in cream the release of SA was retarded, and obtained permeation coefficients were lower compared to cream without levan (189 $g/cm^2/h$ and 201 $g/cm^2/h$). Although thickening induces retarded liberation of an active substance, additional investigation regarding the influence of levan on the specific system's structure is necessary.

Through the preformed set of experiments it was shown that levan can be used as stabilizer and rheology modifier of developed creams, but it also can modify the liberation kinetic of the model substance. This makes levan, together with its natural origin and biodegradability, an attractive multifunctional excipient.

NISKOENERGETSKE NANOEMULZIJE SA ULJEM SEMENKI MALINE I ANTIOKSIDANTNIM EKSTRAKTIMA – OPTIMIZACIJA FORMULACIJE, STUKTURNA I REOLOŠKA ISPITIVANJA

Ana Gledović[1], Veljko Krstonošić[2], Ines Nikolić[1], Danijela Ranđelović[3], Jelena Đoković[1], Sanela Savić[4], Snežana Savić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za farmaciju, Univerzitet u Novom Sadu - Medicinski fakultet, [3]Centar za mikroelektronske tehnologije - ICTM, Univerzitet u Beogradu, [4]DCP Hemigal, Leskovac (Srbija)

Plod maline je bogat izvor kozmetički aktivnih sastojaka: ulje semenki maline (RO) poznato je po visokoj zastupljenosti polinezasićenih masnih kiselina, tokoferola i tokotrienola, a ekstrakt ploda maline sadrži antioksidanse (tanine, vitamin C) i šećere. Niskoenergetske nanoemulzije (NE) formulisane su u cilju očuvanja stabilnosti i aktivnosti prirodnih sastojaka upotrebom metode inverzije faza (EPI) na sobnoj temperaturi. Takođe, izvršena je i karakterizacija tranzicione gel faze kao kritične međufaze u procesu nastanka NE.

NE su izrađene titracijom različitih smeša polisorbata 80 – surfaktant, tokoferil acetata – kostabilizator i organskog RO (hladno ceđeno ulje ili CO_2 ekstrakt) vodenom fazom sa dodatim kosurfaktantima (glicerol ili vodeno-glikolni ekstrakt ploda maline/ francuskog hrasta). Karakterizacija prelaznih gel faza izvršena je vizuelno, polarizacionim (PLM) i optičkim mikroskopom (OM), merenjem provodljivosti i oscilatornim reološkim merenjima. Odgovarajuće NE okarakterisane su vizuelno, merenjem veličine kapi i polidisperznog indeksa (PDI) upotrebom foton korelacione sprektroskopije (PCS) i laserske difrakcije (LD), PLM i OM, mikroskopijom atomskih sila (AFM), merenjem pH vrednosti i provodljivosti kao i kontinualnim reološkim merenjima.

PLM i OM mikroskopija potvrdile su prisustvo izotropne gel međufaze, a viskoelastični parametri (G', G'', kompleksni viskozitet) istovremeno ukazuju na kubnu tečno-kristalnu strukturu gela; odgovarajuće NE nastale iz ovih gel faza ponašaju se kao Njutnovske tečnosti. Iako su NE imale poželjnu veličinu kapi (130 do 150 nm i PDI ≤ 0.1) PLM i OM su detektovale velike aglomerate (do 20 μm) u NE sa RO CO_2 dok su NE sa hladno ceđenim RO imale poneki aglomerat (do 2 μm). AFM je pokazala razliku u topografiji i veličinama uljanih kapi NE izrađenih sa različitim RO i otkrila je da su kapi nepravilnog oblika.

Različite mikroskopske tehnike su pokazale da je izbor sirovina (tipa ulja maline) od ključnog značaja za dobijanje stabilnih NE odgovarajućih karakteristika. Reološka ispitivanja poslužila su u rasvetljavanju strukture veoma viskozne kubne gel faze.

LOW ENERGY NANOEMULSIONS WITH RED RASPBERRY SEED OIL AND ANTIOXIDANT EXTRACTS – FORMULATION OPTIMIZATION, STRUCTURAL AND RHEOLOGICAL INVESTIGATIONS

Ana Gledović[1], Veljko Krstonošić[2], Ines Nikolić[1], Danijela Ranđelović[3], Jelena Đoković[1], Sanela Savić[4], Snežana Savić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department of Pharmacy, University of Novi Sad - Faculty of Medicine, [3]Institute of Microelectronic Technologies - ICTM, University of Belgrade, [4]DCP Hemigal, Leskovac (Serbia)

Red raspberry fruit is a rich source of valuable cosmetic actives: seed oil (RO) is known for high content of polyunsaturated fatty acids, tocopherols and tocotrienols, while fruit extract contains antioxidants (tannins, vitamin C) and sugars. In order to keep the stability and activity of natural ingredients we developed low energy nanoemulsions (LE NEs) by using Emulsion Phase Inversion (EPI) method at room temperature. We also characterized transient gel phase as crucial phase in NE formation process.

NEs were prepared by titrating different mixtures of Polysorbate 80 – surfactant, Tocopheryl acetate – co-stabilizer and organic RO (cold pressed or CO_2 extract) with the water phase (with cosurfactants: glycerol, or hydro-glycolic raspberry fruit/ French oak fruit extracts). Transient gel phases were characterized visually, by polarized light (PLM) and optical microscopy (OM), conductivity and oscillatory rheological measurements. The corresponding NEs were characterized visually;droplet size and polydispersity index (PDI) were measured by photon correlation spectroscopy (PCS) and laser diffraction (LD), PLM and OM, atomic force microscopy (AFM), pH, conductivity, and continual rheological measurements.

Microscopy (PLM, OM) confirmed the presence of isotropic gel phase while viscoelastic parameters (G', G'', complex viscosity) also indicate cubic liquid crystalline gel structure; the corresponding NEs have flow characteristics of Newtonian fluids. Although NEs had droplet sizes from 130 to 150 nm and PDI values ≤ 0.1, PLM and OM detected large agglomerates (up to 20 μm) in NEs prepared with RO CO_2, while NEs with RO cold pressed had a few agglomerates (up to 2 μm). AFM showed the difference in topography and sizes of oil droplets in NEs prepared with different RO and revealed their non-spherical shape.

Different microscopic techniques revealed that raspberry oil type had crucial impact on NE properties and stability. Rheological investigations were useful to elucidate the structure of very viscous cubic gel phase.

RASTVORLJIVE MIKROIGLE – FIZIČKI INHENSERI DERMALNE ISPORUKE ANTIFUNGALNOG LIJEKA

Nataša Bubić Pajić[1], Sonja Vučen[2], Snežana Savić[3]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Banjoj Luci - Medicinski fakultet (Bosna i Hercegovina), [2]Farmaceutski fakultet - Univerzitet u Korku (Irska), [3]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Efikasnost terapije gljivičnih infekcija kože zavisi od potencijala formulacije da isporuči efektivnu količinu lijeka u dublje slojeve kože, naročito u vijabilni epidermis. Rastvorljive mikroigle, kao fizički inhenseri penetracije, omogućuju isporuku lijeka ili formulacije aktivne supstance direktno u/kroz kožu. Cilj ovog rada je formulacija rastvorljivih mikroigala zasnovanih na niskomolekularnom polivinilpirolidonu (Kollidon 17PF), kao nosača za dermalnu isporuku antifungalnog lijeka - sertakonazol-nitrata.

Izrada je vršena metodom punjenja silikonskih kalupa (na kojima je niz od 25 mikroigala visine 500 μm na 1 cm^2) tečnom formulacijom nakon čega su kalupi stavljani u vakuum. Kalupi koji su korišteni za dobijanje rastvorljivih mikroigala bili su izrađeni od polidimetilsiloksana u Nacionalnom Institutu Tyndall (Irska). U cilju utvrđivanja optimalnih uslova za fabrikaciju punih nizova rastvorljivih mikroigala varirana je koncentracija polimera (5, 10, 20 i 30% m/V) i lijeka (5, 25 ili 66,7 mg/ml). Pomoću svjetlosnog mikroskopa su analizirane morfološke karakteristike (fizički integritet, oblik i izgled) dobijenih rastvorljivih mikroigala i izvršena je njihova evaluacija. Odabrana formulacija je podvrgnuta testiranju mehaničke otpornosti i brzine rastvaranja.

Nizovi mikroigala zadovoljavajućeg kvaliteta su dobijeni kada se kao polazni materijal koristi lijek u koncentraciji 25 mg/ml, rastvoren u 30% (m/V) rastvoru povidona u metanolu. Zbog prisustva metanola u formulaciji, kritičan parametar u izradi je očekavano bio način sušenja mikroigala. Dobijene mikroigle su bile pune, pravilnog piramidalnog oblika, oštrih vrhova i pravilnih baza. Mehanička otpornost nizova mikroigala (4,5±0,1 N) je bila zadovoljavajuća za očekivanu inserciju u kožu. Takođe je pokazano da se dobijene mikroigle rastvaraju u potpunosti u ispitivanom medijumu nakon 5 min.

Dobijeni rezultati ukazuju da formulisane rastvorljive mikroigle mogu da se fabrikuju i koriste kao pogodan nosač za brzu isporuku sertakonazol-nitrata u kožu. Međutim, odgovarajućim *ex vivo* i *in vivo* ispitivanjima na koži je potrebno potvrditi da je lijek isporučen u ciljano mjesto u koži.

DISSOLVABLE MICRONEEDLES – PHYSICAL ENHANCERS FOR DERMAL DELIVERY OF AN ANTIFUNGAL DRUG

Nataša Bubić Pajić[1], Sonja Vučen[2], Snežana Savić[3]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Banja Luka - Faculty of Medicine (Bosnia and Herzegovina), [2]School of Pharmacy - University College Cork (Ireland), [3]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

The efficacy of the dermal antifungal treatment is predominantly dependent on the formulation's potential to deliver the effective drug concentration into deeper layers of the skin, particularly into viable epidermis. Dissolvable microneedles, as physical penetration enhancers, aid the delivery of various drugs directly into/through the skin. The aim of this work was formulation of dissolvable microneedles based on low molecular grade polyvinylpyrrolidone (Kollidon® 17PF, BASF, Germany) as a carrier for dermal delivery of an antifungal drug – sertaconazole nitrate.

Microneedles were fabricated by filling microneedle molds with liquid formulation using vacuum. The dimensions of microneedles on the array were 500 μm in height at a density of 25 needles per 1 cm^2. Molds were manufactured from polydimethylsiloxane by the Tyndall National Institute (Ireland). In order to find optimal conditions for microneedle fabrication, polymer concentration (5, 10, 20 and 30% w/v) and drug content (5, 25 and 66.7 mg/ml) were varied. Morphological characteristics and microneedles evaluation were analyzed by using light microscopy. The selected formulation was subjected to the mechanical strength test and dissolution test.

Processing parameters combining povidone and the drug in concentrations of 30% w/V and 25 mg/ml, respectively, produced microneedles which had complete fidelity to the master molds. Due to the presence of methanol, the critical parameter for microneedle fabrication was the drying process. The obtained microneedles had regular shape, pyramidal structure and sharp tips and were able to withstand compression and fracture of 4.5±0.1 N, suggesting a successful insertion into the skin. A complete dissolution of the microneedles was achieved in 5 min.

Our findings indicate that the dissolvable microneedles can be successfully fabricated and used as carriers for rapid dermal delivery of sertaconazole nitrate. However, the appropriate *ex vivo* and *in vivo* skin studies are strongly required to confirm the drug is transported to the targeted skin layers.

POLIMER-MUCIN INTERAKCIJE U OKULARNIM LUBRIKANSIMA NA BAZI POLISAHARIDA: REOLOŠKA RAZMATRANJA

Anđelka Račić[1], Danina Krajišnik[2], Bojan Čalija[2], Jela Milić[2]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Banjoj Luci - Medicinski fakultet (Bosna i Hercegovina), [2]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Nedostatak konvencionalnih okularnih lubrikansa je kratkoročna kontrola simptoma kod sindroma suvog oka. Kako bi se produžilo vreme zadržavanja i posledično delovanje primenjenog preparata, razvijeni su viskozni oftalmološki vehikulumi koji sadrže mukadhezivne polimere. Cilj ove studije je bila procena mukoadhezivnih svojstava i određivanje tipa polimer-mucin interakcije izrađenih okularnih lubrikanasa koji sadrže hidroksipropilguar gumu (HP GG), hitozan (H) i hidroksietilcelulozu (HEC) primenom reološke analize.

Vodeni vehikulumi koji sadrže hitozan (1,0%; F_1), kombinaciju polimera (HP GG 0,5%/H 1,0%; F_2) i (HP GG 0,5%/HEC 1,0%; F_3) pomešani su u jednakim zapreminama sa disperzijom svinjskog mucina (20 % m/m). Na dobijenim smešama (označenim kao F_1M, F_2M, F_3M), u kojima su koncentracije polimera bile jednake onima u kojima bi se koristili u izrađenim okularnim lubrikansima, sprovedeno je ispitivanje mukoadhezivnosti primenom rotacionih reoloških merenja. Mukoadhezivnost je izražena izračunavanjem „normalizovanog reološkog sinergizma" ($\Delta\eta/\eta$). U cilju određivanja tipa polimer-mucin interakcije, sprovedena su dinamička viskoelastična merenja.

Svi ispitivani lubrikansi pokazali su pozitivnu vrednost ($\Delta\eta/\eta$) u opsegu brzine smicanja (50–100 s^{-1}), ukazujući na interakcije sa mucinom. Izračunati reološki paramater imao je sledeći redosled vrednosti (pri 100 s^{-1}): 2,24 (F_2M) > 1,85 (F_1M) > 0,63 (F_3M). Vrednosti izmerenih viskoelastičnih parametara ukazale su primarno na pojavu fizičkog preplitanja između polimera i mucina ($G' \leq G''$). Redosled vrednosti tan δ (pri 1,13 Hz) bio je: 1,22 (F_3M) > 1,14 (F_2M) > 0,69 (F_1M), ukazujući na dominantno elastično ponašanje disperzije F_1M, a više viskozno za F_2M i F_3M, što verovatno ima za posledicu efikasniju interakciju između polimera i mucina.

Disperzija F_2M, koja odgovara izrađenom okularnom lubrikansu koji sadrži HP GG 0,25%/H 0,5%, pokazala je optimalna mukoadhezivna svojstva na osnovu vrednosti izračunatog normalizovanog reološkog sinergizma i celokupnog viskoelastičnog ponašanja. Interakcija između polimera i mucina, utvrđena reološkom karakterizacijom, omogućava duži kontakt lubrikansa sa površinom oka.

POLYMER–MUCIN INTERACTION IN POLYSACCHARIDE-BASED OCULAR LUBRICANTS: A RHEOLOGICAL POINT OF VIEW

Anđelka Račić[1], Danina Krajišnik[2], Bojan Čalija[2], Jela Milić[2]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Banja Luka - Faculty of Medicine (Bosnia and Herzegovina), [2]Department of Pharmaceutical Technology and Cosmetology University of Belgrade - Faculty of Pharmacy (Serbia)

The limitation of conventional ocular lubricants is short duration of dry eye symptom control. To prolong the residence time and consequently the effect of applied preparation, viscous ophthalmic vehicles with mucoadhesive polymers have been developed. The aim of this study was to evaluate mucoadhesive properties and type of mucin-polymer interaction of compounded ocular lubricants containing hydroxypropyl guar gum (HP GG), chitosan (CS) and hydroxyethylcellulose (HEC) by means of rheological evaluation.

Aqueous vehicles containing CS (1.0%; F1), combination of polymers (HP GG 0.5%/CS 1.0%; F2) and (HP GG 0.5%/HEC 1.0%; F3) were mixed in equivalent volumes with porcine mucin (20% m/m) dispersion. The obtained mixtures (denoted as F1M, F2M, F3M), containing polymers in concentrations equal to those in which they would be used in compounded ocular lubricants, were tested for mucoadhesion using rotational rheological measurements. The mucoadhesiveness was expressed by calculating „normalized rheological synergism" ($\Delta\eta/\eta$). To investigate the type of polymer-mucin interaction dynamic viscoelastic measurements were performed.

All the tested lubricants showed positive values of ($\Delta\eta/\eta$) within shear rate range (50–100 s^{-1}), indicating the occurrence of an interaction with mucin. The rank order of calculated parameters (at 100 s^{-1}) was 2.24 (F_2M) > 1.85 (F_1M) > 0.63 (F_3M). The values of viscoelastic parameters pointed on mainly physical entanglements between polymer and mucin ($G' \leq G''$). The rank order of tan δ (at 1.13 Hz) was 1.22 (F_3M) > 1.14 (F_2M) > 0.69 (F_1M), revealing domination of elastic behavior for F_1M, and more viscous for F_2M and F_3M, which probably enables a more efficacious polymer-mucin interaction.

The dispersion F_2M corresponding to compounded ocular lubricant containing HP GG 0.25%/CS 0.5%, showed optimal mucoadhesive properties based on the $\Delta\eta/\eta$ values and overall viscoelastic behavior. The interaction of polymers and mucin, estimated by rheological characterization, provides longer contact time of lubricants with ocular surface.

PREFORMULACIONA STUDIJA SISTEMA KOJI OBRAZUJU FILM NA POVRŠINI KOŽE KAO PROSPEKTIVNIH NOSAČA LEKOVA

Mirjana Timotijević, Ivana Pantelić, Snežana Savić

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Transportni sistemi na bazi polimera, dizajnirani kao noviji nosači lekova koji formiraju tanak film na površini kože i obezbeđuju produženu isporuku aktivne supstance, mogu da budu veoma pogodni za lokalnu primenu na koži i dermalnu isporuku i hidrofilnih i lipofilnih lekova. Ova preformulaciona studija uključuje, različite tipove polimera ili njihove kombinacije, poput Eudragit® RS, Eudragit® NE 30D, Klucel® GF u različitim koncentracijama, kombinovane sa različitim plastifikatorima, uključujući trietil citrat (TEC), tributil citrat (TBC), propilenglikol i glicerol, opciono sa inhenserom penetracije ili nejonskim surfaktantom (polisorbat 80) i sa različitim sistemima rastvarača.

Dobijene formulacije su procenjene u odnosu na organoleptički izgled, vreme sušenja filma na sobnoj temperaturi i na temperaturi kože, lepljivost obrazovanog filma nakon sušenja, morfologiju obrazovanog filma na mikroskopskoj pločici, debljinu filma i stabilnost formulacija. Fleksibilnost i mehanička otpornost filma su ispitivane tehnikom uvijanja na gumenoj traci.

Pre-formulaciona studija je ukazala na 3 različite obećavajuće formulacije sa polimerom Eudragit® RS pri 8,5%, 10% i 17,5%. Ovaj polimer može biti idealno kombinovan sa plastifikatorima TEC ili propilenglikolom (20% m/m suvog polimera). Otkriveno je da nejonski surfaktant polisorbat 80 pri 1 % značajno poboljšava fleksibilnost i mehaničku otpornost filma, čak i pri nižoj koncentraciji Eudragit® RS (8,5%). Povećanje koncentracije Eudragit® RS od 10% na 17,5% nije značajnije uticalo na vreme sušenja filma na 32 °C, dok je prisustvo Polisorbata 80 od 1% produžilo vreme sušenja na 32 °C. Debljina formiranog filma u ispitivanim film-formirajućim sistemima uglavnom zavisi od izabranog polimera i njegove koncentracije. Studija je pokazala da su razvijeni sistemi koji obrazuju film podesni kao prospektivni nosači lekova, podstičući njihov dalji formulacioni razvoj.

PRE-FORMULATION STUDY OF TOPICAL FILM-FORMING SYSTEMS AS PROSPECTIVE DRUG CARRIERS

Mirjana Timotijević, Ivana Pantelić, Snežana Savić

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Polymer-based delivery systems, designed as novel drug carriers which form a thin film on the surface of the skin and provide a sustained delivery of an active substance, might be very convenient for topical application and dermal delivery of both hydrophilic and lipophilic drugs. This pre-formulation study involves different types of polymers or combinations thereof such as Eudragit®RS, Eudragit®NE 30D, Klucel®GF in various concentrations, combined with a diversity of plasticizers including triethyl citrate (TEC), tributyl citrate (TBC), propylene glycol and glycerol, optionally with a penetration enhancer or a nonionic surfactant (polysorbate 80), and with a different solvent systems.

The obtained formulations were evaluated with respect to visual appearance, drying time of the film at room and skin temperature, stickiness of the formed film after drying, the surface of the formed film on a microscopic slide, film thickness, and stability of the formulations. The flexibility and mechanical properties of the films were evaluated by a folding technique on a rubber band.

A pre-formulation study indicated on 3 different promising formulations with polymer Eudragit®RS at 8.5%, 10%, and 17.5%. This polymer can be ideally combined with the plasticizers TEC or propylene glycol (20% w/w of the dry polymer). It was found that the nonionic surfactant polysorbate 80 at 1% significantly enhances flexibility and mechanical resistance of the film, even at lower (8,5%) Eudragit®RS concentration. Increasing the concentration of Eudragit®RS from 10% to 17,5% had no significant influence on film drying time at 32 °C, while the presence of 1% of polysorbate 80 prolonged the drying time at 32 °C. The thickness of the formed film in evaluated film-forming systems depends principally on the chosen polymer and its concentration. A study has shown that the developed film-forming systems are feasible as prospective drug carriers, encouraging their further formulation development.

EMULZIJE TIPA ULJE U VODI KOJE PODLEŽU BRZOJ INVERZIJI FAZA NA KOŽI SA INKORPORIRANIM ANTIOKSIDANSIMA BILJNOG POREKLA: *IN VITRO* ODREĐIVANJE FAKTORA ZAŠTITE OD SUNCA

Radava Martić[1], Danina Krajišnik[1], Anđelija Malenović[2], Jela Milić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za analitiku lekova, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

SWOP (engl. *Switch-Oil-Phase)* emulzije koje karakteriše brza inverzija faza u emulzije tipa voda u ulju, kao i formiranje vodootpornog sloja tokom njihove primene na koži, prepoznate su kao pogodni nosači za kozmetičke sirovine u proizvodima za zaštitu od sunčevog zračenja. Flavonoidi kvercetin (Q) i dihidrokvercetin (DHQ), kao i β-karoten (βC) se koriste kao antioksidansi u kozmetičkim proizvodima. Dodatno, flavonoidi se mogu koristiti za smanjenje oštećenja kože uzrokovanih sunčevim zračenjem zbog njihove apsorpcije u UV oblasti. Cilj ove studije je bio da u *in vitro* uslovima utvrdi faktor zaštite od sunca (eng. *Sun Protection Factor – SPF*) SWOP emulzija sa 0,5% Q (S_Q), 0,5% DHQ (S_{DHQ}) i kombinacijom 0,5% DHQ i 0,2% βC ($S_{DHQβC}$) primenom UV spektrofotometrije.

SWOP emulzija (S) i SWOP emulzija sa dodatim antioksidansima (S_Q, S_{DHQ} i $S_{DHQβC}$) pripremljene su postupkom emulgovanja toplo/toplo. Apsorbancije kozmetičkih sastojaka (u oblasti 200 do 370 nm) merene su u etanolnim ekstraktima ispitivanih emulzija. Vrednosti SPF su izračunate pomoću *Mansur*-ove jednačine. Za poređenje je korišćen komercijalni kozmetički proizvod koji sadrži βC (SPF 6).

Emulzija S_{DHQ} je pokazala bolju UV apsorbanciju u poređenju sa S_Q (SPF 4,65, tj. 3,35) što ukazuje da je DHQ bolji UV apsorber od Q. SPF emulzije $S_{DHQβC}$ je najviši (5,19) verovatno zbog zajedničkog doprinosa DHQ i βC. Emulzija S je imala zanemarljiv SPF (1,67), dok je SPF komercijalnog proizvoda iznosio 6,81.

Dobijeni rezultati pokazali su da je faktor zaštite od sunca za SWOP emulziju sa inkorporiranim DHQ i βC veći u poređenju sa emulzijom koja sadrži samo DHQ. Iako nije tipičan UV-apsorber, βC verovatno zbog svoje antioksidantne aktivnosti, štiti DHQ od oksidacije i doprinosi njegovoj apsorpciji u UV oblasti. Upotrebom UV spektrofotometrijskog postupka određene su i dobijene uporedive vrednosti SPF za $S_{DHQβC}$ emulziju i komercijalni proizvod koji sadrži βC.

FAST INVERTED OIL-IN-WATER EMULSION CONTAINING PLANT ORIGIN ANTIOXIDANTS: *IN VITRO* DETERMINATION OF SUN PROTECTION FACTOR

Radava Martić[1], Danina Krajišnik[1], Anđelija Malenović[2], Jela Milić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department of Drug Analysis, University of Belgrade - Faculty of Pharmacy (Serbia)

The *Switch-Oil-Phase* (SWOP) emulsions characterized by fast inversion into water-in-oil emulsions during application on the skin and consequent formation of a water-resistance layer are recognized as suitable cosmetic vehicles in sun protection products. Flavonoids quercetin (Q) and dihydroquercetin (DHQ), as well as β-carotene (βC) are used as antioxidants in cosmetics. Additionally, flavonoids may be used for diminishing skin damage caused by solar radiation due to their absorption in UV spectrum. The aim of study was *in vitro* determination of sun protection factor (SPF) for SWOP emulsions containing 0.5% Q (S_Q), 0.5% DHQ (S_{DHQ}) and combination of 0.5% DHQ and 0.2% βC ($S_{DHQ\beta C}$) by UV spectrometry.

The SWOP emulsion base (S) and the SWOP emulsion with incorporated antioxidants (S_Q, S_{DHQ} and $S_{DHQ\beta C}$) were prepared using hot/hot emulsification procedure. Absorbance of the cosmetic ingredients (from 200 to 370 nm) were determined in ethanolic extracts of the tested emulsions. SPF values were calculated using Mansur equation. A commercial cosmetic product containing βC (SPF 6) was used for comparison.

The S_{DHQ} showed better UV absorption compared with S_Q (SPF 4.65, *i.e.*, 3.35, respectively) indicating that DHQ absorbed better in UV spectrum than Q. The SPF of $S_{DHQ\beta C}$ was the highest (5.19) probably due to contribution of both DHQ and βC. While the SPF of emulsion base S was negligible (1.67), determined SPF of the commercial product was 6.81.

Obtained results showed that the SPF of SWOP emulsion with incorporated both DHQ and βC was higher compared with the emulsion containing only DHQ. Although βC is not a typical UV absorber, due to its antioxidant activity, it probably protects DHQ from oxidation and supports its absorbance in UV spectrum. Using UV spectrometric method, comparable SPF values of $S_{DHQ\beta C}$ emulsion and the commercial product containing βC were obtained.

IN VITRO ISPITIVANJE ANTIOKSIDATIVNE AKTIVNOSTI ANTIOKSIDANASA BILJNOG POREKLA INKORPORIRANIH U EMULZIJE TIPA ULJE U VODI KOJE PODLEŽU BRZOJ INVERZIJI FAZA NA KOŽI

Radava Martić[1], Danina Krajišnik[1], Jelena Kotur-Stevuljević[2], Vesna Spasojević-Kalimanovska[2], Jela Milić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za medicinsku biohemiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Flavonoidi kvercetin (QUE) i dihidrokercetetin (DHQ), kao i β-karoten (βC) se koriste kao antioksidansi u kozmetičkim proizvodima. Iako njihova antioksidativna aktivnost sama po sebi može biti merena korišćenjem različitih analitičkih tehnika, procena njihove biohemijske aktivnosti u gotovom proizvodu predstavlja izazov zbog složenog sastava kozmetičkih formulacija. Cilj ove studije je bio da se utvrdi antioksidativna aktivnost ovih kozmetičkih sastojaka ugrađenih u emulziju tipa ulje u vodi koja podleže brzoj inverziji faza na koži (*SWOP* emulzija): 0,5% QUE (S_{QUE}), 0,5% DHQ (S_{DHQ}) i kombinacija 0,5% DHQ i 0,2 % βC ($S_{DHQβC}$) pri *in vitro* izazvanom oksidativnom stresu u biološkom uzorku i upoređivanje njihovog antioksidativnog potencijala.

Rastvori emulzija S_{QUE}, S_{DHQ} i $S_{DHQβC}$ (1%) i QUE i DHQ (0,005%) u propilenglikolu (PG) pomešani su sa serumom sakupljenim od zdravih dobrovoljaca, u ekstracelularnom model sistemu za *in vitro* procenu antioksidativnih osobina. Efekati različitih antioksidanasa bez i sa serumom, uz dodatak 0,5 mmol/l terc-butil hidroperoksida (TBH-egzogeni prooksidans) praćeni su u odnosu na njihov uticaj na parametre oksidativnog stresa i antioksidativne parametre. Analize su izvedene na 20 °C i 37 °C.Vrednosti posmatranih parametara analizirane su korišćenjem Kruskal-Wallis i post-hoc Mann-Whitney testa. Antioksidativne vrednosti na 20 °C bile su redom: QUE/PG i S_{QUE}/PG -0,33 (-5,11–6,17) > $S_{DHQβC}$/PG -5,50 (-14,67–3,67) > DHQ/PG i S_{DHQ}/PG -9,33 (-9,89–(-7,50), sa značajnom razlikom između poslednje dve grupe. Na 37 °C, redosled antioksidativne vrednosti bio je: QUE/PG i S_{QUE}/PG -7,34 (-14,50–(-3,00)) > $S_{DHQβC}$/PG -33,50 (-45,67–(-21,33)) > DHQ/PG i SDHQ/PG -37,33 (-39,00–(-34,67)), dok razlika između poslednje dve grupe nije bila značajna.

Emulzija tipa ulje u vodi koja podleže brzoj inverziji faza na koži i sadrži kombinaciju DHQ i βC pokazala je blagi porast antioksidativnog efekta u odnosu na emulziju sa DHQ i značajno smanjenje egzogenih prooksidativnih efekata izazvanih dodatkom TBH.

IN VITRO ANTIOXIDANT ACTIVITY TESTING OF PLANT ORIGIN ANTIOXIDANTS INCORPORATED INTO FAST INVERTED OIL-IN-WATER EMULSIONS

Radava Martić[1], Danina Krajišnik[1], Jelena Kotur-Stevuljević[2], Vesna Spasojević-Kalimanovska[2], Jela Milić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department of Medical Biochemistry, University of Belgrade - Faculty of Pharmacy (Serbia)

Flavonoids quercetin (QUE) and dihydroquercetin (DHQ), as well as β-carotene (βC) are used as antioxidants in cosmetic products. Although their antioxidant activity *per se* can be measured using different analytical techniques, estimation of their biochemical activity in a finished product is a challenging task due to the complex composition of cosmetic formulations. The aim of this study was to determine antioxidant activity of these cosmetic ingredients incorporated into fast inverted oil-in-water emulsion (*SWOP* emulsion): 0.5% QUE (S_{QUE}), 0.5% DHQ (S_{DHQ}) and combination of 0.5% DHQ and 0.2% βC ($S_{DHQ\beta C}$) at *in vitro* induced oxidative stress in biological sample and to compare their antioxidant potential.

Solutions in propylene glycol (PG) of S_{QUE}, S_{DHQ} and $S_{DHQ\beta C}$ (1%) and both QUE and DHQ (0.005%) were prepared and mixed with serum pool collected from healthy volunteers, in an extracellular model system for *in vitro* antioxidative properties estimation. The effects of different antioxidants alone, or in serum with 0.5 mmol/l tert-butyl hydroperoxide (TBH-exogenous prooxidant) added, were monitored regarding their influence on oxidative stress parameters and parameters of antioxidative protection. The analyses were performed at 20 °C and 37 °C, respectively. Values of the monitored parameters were analyzed using Kruskal-Wallis test and Mann-Whitney post-hoc test. Antioxidative score values at 20 °C were in range QUE/PG and S_{QUE}/PG-0.33 (-5.11–6.17)>$S_{DHQ\beta C}$/PG -5.50 (-14.67–3.67)> DHQ/PG and S_{DHQ}/PG -9.33 (-9.89–(-7.50), with significant difference between last two groups. At 37 °C, the rank order was QUE/PG and S_{QUE}/PG -7.34 (-14.50–(-3.00))>$S_{DHQ\beta C}$/PG -33.50 (-45.67–(-21.33))> DHQ/PG and S_{DHQ}/PG -37.33(-39.00–(-34.67)), and the difference between last two groups was insignificant.

Fast inverted oil-in-water emulsion containing combination of DHQ and βC showed slight antioxidative effects amplification compared to the same cosmetic vehicle with DHQ, and significant decrease in exogenous prooxidative effects, caused by TBH.

FORMULATION, PREPARATION AND CHARACTERIZATION OF A PHOTOPROTECTIVE EMULSION BASED ON A NEW BENZIMIDAZOLE COMPOUND ASSOCIATED WITH VEGETAL EXTRACTS

Emma Adriana Cretu[1], Teodora Dalila Balaci[1], Cătălina Ancuta Fita[1], Eleonora Mircia[2], Cerasela Elena Gîrd[1]

[1]University of Medicine and Pharmacy „Carol Davila" Bucharest, Faculty of Pharmacy, [2]University of Medicine and Pharmacy, Targu Mures, Faculty of Pharmacy (Romania)

The exposure to UV radiation is responsible for damaging the skin's natural defense, leading to various adverse effects, from sunburns to skin cancer; making necessary to apply on the skin photoprotective products which are safe and efficient. The studies consist in the following: selection of the active ingredients and the use of a proper technological process for preparation of a dermo-cosmetic emulsion having a good physical and chemical stability, suitable organoleptic and rheological properties in order to ensure the innocuity and pleasant administrating features.

We have used one new organic filtering photo protective substance: 1-(4-dimethylamino)benzyl-2-(4-dimethylaminophenyl)-H-1,3 benzimidazole. In order to reduce the toxicity and the amount of UV filters used in cosmetic formulations, UV filters were incorporated into nanostructured lipid carriers (NLCs). Besides organic compound we have also used: two inorganic screen photoprotective substances: titanium dioxide (coated with alumina and silicon) and zinc oxide; vegetal extracts rich in flavonoids with antioxidant action and protective capillary and coumarins with screen effect, collagen used for theskin elasticity, hydration and revitalizing effect, vitamins, natural products having a slight photoprotective, hydrating and emollient actions. The preparation of NLCs was the melt emulsification method coupled with high shear homogenization. NLCs characterization was based on particle size analysis (by dynamic light scattering), PdI and Zeta potential analysis, after this, they were included in a dermato-cosmetic emulsion which was studied under the following aspects: the organoleptic properties, pH, spreadibility, viscosity, the degree of hydration, in vitro determination of SPF.

Starting from the lyophilized benzimidazole-lipid nanostructures, efficient cosmetic formulations with broad photoprotective properties were obtained by using the new benzimidazole compound as organic UV filter, metal oxides and vegetable extracts, oils and other ingredients. The obtained emulsion has proved qualities for skin application possessing suitable physicochemical characteristics.

HIDROGEL SA EKSTRAKTOM *ALCHEMILLA VULGARIS* L.: *IN VIVO/IN VITRO* PROCENA BEZBEDNOSTI I UTICAJA NA ZARASTANJE MANJIH RANA NA KOŽI

Marija Tasić Kostov[1], Ivana Arsić[1], Dragana Pavlović[1], Sanja Stojanović[2], Stevo Najman[2], Dušan Ilić[3], Vanja Tadić[4]

[1]Katedra za farmaciju, Univerzitet u Nišu - Medicinski fakultet, [2]Univerzitet u Nišu - Medicinski fakultet, [3]ZUA Dona farm Niš, [4]Institut „Dr Josif Pančić" Beograd (Srbija)

Rane na koži, prvenstveno hronične, predstavljaju zdravstveni problem globalnih razmera; lečenje zahteva lokalni tretman. Novija relevantna naučna istraživanja ukazuju na veliki potencijal upotrebe biljnih ekstrakata u ove svrhe. Uzimajući u obzir značaj izbora nosača/podloge, cilj rada je bio formulacija i ispitivanje hidrogela za lokalni tretman manjih rana sa ekstraktom *Alchemilla vulgaris* L. Ispitivani gel označen je sa GAE i izrađen inkorporiranjem 2% etanolnog ekstrakta *Alchemilla vulgaris* L. u karbomerni gel koji je služio kao placebo kontrola-P. Bezbednost primene na koži je određivana *in vitro* (test citotoksičnosti na fibroblastima) i *in vivo* merenjem biofizičkih parametara kože: transepidermalni gubitak vode (TEGV), električna kapacitivnost (EC) i eritema indeks (EI). Određivanje efikasnosti kao uticaja na zarastanje manjih rana vršeno je *in vivo* (merenjem TEGV i EC nakon oštećenja barijere SC surfaktantom) i *in vitro* (merenjem brzine zatvaranja veštački napravljene rane u sloju L929 fibroblasta i migracije ćelija). Uzorak P je bio negativna, a medijum za rast ćelija pozitivna kontrola. Određen je sadržaj fenola u GAE uzorku HPLC metodom.

Oba uzorka pokazuju povoljan profil bezbednosti na koži *in vitro* i *in vivo*, u količinama uobičajenim pri aplikaciji dermofarmaceutskih preparata. Uzorak GAE pokazuje procentualno veći potencijal da ubrza zarastanje (45% zatvaranja u odnosu na dimenzije inicijalne rane) u odnosu na P (28%), ali niži u odnosu na pozitivnu kontrolu - medijum kao idealnu sredinu za rast ćelija (80%). U *in vivo* studiji sedmodnevna primena uzorka GAE je, u odnosu na uzorak P i netretiranu oštećenu kožu, značajno smanjila TEGV, a povećala EC; normalizuju se vrednosti parametara poremećene delovanjem surfaktanta. HPLC analizom identifikovano je 8 fenolnih jedinjenja kao potencijalnih aktivnih supstanci. *In vivo/in vitro* ispitivanjima utvrđeni su pozitivni efekti GAE na proces zarastanja manjih rana su u korelaciji sa fenolnim sastavom. Rezultati ukazuju na mogućnost primene hidrogela sa ekstraktom *Alchemilla vulgaris* L. u tretmanu manjih i prevenciji nastanka hroničnih rana na koži.

Rad je podržan od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije (projekat III45017).

ALCHEMILLA VULGARIS L. EXTRACT IN HYDROGEL VEHICLE: *IN VIVO/IN VITRO* EVALUATION OF SKIN SAFETY PROFILE AND WOUND HEALING POTENTIAL IN THE TREATMENT OF MINOR CUTANEOUS WOUNDS

Marija Tasić Kostov[1], Ivana Arsić[1], Dragana Pavlović[1], Sanja Stojanović[2], Stevo Najman[2], Dušan Ilić[3], Vanja Tadić[4]

[1]Department of Pharmacy, University of Niš - Faculty of Medicine, [2]University of Niš - Faculty of Medicine, [3]Pharmacy Dona farm Niš, [4]Institute „Dr Josif Pančić" Belgrade (Serbia)

Treatment and management of wounds, particularly chronic wounds, became a multibillion-dollar global health problem. The use of plant extracts is an important trend in this area, as proven by numerous scientific studies. Regarding the importance of a proper vehicle, we aimed at developing hydrogel with *Alchemilla vulgaris* L. extract, intended for topical treatment of minor wounds.

Carbomer gel (marked as placebo - P) was used as a vehicle for 2% of ethanolic *Alchemilla vulgaris* L. extract (active sample GAE). Skin safety profile was evaluated using both *in vitro* (cytotoxicity assay on L929 fibroblasts) and *in vivo* methods. Skin parameters measured were transepidermal water loss (TEWL), electrical capacitance (EC) and erythema index (EI). To analyze the wound healing potential, we used complementary methods - *in vitro* wound healing assay with L929 fibroblasts (placebo sample was negative, while cell culture medium served as positive control) and *in vivo* assessment of skin barrier repair potential (TEWL and EC measurements) after the barrier impairment induced by surfactant. Chemical profile of the GAE sample was achieved applying HPLC method. Both P and GAE showed satisfying *in vivo/in vitro* skin safety profile, when used in quantities usual for real application regime of dermopharmaceuticals. GAE induced a higher extent of wound closure (45% of closure compared to initial wound) *in vitro* compared to P (28%), but this potential was lower when compared to positive control (80%). Regarding *in vivo* study, significant barrier repair and skin hydrating potential of active sample was recorded after seven days of application compared to P or untreated impaired skin. Application of GAE reversed the values of TEWL and EC disturbed by surfactant. In total, 8 phenolic compounds were identified by HPLC. Our study offers *in vivo/in vitro* evidences on the folkloric use of *Alchemilla vulgaris* in a treatment of minor wounds; phenolic compounds could be considered responsible for recorded wound healing activity. Investigated gel could be used in the treatment of minor wounds and prevention of chronic wound formation.

This work was supported by the Ministry of Education, Science and Technological Development, Republic of Serbia (projekt III45017).

ANTIOKSIDATIVNA AKTIVNOST HIDROLIZATA DOBIJENIH PROTEOLIZOM KOZJEG MLEKA RAZLIČITIM PROTEAZAMA

Mila Vukašinović[1], Zorica Knežević Jugović[2], Snežana Savić[3]

[1]Služba za farmaceutsku delatnost i snabdevanje - Klinički centar Srbije, [2]Katedra za biohemijsko inženjerstvo i biotehnologiju, Univerzitet u Beogradu - Tehnološko–metalurški fakultet, [3]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Peptidi dobijeni iz proteina hrane pokazuju širok spektar bioloških aktivnosti (antioksidativno, antiinflamatorno, antimikrobno, antikancerogeno). Cilj ovog rada je procena sposobnosti smeša peptida dobijenih enzimskom hidrolizom proteina kozjeg mleka da hvataju slobodne radikale.

Proteini kozjeg mleka razloženi su jednostepenom metodom pomoću tri komercijalne proteaze različitog porekla: alkalaze, papaina i pankreatina. Hidroliza je sprovedena na temperaturi i pH optimalnim za svaki enzim. Reakcija je praćena pH-stat metodom. Obim proteinske hidrolize procenjen je određivanjem stepena hidrolize (DH). Antioksidativna aktivnost hidrolizata ispitana je ABTS [2.2'-azino-bis (3-etilbenztiazolin-6-sulfonska kiselina)], 2.2-difenil-1-pikrilhidrazil (DPPH) i deoksiriboza (aktivnost hvatanja hidroksil radikala) metodama.

Najveći stepen hidrolize dobijen je primenom papaina, a najmanji sa pankreatinom. Tokom ispitivanja antioksidativne aktivnosti, svi hidrolizati pokazali su značajan potencijal hvatanja slobodnih radikala u trima metodama, koji je direktno proporcionalan koncentraciji peptida. Registrovan je i veći potencijal inhibicije slobodnog ABTS•+ radikala, u poređenju sa inhibicijom hidroksil odnosno slobodnog DPPH• radikala.

Dobijeni rezultati pokazuju da razlaganje proteina kozjeg mleka proteolitičkim enzimima generiše hidrosolubilne peptide značajne sposobnosti hvatanja raznovrsnih slobodnih radikala, pa se mogu koristiti kao prirodni bioaktivni sastojci koji poboljšavaju antioksidativna svojstva različitih prehrambenih, farmaceutskih i kozmetičkih proizvoda.

ANTIOXIDATIVE ACTIVITY OF HYDROLYSATES OBTAINED BY PROTEOLYSIS OF GOAT MILK WITH VARIOUS PROTEASES

Mila Vukašinović[1], Zorica Knežević Jugović[2], Snežana Savić[3]

[1]Department of Pharmaceutical Service and Supply - Clinical Center of Serbia, [2]Department od Biochemical Engeneering and Biotechnology, University of Belgrade - Faculty of Technology and Metallurgy, [3]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Peptides derived from dietary proteins have been reported to display a wide spectrum of biological activities (antioxidant, antiinflamatory, antimicrobial, anticancer). The objective of this work was to evaluate radical scavenging activity of peptide mixtures obtained by the enzymatic hydrolysis of goat milk proteins.

Goat milk proteins were digested via one step method with three commercial food grade proteases of different origin: alcalase, papain and pancreatin. Hydrolysis was carried out at temperature and pH optimal for each enzyme. The reaction was monitored by the pH-stat procedure. Extent of protein hydrolysis was evaluated by measuring the degree of hydrolysis (DH). The antioxidant activity of the hydrolysates was tested by ABTS [2.2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid)], 2.2-diphenyl-1-picrylhydrazyl (DPPH) and deoxyribose (hydroxyl radical scavenging activity) methods.

The highest DH value was obtained by using papain and the lowest by pancreatin. Determining the antioxidant activity, all hydrolysates showed meaningful concentration dependent radical scavenging potency in all three assays; higher inhibition of free radical ABTS•+ was detected in all peptide mixtures compared to inhibition of hydroxyl radical and free radical DPPH•.

The results demonstrate that digestion of goat milk proteins with proteolytic enzymes generates soluble peptides with notable ability to scavenge various radicals and that could be used as natural bioactive ingredients in enhancing antioxidant properties of different food, pharmaceutical and cosmetic products.

ARGANOVO ULJE – RIZNICA DRAGOCENIH EFEKATA

Bojana Vučelić, Marija Bajčić, Mira Stojanović

Apoteka „Beograd" (Srbija)

Arganovo ulje je biljno ulje proizvedeno iz semena arganovog drveta (*Argania Spinosa, Sapotaceae*). Ovo drvo je endemska biljna vrsta u Maroku i ima veliku ekološku i socioekonomsku vrednost u ovom području. Poznato je i kao „marokansko ulje".

Arganovo ulje, koje se koristi u kozmetičkoj industriji, dobija se hladnim ceđenjem - gnječenjem neprženih semena arganovog ploda i odlikuje se zlatno žutom bojom. Bogato je vitaminom E, polifenolima, karotenoidima i masnim kiselinama, posebno omega-6 i omega-9. Sadrži oko 40-50% oleinske kiseline i oko 30-40% linoleinske kiseline.

Koristi se u kozmetičkim proizvodima za negu i omekšavanje kože, a posebno je efikasno u smanjenju vidljivosti bora i hiperpigmentacija. Takođe se koristi za negu i zaštitu osetljive dečije kože. Ima i pozitivne efekte u prevenciji nastanka strija. Izražen je efekat arganovog ulja na poboljšanje kvaliteta kose i noktiju, a za njihovu negu najčešće se koristi u svom čistom obliku.

Osim kozmetičkih efekata nege i zaštite kože, kose i noktiju, arganovo ulje može biti efikasno i u tretmanu određenih kožnih oboljenja. Koristi se u tretmanu mladalačkih akni i bubuljica, kao i u tretmanu ekcema i psorijaze. Delotvorno je i kod šuge, opekotina i rana kada se koristi u čistom obliku ili inkorporiran u odgovarajuću podlogu.

U skorije vreme arganovo ulje je postalo predmet brojnih medicinskih istraživanja pa dobija novu oblast upotrebe i postaje veoma efikasano u tretmanu mnogih bolesti, kao što su srčane bolesti, gojaznost, povišene koncentracije holesterola i triglicerida u krvi, reumatizam, varenje, hormonski disbalans i drugo. Ovi efekti se ispoljavaju nakon peroralne upotrebe čistog arganovog ulja.

ARGAN OIL - A TREASURE TROVE OF VALUABLE EFFECTS

Bojana Vučelić, Marija Bajčić, Mira Stojanović

Pharmacy „Belgrade" (Serbia)

Argan oil is a vegetable oil produced from argan wood (*Argania Spinosa, Sapotaceae*). This tree is an endemic plant species in Morocco and has great ecological and socioeconomic value in this area. It is also known as „Moroccan oil".

Argan oil used in the cosmetics industry is obtained by cold sealing - crushing untried seeds of argan fruit and distinguished by a golden yellow color. It is rich in vitamin E, polyphenols, carotenoids and fatty acids, especially omega-6 and omega-9. It contains about 40-50% oleic acid and about 30-40% of linoleic acid.

It is used in cosmetic products for the skin care and softening, and is especially effective in reducing the visibility of wrinkles and hyperpigmentation. It is also used for the care and protection of sensitive baby skin. There are also positive effects in the prevention of stretch marks. The effect of argan oil on the improvement of hair and nails quality is expressed, and for their care is most often used in its pure form.

Apart from the cosmetic effects of skin care and protection, hair and nails, argan oil can be effective in the treatment of certain skin diseases. It is used in the treatment of teenage acne and pimples, as well as in the treatment of eczema and psoriasis. It is also effective in sprays, burns and wounds when used in pure form or incorporated into a suitable base.

More recently, argan oil has become the subject of numerous medical research and has been given a new field of use and has become very effective in the treatment of many diseases, such as heart disease, obesity, high blood cholesterol and triglyceride levels, rheumatism, digestion, hormonal imbalance and other. These effects appear after oral administration of pure argan oil.

INTELLECTUAL PROPERTY RIGHTS AND ADVERTISING OF COSMETIC PRODUCTS

Biljana Nestorovska-Gjoshevska, Katerina Ancevska-Netkovska, Marija GlavasDodov

Ss. Cyril & Methodius Universityof Skopje - Faculty of Pharmacy (Macedonia)

When launching an advertising campaign, businesses may need to comply with a range of laws and regulations governing. These laws differ from country to country and depending on the content of the advertisement. Today, it is impossible to be a successful advertiser without understanding the legal framework surrounding the business of advertising. A lack of caution can lead to the loss of a company's own intellectual property (IP) rights or liability for infringing the IP rights of others. To avoid costly mistakes, businesses should conduct rigorous checks both from the general legal perspective and from an IP perspective before launching a new advertising campaign. Misleading advertising means any advertising which, including its presentation,deceives or is likely to deceive the persons to whom it is addressed or whom it reaches and which by reason of its deceptive nature, is likely to affect their economic behavior or which, for those reasons, injures or is likely to injure a competitor.

Facing with problems with misleading and comparative advertisingand taking into consideration intellectual property rights we would to point out the possible ways for protection of the consumers and traders. The method used is a research followed by a descriptive study. Secondary data were collected from available scientific publications, databases and books provided. A survey about consumers' reactions on advertising cosmetic products was prepared and analyzed. Through the research we have obtaineda clearer picture on the perception, awareness and behavior of the consumers on misleading advertising. As misleading and unfair comparative advertising are very present nowadays and can harm both consumers and traders, very important is to have clear and defined ways of dealing with them according to actual regulative taking in consideration how regulative is harmonized from country to country.

UTICAJ ULJANOG EKSTRAKTA SMILJA NA ORGANOLEPTIČKE KARAKTERISTIKE KOZMETIČKIH KREMA

Marina Kalić[1], Miroslav Sarač[1], Nataša Jovanović Lješković[1], Zorica Mrkonjić[1], Manda Dizdar[1], Branislava Teofilović[1], Tatjana Miljković[2]

[1]Univerzitet Privredna Akademija u Novom Sadu - Farmaceutski fakultet Novi Sad, Srbija, [2]Univerzitet u Novom Sadu - Medicinski fakultet (Srbija)

Zahvaljujući velikoj potražnji u Evropi i svetu, poslednjih godina je uzgajanje smilja doživelo pravu ekspanziju. Sastojci izolovani iz cvetova smilja (α-pinen, neril acetat) ispoljavaju različite kozmetičke efekte, zbog čega je ekstrakt smilja sve češći sastojak kozmetičkih proizvoda. Cilj rada je bio izrada uljanog ekstrakta smilja metodom maceracije, različite dužine trajanja, zatim izrada krema sa 10% (m/m) i 20% (m/m) uljanog ekstrakta i praćenje organoleptičkih karakteristika (boje i mirisa, razmazivosti, aplikativnog i rezidualnog efekta nakon primene), kao i fizičke stabilnosti (odvajanje faza) izrađenih krema, tokom šest nedelja.

Uljani ekstrakti su izrađeni koristeći 15 g suvih cvetova smilja (*Helichrysum italicum* (Roth) G. Don fil.) i 370 g maslinovog ulja. Dužina maceracije je iznosila 14, 28 i 42 dana. Izrađeni uljani ekstrakti su ručno inkorporirani u komercijalnu ambifilnu podlogu (Belobaza®), u koncentracijama od 10% (m/m) i 20% (m/m). Nakon izrade, kreme su ostavljene u plastičnoj ambalaži na sobnoj temperaturi, na suvom i tamnom mestu i praćene su promene tokom šest nedelja.

Sve kreme sa 10% uljanog ekstrakta smilja, koji su dobijeni maceracijom različite dužine trajanja, bile su svetložute boje, slabog karakterističnog mirisa na maslinovo ulje, dobre razmazivosti i prijatnog aplikativnog i rezidualnog efekta na koži, tokom šest nedelja praćenja. Kreme sa 20% uljanog ekstrakta smilja su bile tamnije boje. Kod njih su se prvi znaci nestabilnosti javili nakon treće nedelje praćenja, u vidu odvajanja faza, što ih čini neprihvatljivim za upotrebu.

Na organoleptičke osobine i kratkoročnu fizičku stabilnost ispitivanih krema utiče koncentracija uljanog ekstrakta smilja. Sve kreme izrađene sa 10% uljanog ekstrakta smilja, koji su dobijeni maceracijom različite dužine trajanja, su bile prihvatljivog izgleda, razmazivosti, aplikativnog i rezidualnog efekta na koži, bez znakova odvajanja faza u periodu od šest nedelja.

INFLUENCE OF IMMORTELLE OIL EXTRACTS ON ORGANOLEPTIC CHARACTERISTICS OF COSMETIC CREAMS

Marina Kalić[1], Miroslav Sarač[1], Nataša Jovanović Lješković[1], Zorica Mrkonjić[1], Manda Dizdar[1], Branislava Teofilović[1], Tatjana Miljković[2]

[1]University Business Academy in Novi Sad - Faculty of Pharmacy Novi Sad,
[2]University of Novi Sad - Faculty of Medicine (Serbia)

Cultivation and processing of immortelle has drastically expanded in the past few years. Its ingredients (α-pinene, neryl acetate) show cosmetic effects, what makes immortelle extract common ingredient in cosmetic products nowadays. The aim of this work was to prepare immortelle oil extracts by using different maceration times, to make creams containing 10% (w/w) and 20% (w/w) of these extracts, and to evaluate organoleptic characteristics (odour, color, spreadability, applicative and residual effects) and stability (phase separation) of such preparations over six weeks.

Oil extracts were made using 15 g of dry immortelle (*Helichrysum italicum* (Roth) G. Don fil.) flowers and 370 g of olive oil. Maceration length was 14, 28 and 42 days. Finished oil extracts were incorporated in commercial ambiphilic cream (Belobaza®) by hand, reaching concetrations of 10% (w/w) and 20% (w/w). After that, creams were placed in plastic containers and left on room temperature, in a dark, dry place and their characteristics were observed over six weeks of storage.

All creams containing 10% of oil extract remained light yellow, having weak typical olive oil scent throughout the six weeks, regardless maceration length, with very good spreadability and pleasant applicative and residual effects. Creams containing 20% of oil extract were darker at the beginning. First instability signs occurred at third week of storage, as phase separation, which made them unacceptable as cosmetic products.

Organoleptic characteristics and short-term stability of creams are affected by the amount of added immortelle oil extract. Texture and appearance, as well as general liking of creams containing 20% of oil extract, were significantly lower than with preparations containing 10% of oil extract.

FORMULACIJA I KARAKTERIZACIJA INVASOMA SA KOENZIMOM Q10

Nina Dragićević[1], Danijela Pecarski[2], Alfred Fahr[3]

[1]Apoteka "Beograd", [2]Visoka zdravstvena škola strukovnih studija, Beograd (Srbija), [3]Katedra za farmaceutsku tehnologiju, Friedrich-Schiller Univerzitet, Jena (Nemačka)

Koenzim Q_{10} (Q_{10}) se uspešno koristi zahvaljujući svojoj osobini „hvatača radikala“ u lečenju neurodermatitisa, psorijaze i sprečavanju fotostarenja. Međutim, Q_{10} pokazuje i nedostatke, kao što su osetljivost na oksidaciju, posebno u aerobnim uslovima i pod uticajem svetlosti. Q_{10} je liposolubilan i stoga je njegovo inkorporiranje u kozmetičke proizvode komplikovano, jer je u većini kozmetičih preparata spoljašnja faza hidrofilna.

Cilj ovog rada je bio da se Q_{10} inkorporira u nanonosač kako bi se povećala njegova stabilnost i olakšalo inkorporiranje u formulacije. Stoga smo razvili invasome sa Q_{10}. Invasomi za razliku od konvencionalnih liposoma sadrže u membranama pored fosfolipida, i terpene usled čega poseduju elastične membrane, te su bolji ubrzivači penetracije supstanci u/kroz kožu od konvencionalnih liposoma.

Izrađene su invasomske disperzije sa Q_{10} i različitim sadržajem terpena tj. cineola 1, 1,5 i 2%, u cilju povećanja fleksibilnosti membrana invasoma. Ispitana je veličina čestica invasomske disperzije, distribucija veličine čestica (indeks polidisperziteta (PDI)), zeta potencijal, Q_{10}-sadržaj, pH vrednost i oksidacioni indeks. Ispitivana je stabilnost invasomskih disperzija zaštićenih od svetlosti, čuvanih na temperaturi 4°C u trajanju od 6 meseci.

Invasomi su nakon izrade bili male veličine (od 104,8±0,4 do 155,8±0,6 nm), negativno naelektrisani (od -19,1±1,3 do -20,6±1,1 mV), disperzije su bile homogene (PDI od 0,075±0,005 do 0,095±0,007), blago kisele pH vrednosti, sa prihvatljivim oksidacionim indeksom i sadržajem Q_{10} u okviru deklarisanog sadržaja. Krio-elektronskom mikroskopijom je pokazano da su vezikule bile pretežno sfernog oblika i unilamelarne. Sa porastom sadržaja cineola od 1 do 2% rastao je broj deformisanih vezikula u invasomskim disperzijama, ukazujući na visoku deformabilnost/elastičnost invasoma sa višim sadržajem cineola. Studija stabilnosti je pokazala da se fizički parametri invasomskih disperzija nisu značajno menjali tokom šestomesečnog čuvanja, ukazujući na visoku fizičku stabilnost invasoma. Većina hemijskih parametara se nije menjala tokom čuvanja invasoma, izuzev sadržaja Q_{10} koji se značajno smanjio.

Q_{10}-invasomska disperzija sa 1% cineola pokazala se kao fizički i hemijski najstabilnija formulacija.

FORMULATION AND CHARACTERIZATION OF COENZYME Q10-LOADED INVASOMES

Nina Dragićević[1], Danijela Pecarski[2], Alfred Fahr[3]

[1]Pharmacy "Belgrade", [2]College of Professional Health Studies, Belgrade (Serbia), [3]Department of Pharmaceutical Technology, Friedrich-Schiller-University, Jena (Germany)

Coenzyme Q_{10} (Q_{10}) has been successfully applied due to its radical scavenger properties in treating neurodermatitis, psoriasis and in preventing photoageing. Q_{10} shows also disadvantages, such as susceptibility to oxidation, especially under aerobic conditions and light exposure. Q_{10} is liposoluble and its incorporation into cosmetic formulations is complicated, as in most cosmetic formulations the outer phase is hydrophilic. The aim of this study was to incorporate Q_{10} into a nanocarrier system in order to enhance its stability, as well as to make its incorporation into formulations easier. Thus, we developed invasomes loaded with Q_{10}. Invasomes, in contrast to conventional liposomes, contain in their membranes besides phospholipids also terpenes, due to which they possess elastic membranes, and are more potent percutaneous penetration enhancers compared to conventional liposomes.

Q_{10}-loaded invasome dispersions with different terpene i.e. cineole content 1, 1.5 and 2% were prepared and characterized for particle size, size distribution (polydispersity index (PDI)), zeta potential, Q_{10}-content, pH value and oxidation index, and subjected to a stability investigation during 6 months storage at 4°C, under light protection.

Invasomes were, after preparation, of small particle size (from 104.8±0.4 to 155.8±0.6 nm), negatively charged (from -19.1±1.3 to -20.6±1.1 mV), dispersions were homogeneous (PDI from 0.075±0.005 to 0.095±0.007), of mild acid pH value, acceptable oxidation index and contained Q_{10} in the declared concentration range. Cryo-electron microscopy revealed that vesicles were mostly of spherical shape and unilamellar. With the increase of cineole content from 1 to 2%, the number of deformed vesicles increased, indicating high deformability/elasticity of invasomes containing higher cineole amount. The stability investigation revealed that physical parameters did not change significantly during storage indicating high physical stability of invasomes. Most chemical parameters did not change during storage of invasomes, except the Q_{10}-content which decreased significantly.

Q_{10}-loaded invasome dispersion with 1% cineole has shown to be the physically and chemically most stable formulation.