Polučvrsti oblici za vaginalnu primjenu lijekova

Prižmić, Lucija

SVEUČILIŠTE U ZAGREBU
FARMACEUTSKO-BIOKEMIJSKI FAKULTET

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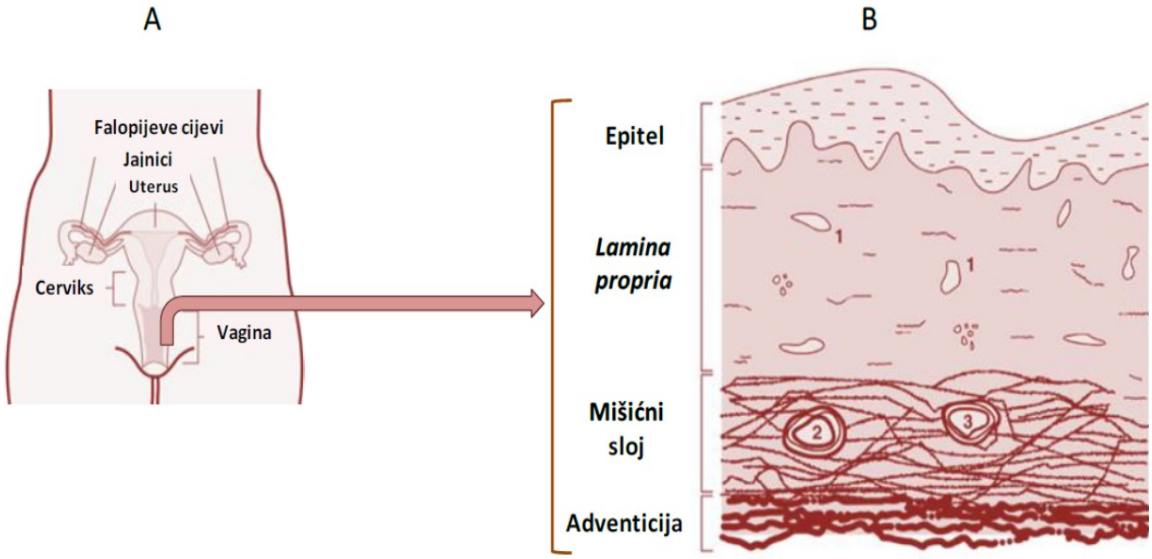
SADRŽAJ

1. UVOD

1.1. ANATOMIJA, HISTOLOGIJA I FIZIOLOGIJA RODNICE

Rodnica (lat. vagina) je ženski spolni organ koji povezuje cerviks uterusa i stidnicu, a smještena je između rektuma, mokraćnog mjehura i mokraćne cijevi (Slika 1A). To je mišićno- membranski organ, cijevastog oblika duljine od 8,4 do 11,3 centimetra (de Araújo Pereira i Bruschi, 2012). Rodnica, kao dio porođajnog kanala, ima funkciju odvoda cervikalne sluzi i menstruacijske krvi te zaštitnu ulogu u obrani od infekcija gornjih dijelova spolnog sustava (Pavelić, 2005). Građena je od 4 sloja (Slika 1B): nesekretornog skvamoznog epitelnog sloja, lamine proprie, mišićnog sloja i adventicije te je bogato opskrbljena živcima, limfnim i krvnim žilama osobito venama (das Neves, 2006).

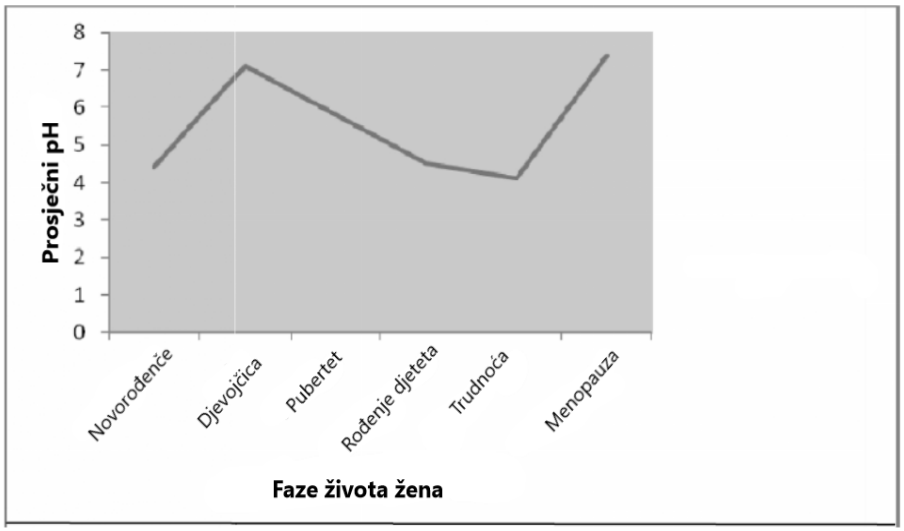


Slika 1. Shematski prikaz ženskih spolnih organa (A) i poprečnog presjeka vaginalne stijenke (B): 1-kapilare, 2-arterija, 3-vena. Preuzeto iz *Vanić i sur.,* (2014) uz dozvolu *Hrvatskog farmaceutskog društva*

Epitelni sloj i lamina propria tvore sluznicu čiji poprečni nabori (*rugae vaginales*) povećavaju ukupnu površinu te osiguravaju prilagodbu i rastezljivost (de Araújo Pereira i Bruschi, 2012). Debljina epitelnog sloja varira pod utjecajem hormona tijekom menstrualnog ciklusa pri čemu progesteron potiče izgradnju epitela do intermedijalnog sloja, a estrogen potom omogućuje daljnju diferencijaciju stanica (Pavelić, 2005). Iako rodnica ne posjeduje žlijezde, izlučuje vaginalni iscjedak (sekret) sastavljen od transudata krvnih žila, odljuštenih stanica epitela i cervikalnog sekreta te u manjim količinama sekreta Falopijevih cijevi i endometrija (de Araújo Pereira i Bruschi, 2012). Kemijski gledano, vaginalni iscjedak je smjesa enzima,

proteina, aminokiselina, ugljikohidrata, imunoglobulina i ostalih komponenti (Vanić i sur., 2014).

Tijekom menstrualnog ciklusa osim debljine epitela mijenja se sastav i količina vaginalnog iscjetka te pH vrijednost. Normalna pH vrijednost vaginalne tekućine iznosi 3,5-4,5, a posljedica je prisutnosti bakterija *Lactobacilli* koje razgrađuju glikogen do mliječne kiseline. Snižavanjem pH i stvaranjem bakterijskih komponenti, bakterije vaginalne mikroflore štite rodnicu od patogena. Promjene se mogu dogoditi i uslijed trudnoće kada pH iznosi od 3,8 do 4,4. U menopauzi se pH povećava (7,0-7,4) zbog promjena u sastavu glikogena, a zbog alkalnog ejakulata u žena reproduktivne dobi, pH rodnice tijekom spolnog odnosa iznosi oko 7 (Cook i Brown, 2018). Navedene promjene pH vrijednosti (Slika 2) i sastava vaginalne tekućine mogu bitno utjecati na bioraspoloživost lijekova. Također treba uzeti u obzir i prisustvo enzima (beta-glukuronidaza, sukcin-dehidrogenaza, kiselih fosfataza, alfa-naftilesteraza, fosfoamidaza) i bakterija koji mogu uzrokovati razgradnju peptidnih, ali i ostalih nestabilnih lijekova (de Araújo Pereira i Bruschi, 2012; Vanić i sur., 2014.).



Slika 2. pH u različitim fazama života žena. Preuzeto i prilagođeno iz *Kale i Ubgade,* (2013) uz dozvolu *Creative Commons Attribution License*-a.

1.2. VAGINALNI PUT PRIMJENE LIJEKOVA

Iako je većina registriranih lijekova za vaginalnu primjenu namijenjena lokalnoj terapiji, vaginalni put pokazuje veliki potencijal u vidu dostave lijeka u sistemsku cirkulaciju (Pavelić, 2005). Lokalna terapija bazira se na primjeni antimikrobnih lijekova za liječenje infektivnih oboljenja, primjeni kontraceptiva, spolnih hormona, lijekova za poticanje trudova i spermicida. Vaginalni put primjene u odnosu na ostale puteve primjene lijekova pogodan je iz nekoliko razloga:

- povećane apsorpcije i bioraspoloživosti,
- minimalnih sistemskih nuspojava,
- smanjene doze lijeka u odnosu na oralni put primjene,
- brzog nastupa djelovanja,
- jednostavne primjene, te
- smanjenih gastrointestinalnih smetnji (Sahoo i sur., 2013; Vanić i sur., 2014).

Apsorpcija vaginalno primijenjenog lijeka može se odviti na tri načina: transcelularno (difuzijom kroz stanice), paracelularno (putem *tight junctions*-a) i transportom posredovanim vezikulama ili receptorima (Sahoo i sur., 2013).

Razlozi povećane apsorpcije i bioraspoloživosti vaginalno primijenjenog lijeka su zaobilazak prvog prolaska kroz jetru, povećana prokrvljenost rodnice te velika površina sluznice zbog vaginalnih nabora (*rugae vaginales*) (Vanić i sur., 2014). Apsorpcija vaginalno primijenjenog lijeka odvija se u dva bitna koraka; otapanje lijeka i prolazak kroz membranu. Svaki fiziološki faktor koji potencijalno može interferirati s ta dva koraka promijenit će apsorpcijski profil lijeka (Ashok i sur., 2012). Većina lijekova primijenjena vaginalno ubrajaju se u slabe elektrolite. Stoga će promjena pH sluznice dovesti do promjene njihove ionizacije, a time smanjiti apsorpciju, topljivost i stabilnost. Brojni fiziološki parametri (Tablica 1) mijenjaju se ovisno o životnoj dobi i menstrualnom ciklusu: debljina epitela, promjene u reološkim svojstvima, sastavu i volumenu vaginalne tekućine. Estrogen i progesteron imaju značajan utjecaj na debljinu epitela, a njihova razina se mijenja tokom života. Tako je u razdoblju prije puberteta, zbog smanjene razine spolnih hormona, smanjena debljina epitela, a time i povećana apsorpcija. Povećanjem razine hormona jajnika u reprodukcijskoj dobi, povećava se i debljina epitelnog sloja, a time se i smanjuje apsorpcija. Period menopauze je karakteriziran niskom razinom hormona i smanjenom debljinom epitela te je za očekivati povećanu apsorpciju. Međutim, zbog smanjene prokrvljenosti i povećanog pH rodnice apsorpcija je smanjena (Vanić i sur., 2014). Do porasta pH u menopauzi dolazi zbog smanjene razine

glikogena i nemogućnosti stvaranja mliječne kiseline koja će održavati pH niskim što dovodi do stvaranja uvjeta pogodnih za razvoj infekcija (Vanić i sur., 2014). Vaginalna tekućina može djelovati i povoljno i nepovoljno na apsorpciju lijekova. Povećanim stvaranjem vrlo viskozne tekućine stvorit će se barijera koja će onemogućiti apsorpciju lijekova. Nadalje, promjenom volumena, viskoznosti i pH vaginalne tekućine koja je zapravo glikoproteinski gel, povećat će se apsorpcija slabo topljivih lijekova (Ashok i sur., 2012).

Tablica 1. Utjecaj fizioloških i formulacijskih parametara na učinkovitost vaginalne dostave lijeka. Preuzeto i prilagođeno prema *Kale i Ubgade,* (2013) uz dozvolu *Creative Commons Attribution License*-a i *Vanić i sur.* (2014) uz dozvolu *Hrvatskog farmaceutskog društva.*

Fiziološki parametri	**Formulacijski parametri**	**Učinak na mjestu primjene**
Položaj rodnice	Vrijeme zadržavanja pripravka	Istjecanje lijeka (utjecaj gravitacije)
	Distribucija lijeka	Nejednaka raspodjela lijeka na sluznici
Površina sluznice (*rugae vaginales)*	Brzina apsorpcije lijeka	Povećanjem površine se povećava apsorpcija lijeka
Vaginalna tekućina	Količina otopljenog lijeka	Mijenja se tijekom mjesečnog ciklusa
Prisutnost sluzi	Permeabilnost lijeka	Varijabilnost apsorpcije lijeka ovisno o viskoznosti sluzi; slabija permeabilnost kroz viskozniju sluz, bolja kroz manje viskoznu sluz
Debljina epitela	Permeabilnost lijeka	Slabija permeabilnost kroz deblji epitel, bolja kroz tanji epitel
pH	Topljivost i stabilnost lijeka	Ioniziranost lijeka se mijenja zbog promjena pH unutar rodnice što utječe na topljivost, apsorpciju i stabilnost lijeka

Osim fizioloških faktora, važno je poznavati i utjecaj fizikalno-kemijskih svojstava lijeka na vaginalnu apsorpciju. To su lipofilnost, molekulska masa, ionizacija, površinski naboj i kemijska priroda lijeka (Sahoo i sur., 2013). Tako se, primjerice, permeabilnost nerazgranatih alifatskih alkohola povećava proporcionalno s duljinom alkilnog lanca. Također, lipofilni lijekovi male molekulske mase bolje će se apsorbirati u usporedbi s hidrofilnim ili lipofilnim lijekovima velike molekulske mase (Ashok i sur., 2012). Primjer utjecaja lipofilnosti je razlika u apsorpciji između lipofilnih (estrona, progesterona) i hidrofilnih (testosteron, hidrokortizon) steroida, pri čemu lipofilni steroidi imaju bolju apsorpciju od hidrofilnih (Sahoo i sur., 2013).

Da bi se postigla terapijska učinkovitost i sigurnost primjene lijeka, ljekoviti oblik mora osigurati ravnomjernu distibuciju lijeka na mjestu primjene kroz određeni vremenski period i očuvati pH vaginalne sluznice. Iako se vaginalni put generalno smatra kao siguran i efektivan put primjene lijekova, često je povezan s nelagodnom i teškom primjenom. To su ograničavajući faktori za postizanje terapijskog učinka, pogotovo kod dugotrajnije terapije (Sahoo i sur., 2013). Stoga je prilikom formuliranja važno da je ljekoviti oblik jednostavan za primjenu, siguran prilikom učestale primjene te prihvatljive cijene (Vanić i sur., 2014).

Danas postoji veliki broj oblika za vaginalnu primjenu lijekova. Supozitoriji i vaginalete izrađuju se od podloga na bazi glicerola i želatine koje mogu uzrokovati lokalne iritacije. Za dugotrajniju dostavu lijekova koriste se vaginalni prstenovi koji se temelje na produženom oslobađanju aktivne tvari kroz nekoliko mjeseci ili godina. Izrađuju se od polimernih ili silikonskih elastomera povećane krutosti kao što je etilen-vinil acetat kopolimer. Također postoje i manje zastupljeni oblici: spužve, filmovi, vaginalne tablete (Cook i Brown, 2018). Polučvrsti oblici uključuju vaginalne kreme i gelove te su najkorišteniji oblici zbog svoje jednostavne primjene i niske cijene (Vanić i sur., 2014).

1.3. INDIKACIJE ZA VAGINALNU PRIMJENU LIJEKOVA

Vaginalne infekcije

Vaginalne infekcije su jedne od najčešćih problema s kojim se žene susreću i zbog kojeg traže medicinsku pomoć (Donders, 2007; Mardh i sur., 2002). Procijenjeno je da se više od 70% žena susrelo s nekim oblikom vaginalne infekcije te su koristile vaginalne ljekovite oblike za liječenje infekcije (Nappi i sur., 2006; Palmeira-de-Oliveira i sur., 2014). Infekcije rezultiraju upalnim procesima, svrbežom, boli i nelagodom prilikom spolnog odnosa ili prilikom

uriniranja (Reichmann i Sobel, 2014). Istodobna pojava različitih infekcija može uzrokovati poteškoće pri dijagnosticiranju problema te posljedično dovesti do neadekvatne terapije (Palmeira-de-Oliveira i sur., 2015). Najčešći oblici vaginalnih infekcija su bakterijska vaginoza, kandidijaza i trihomonijaza (Cook i Brown, 2018). Tablica 2 prikazuje glavne patofiziološke značajke infekcija.

Bakterijska vaginoza je infekcija uzrokovana endogenim bakterijama kao što su *Gardnerella vaginalis*, *Bacteroides* spp., *Atropobium vaginae*, *Prevotella* spp*, Mycoplasma hominis*, *Peptostreptococcus* spp. i *Mobiluncus* spp. (Ferris i sur., 2004; Fredricks i sur., 2005; Smayevsky i sur., 2001; Verhelst i sur., 2004). Porastom broja endogenih patogena narušava se prirodna mikroflora rodnice što dovodi to smanjenja broja protektivnih laktobacila i porasta pH rodnice na pH>4 (Beigi i sur., 2005; Biagi i sur., 2009; Martinez Oliveira, 1993). Također, *G. vaginalis* kolonizira urogenitalni trakt, stvara biofilmove i ima sposobnost stvarati enzime koji razgrađuju mucin smanjujući viskoznost vaginalne tekućine (Patterson i sur., 2007; Swidsinski i sur., 2008). Bakterijska vaginoza je najčešća vaginalna infekcija kod žena reproduktivne dobi, a zahvaća i žene u menopauzi (Schwebke i sur., 2004; Sobel, 2000). Iako je najučestalija, bakterijska vaginoza je često asimptomatska te ju je još uvijek teško dijagnosticirati (Donders, 2007; Haggerty i sur., 2004; Hay i sur., 1994; Spiegel, 1991). Dijagnoza se provodi pomoću Amselovih kriterija (eng. *Amsel diagnostic criteria)* koji uključuju homogeni vaginalni iscjedak, pozitivan *Whiff* test (miris po ribi nakon dodatka 10% KOH), nalaz tzv. *clue* stanica u mikroskopskom preparatu i pH vaginalnog sekreta veći od 4,5. *Clue* stanice su stanice prekrivene s *G. vaginalis* koje se mikroskopski promatraju i čine osnovu Amselovih kriterija. Miris je najčešći simptom povezan s metabolizmom amina kojeg stvaraju patogeni i porastom pH uslijed smanjenja broja laktobacila (Amsel i sur., 1983; Schmid, 1999; Schwebke i sur., 2004; Sobel, 2000).

Za liječenje bakterijske vaginoze koriste se oralni i lokalni pripravci s ciljem ublažavanja simptoma i smanjenja broja bakterija koje bi mogle dovesti do daljnjih komplikacija. Istraživanja su pokazala da je uspješnost oralne i lokalne terapije bakterijske vaginoze 75-86% iako je lokalnom terapijom zabilježeno manje štetnih učinaka. Metronidazol i klindamicin su najčešće korišteni lijekovi te su dostupni u oblicima i za oralnu i za lokalnu primjenu (Ferris i sur., 1995; Mikamo i sur., 1997; Palmeira-de-Oliveira i sur., 2015). Većina žena uspješno je liječena navedenim antibioticima, međutim kod 30% zabilježen je povratak simptoma unutar 4 tjedna. Razlog tomu je neuspješno uspostavljanje normalne mikroflore,

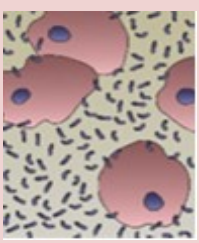
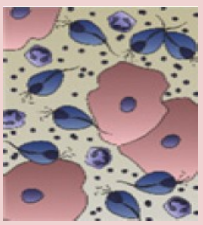
nepotpuno uklanjanje patogena i razvoj rezistencije (Bradshaw i sur., 2006; Schmid, 1999; Sobel, 2000).

Kandidijaza je infekcija uzrokovana gljivicom *Candida* spp., oportunističkim patogenom koji prianja na epitelne stanice i stvara kolonije. *Candida* ima sposobnost stvaranja proteolitičkih enzima, toksina i fosfolipaza koje narušavaju prirodnu zaštitu rodnice (Fidel i Sobel, 1996; Sobel, 2007). Također formira biofilmove što je bitno saznanje u razumijevanju patogeneze kandidijaze (Al-Fattani i Douglas, 2004; Chandra i sur., 2001; Lamfon i sur., 2004; Ramage i sur., 2005). Najčešći simptomi kandidijaze su svrbež, peckanje, iritacija i otekline. Ti simptomi nisu specifični samo za kandidijazu, no popraćeni ″sirastim″ iscjedkom bez neugodnog mirisa daju tipičnu kliničku sliku kandidijaze. Daljnjim pregledom može se utvrditi crvenilo rodnice, eritemi, otekline i fisure (Eckert i sur., 1998; Sobel, 2007). Obzirom da simptomi nisu karakteristični isključivo za kandidijazu, za dijagnozu je potreban mikroskopski pregled vaginalne tekućine i detekcija micelarnog oblika stanica kvasca koji se smatra patogenim fenotipom. Ukoliko se na uzorku vaginalnog razmaza uoče pseudohife ili blastospore potrebno je izraditi kulturu stanica na Sabouraud dekstroznom agaru uz dodatak antibiotika (Mendling, 1988; Sobel, 2007).
Kandidijaza je druga najučestalija infekcija nakon bakterijske vaginoze. Prema literaturnim podacima 70-75% žena barem jednom u životu dobije kandidijazu, a više od polovice njih su u životnoj dobi do 25. godine života (Sobel, 1985). Također kod 40-50% žena bilježi se povratak simptoma, a njih 5-8% razvije rezistentan oblik kandidijaze (Foxman i sur., 1998; Hurley i De Louvois, 1979).
Liječenje kandidijaze se vrlo uspješno provodi topikalnim pripravcima koji sadrže azole. Također je dostupan i topikalni pripravak koji sadrži antibiotik nistatin, no on je manje djelotvoran u odnosu na azole. Terapijom se želi postići što brže olakšanje simptoma (unutar 24-48 sati) te potpuno izlječenje unutar 4-7 dana (Pappas i sur., 2004). Teži slučajevi koji se javljaju kod 10% pacijenatica zahtijevaju dužu terapiju uz kombinaciju oralnih i topikalnih pripravaka (Pappas i sur., 2004; Sobel i sur., 2001).

Trihomonijaza je najčešća spolno prenosiva bolest na svijetu. Uzrokuje ju protozoa *Trichomonas vaginalis* koja pomoću nekoliko adhezina prianja na stanice vaginalnog epitela i postepeno ih uništava. Narušava prirodnu mikrofloru te na taj način omogućava rast drugih anaeroba, što predstavlja rizik za razvoj drugih vaginalnih infekcija (Fichorova i sur., 2013; Hernandez i sur., 2004; Lehker i Alderete, 2000; Mendoza-Lopez, 2000; World Health Organization, 2001).

U 80% slučajeva trihomonijaza je asimptomatska, stoga su podaci o prevalenciji i dalje ograničeni (Sutton i sur., 2007). Ukoliko su simptomi prisutni, tada su to najčešće iritacije lokalnog tkiva, svrbež, pjenasti, žuto-zeleni iscjedak neugodna mirisa te pH>4,5 (Pastorek i sur., 1996). Liječenje se provodi oralnim pripravcima koji sadrže metronidazol ili tinidazol. Lokalni pripravci nisu preporuka zbog mogućnosti nakupljanja aktivne tvari u mokraćnoj cijevi ili žlijezdama (Forna i Gulmezoglu, 2003). Rezistencija na lijekove se javlja vrlo rijetko (2-5% slučajeva na metronidazol) stoga je najčešći uzrok neuspjele terapije nesuradljivost pacijenata ili ponovna zaraza od strane neliječenog partnera (Petrin i sur., 1998; Schmid i sur., 2001; Schwebke i Barrientes, 2006).

Tablica 2. Glavne patofiziološke karakteristike vaginalnih infekcija (prilagođeno prema *Palmeira-de-Oliveira i sur*., (2015) uz dozvolu *Elsevier*-a

	Zdrava sluznica	**Bakterijska vaginoza**	**Kandidijaza**	**Trihomonijaza**
Vaginalni iscjedak	Bijeli, bez ili s mliječnim mirisom, prije menstruacije slabo flokularan, varijabilne viskoznosti tijekom ciklusa	Obilan, kremast, bijelkasto sivi, miris ribe, niske viskoznosti	Bijeli, bez mirisa ili miris na fermentaciju, sirasti izgled, kremast ili folikularan, visoke viskoznosti	Žuto/zeleni, riblji/gnjio miris, niska viskoznost
pH vaginalne tekućine	3,5-4,5	> 4,5	3,5-4,5	> 4,5
Upala i klinički simptomi	Nema	Nema ili slabo peckanje	Crvenilo, oteknuće, peckanje, pruritis	Eritem, crveni plakovi, iritacije i pruritis
Mikroskopska obilježja	Normalne srednje i površinske stanice, brojni laktobacili, rijetko leukociti 	*Clue* stanice, mali broj ili bez leukocita, mnoštvo bakterija 	Varijabilna količina laktobacila i leukocita, blastokonidije i pseudohife 	Prisustvo protozoe, veliki broj bakterija i leukocita, puno parabazalnih stanica 

Kontracepcija

Vaginalni put primjene lijekova može biti namijenjen i za primjenu kontraceptiva. Takvi pripravci mogu sadržavati spolne hormone ili spermicide. Hormonska kontracepcija temelji se smanjenju plodnosti tako što sprječava ovulaciju, potiče zadebljanje cerviksa i tako stvara nepovoljne uvijete za oplodnju. Najčešće se koristi kombinacija steroidnih hormona estrogena i progesterona ili progesteron sam (Lete i sur., 2013). Druga opcija je uporaba spermicida koji djeluju na način da imobiliziraju spermije kako ne bi došlo do oplodnje jajne stanice. Najkorišteniji spermicid je nonoksinol-9 koji oštećuje membranu spermija (Cook i Brown, 2018).

Indukcija poroda

Tijekom poroda niz je čimbenika koji određuju njegovo trajanje. Jedan od tih čimbenika je i zrelost vrata maternice. Ukoliko vrat maternice nema povoljne značajke koje ga čine spremnim za porod ili je zdravstveno stanje majke ili djeteta u opasnosti, potrebno je provesti induciranje porođaja. Induciranje porođaja je danas sve češći proces koji se provodi intravaginalnom primjenom prostaglandina. Prostaglandini u upotrebi su dinoproston (prostaglandin E2) i misoprostol (sintetski analog prostaglandina E1). Najčešće dolaze u obliku vaginalnih gelova (Stewart i sur., 1998; Tenore, 2003).

Profilaksa infekcija uzrokovanih virusom humane imunodeficijencije (HIV)

Virus humane imunodeficijencije (HIV) je spolno prenosivi retrovirus koji uzrokuje stečeni sindrom imunodeficijencije (AIDS). Postoje dva podtipa: HIV-1 i HIV-2. Prenosi se putem sjemene tekućine koja sadrži slobodni virus i zaražene stanice (Ferguson i Rohan, 2011). Provedeno je nekoliko ispitivanja djelotvornosti vaginalno primijenjenog antiretrovirotika u obliku gela u prevenciji HIV-a. CAPRISA 004 faza IIb kliničkih ispitivanja procjenjivala je djelotvornost 1% tenofovir vaginalnog gela. Tenofovir je inhibitor reverzne transkriptaze koji smanjuje prijenos HIV-a tijekom spolnog odnosa. Ispitivanja su pokazala da nanošenje gela prije i nakon spolnog odnosa smanjuje infekciju HIV-om za 39% te da se ženama koje su redovno koristile gel rizik infekcije smanjio za 54%. Ispitivanje se nastavilo u FACTS001 fazu III kliničkih ispitivanja koje je provedeno na 2059 žena iz Južne Amerike. Gel nije

pokazao djelotvornost jer je zahtjevao primjenu u više od 72% spolnih odnosa što je smanjilo adherenciju pacijentica (Abdool i sur., 2010; Mehendale i sur., 2012).

Suplementi endogenih bakterija za profilaksu i liječenje bakterijskih vaginoza

Poznato je da uzročnici bakterijskih vaginoza narušavaju prirodnu vaginalnu mikrofloru smanjujući broj laktobacila koji imaju zaštitnu ulogu. Vaginalnom primjenom probiotika poboljšalo bi se zdravlje vaginalne mikroflore te na taj način spriječilo širenje i rast patogenih bakterija. Na tržištu postoji nekolicina pripravaka za vaginalnu primjenu koji sadrže bakterije roda *Lactobacillus* i *Bifidobacterium*, no nužno je provesti detaljnija istraživanja o djelotvornosti ove terapije (Anukam i sur., 2006; Reifer i Miller, 2010).

2. OBRAZLOŽENJE TEME

Vaginalne infekcije i njihovi simptomi najčešći su uzrok smanjene kvalitete života žena zbog negativnog utjecaja na fizičko, ali i mentalno zdravlje. Prednost vaginalnog puta primjene lijekova nad oralnim putem primjene je zaobilaženje prvog prolaska lijeka kroz jetru, smanjenje sistemske apsorpcije lijekova namijenjenih lokalnoj terapiji, smanjenje neželjenih sistemskih nuspojava, postizanje veće koncentracije lijeka na ciljanom mjestu te jednostavna i bezbolna primjena. Iako na tržištu postoje različiti oblici pripravaka za vaginalnu primjenu, polučvrsti oblici poput krema, gelova i pjena, pokazali su se najprihvatljivijim i najčešće korištenim ljekovitim oblicima. Stoga je svrha ovog rada pružiti detaljan pregled polučvrstih oblika za vaginalnu primjenu, njihove tehnološke značajke i nove pristupe u razvoju terapijski učinkovitih formulacija. Prikazani su rezultati odabranih pretkliničkih i kliničkih istraživanja polučvrstih oblika za vaginalnu primjenu lijekova.

3. MATERIJALI I METODE

Za proučavanje literature i izradu diplomskog rada korišteni su članci objavljeni u znanstvenim i stručnim časopisima, a pronađeni pretraživanjem *on-line* baza podataka: *Scopus*, *Science direct, Elsevier, Pub Med* i *CROSBI*. Prilikom pretraživanja korištene su ključne riječi na engleskom jeziku: *vaginal drug delivery, vaginal anatomy, vaginal mucosa, drug delivery systems, semi-solid formulations, vaginal gel, mucoadhesive drug delivery, vaginal infections, vaginal atrophy, aerosol foams, foams in gynecology, vaginal cream, vaginal emulsion, vaginal lubricants, thermogelling gels, thermosensitive gels, bioadhesive polymers, vaginal dosage forms,.* Također je korištena i baza lijekova *Hrvatske agencija za lijekove i medicinske proizvode* (HALMED).

Kako bi se definirao znanstveni i stručni problem, znanstvena literatura je proučavana analitički i kritički. Kroz pretraživanje i proučavanje znanstvene literature traženi su odgovori na problematiku ovog rada te su izdvojeni značajniji rezultati istraživanja kao i rasprave i zaključci.

4. RASPRAVA

4.1. KREME

Kreme su polučvrste emulzije U/V tipa (hidrofilna krema) ili V/U tipa (lipofilna krema) koje se većinom primjenjuju na kožu. Uljnu fazu čine ugljikovodici (vazelin, tekući parafin, voskovi), masne kiseline (stearinska, palmitinska) i njihovi esteri (-mono, -di, -tristearati), biljna ulja, masni alkoholi (cetilni, stearilni, oleilni) i druge tvari topljive u ulju. Za razliku od uljne faze, vodenu fazu čine humektansi (sorbitol, glicerol, propilen-glikol), ugušćivači (škrob, alginati, karbopoli, tragant, derivati celuloze i dr.) te ostale tvari topljive u vodi. Osim emulgiranih krema, koje sadrže dvije faze, postoje i bezvodne kreme koje su izrađene od 100% uljne faze, bez dodatka vode. Budući da su kreme s tehnološkog aspekta emuzije, one sadrže emulgatore koji mogu biti ionogeni (anionaktivni i kationaktivni), neionogeni ili amfoterni (ovisno o ionskom karakteru molekule). Za osiguranje stabilnosti, kremama se dodaju konzervansi i antioksidansi (Filipović-Grčić, 2001). Konzervansi su uglavnom topljivi u vodi i to su sorbinska kiselina i kalijev sorbat do 0,3%, natrijev benzoat do 0,1% i *pulvis conservans* kojem se propil-paraben ugradi u masnu fazu, a metil paraben u vodenu. Antioksidansi se dodaju kako bi se sprječila oksidacijska razgradnja uljne faze. Kao antioksidansi se koriste butilhidroksitoluen s butilhidroksianisolom (BHT i BHA) do 0,2%, askorbil-oleat i askorbil palmitat do 0,3% (Filipović-Grčić; 2001; Garg i sur., 2001).

Osim na kožu, kreme se primjenjuju i vaginalno za tretiranje simptoma menopauze, vaginalne atrofije te liječenje vaginalnih infekcija. Tablica 3 donosi pregled komercijalno dostupnih registriranih vaginalnih krema na području Republike Hrvatske.

4.1.1. Vaginalna primjena krema

Vaginalne kreme za tretiranje vaginalne atrofije

Menopauza je prirodan proces u životu svake žene koji označava kraj fizioloških menstrualnih krvarenja, odnosno kraj reproduktive dobi žene. U 45% žena u menopauzi javljaju se simptomi vaginalne suhoće, iritacije, svrbež te kod spolno aktivnih žena dispareunija (Haspel i sur., 1981). Kao najučinkovitija terapija pokazao se oralno i vaginalno primijenjen estrogen koji smanjuje vaginalnu suhoću i vaginalnu atrofiju (Lindahl, 2014). Dickerson i suradnici (1979) proveli su studiju kako bi odredili razinu estrogena nakon noćne primjene kreme s estradiolom te učinkovitost pripravka na simptome menopauze. 20 pacijentica primjenjivalo je 0,01% kremu s estradiolom kroz 14 dana navečer prije spavanja.

Nakon 14 dana razina estradiola u plazmi iznosila je 70,4 pg/ml te se krema pokazala učinkovitom u smanjivanju vaginalne atrofije.

Kako bi usporedili uspješnost terapije estrogenom korištenjem vaginalnih tableta i kreme, Rioux i suradnici (2018) uspoređivali su 17β-estradiol vaginalne tablete (Vagifem®) s vaginalnom kremom konjugiranog konjskog estrogena (Premarin® Vaginal Cream). Obje formulacije su bile djelotvorne u uklanjanju simptoma vaginalne atrofije (suhoća, iritacija, osjetljivost), no povećanje serumske koncentracije estradiola i supresija folikulo-stimulirajućeg hormona bilo je značajnije kod pacijentica koje su koristile vaginalnu kremu. Također, kod nekoliko pacijentica koje su koristile vaginalne tablete zabilježena je proliferacija ili hiperplazija endometrija, dok kod pacijentica koje su koristile vaginalnu kremu nije.
Učinak vaginalne kreme na vaginalnu atrofiju uspoređivan je i s vaginalnim prstenom. U studiji Barentsen i suradnika (1997) uspoređivana je učinkovitost terapije estradiolom primjenom vaginalnog prstena (Estring®) te estriolom primjenom kreme (Synapause®) u trajanju od 12 tjedana. Studija je pokazala jednaku djelotvornost oba pripravka na smanjenje simptoma vaginalne atrofije, obnavljanje vaginalne mukoze i smanjenje vaginalnog pH.

Iako su u posljednja dva desetljeća vaginalne kreme s estrogenima najuspješnija terapija postmenopauzalne vaginalne atrofije, sve je veći broj nuspojava povezanih s njihovom primjenom. Proliferacija endometrija i mastodinija samo su neke od nuspojava koje nastaju zbog povećane koncentracije estrona (E1) i estradiola (E2). Primjenom vaginalnih krema koje sadrže niske doze estriola (E3) može se postići djelotvorna terapija bez navedenih nuspojava. To je potvrđeno u studiji koju su proveli Kicovic i suradnici (1980) s Ovestin® vaginalnom kremom.

Jedna od alternativa terapiji estrogenom je korištenje pripravaka s fitoestrogenima (Jassim, 2011; Thacker, 2011). To su biljne tvari s estrogenim djelovanjem, a jedan od njih je i sladić (*Glycyrrhiza glabra)*. Sladić sadrži izoflavone, fitoestrogene slične estronu i estradiolu koji povoljno utječu na hormonsku ravnotežu (Hajirahimkhan i sur., 2013). Sadeghi i suradnici (2018) su ispitivali utjecaj vaginalne kreme s 2% tekućeg ekstrakta sladića na simptome i znakove vaginalne atrofije kod postmenopauzalnih žena. Osnovu kreme u koju je uklopljen tekući ekstrakt sladića činili su vazelin (17% w/w), mineralno ulje (10% w/w), acetilni alkohol (13% w/w) u uljnoj faze te voda (30% w/w) i benzilni alkohol (30% w/w) u vodenoj fazi. Nakon 8 tjedana terapije simptomi su se značajno smanjili, vaginalna sluznica se obnovila te se pH značajno snizio. Osim sladića, i komorač (*Foeniculum vulgare*) povoljno

djeluje u tretiranju vaginalne atrofije. Komorač sadrži trans-anetol i dianetol s estrogenskim djelovanjem čime se smanjuju simptomi vaginalne atrofije (Abedi i sur., 2016).

Kemoterapija i povećana upotreba inhibitora aromataze u pacijentica s karcinomom dojke dovodi do smanjenja razine estrogena, a time i do prijevremene menopauze (Chin i sur., 2009; Kwan i Chlebowski, 2009; Partridge, 2015). Upotreba pripravaka s estrogenom u takvoj skupini pacijentica je rizična te se stoga kao alternativa u liječenju simptoma menopauze koriste pripravci bez hormona. Radi se o lubrikantima, odnosno gelovima koji pružaju kratkotrajni hidratizirajući učinak na sluznicu. S druge strane, vaginalne kreme sadrže, uz vodeni dio koji hidratizira sluznicu i lipide koji stvaraju film i sprječavaju gubitak vode, čime se osigurava dugotrajniji terapijski učinak na sluznicu (Carter i sur., 2011; Sinha i Ewies, 2013; Sturdee i Panay, 2010). Chatsiproios i suradnici (2019) proveli su studiju na pacijenticama s karcinomom dojke koje primaju kemoterapiju ili hormonsku terapiju te pate od vaginalne suhoće. Pacijentice su primjenjivale U/V emulziju (Vagisan® hidratantnu kremu) koja sadrži 23% lipida. pH kreme prilagođen je s mliječnom kiselinom na vrijednost 4,5, a osmolalnost pripravka iznosila je 374 mOsmol/kg. Nakon terapije u trajanju od 2-4 tjedna, pacijenticama su smanjeni simptomi vaginalne suhoće (crvenilo, točkasto krvarenje, stanjen epitel).

Vaginalne kreme s progesteronom

Progesteron je na tržištu dostupan u oblicima za oralnu i parenteralnu primjenu. Premda je parenteralna terapija učinkovita jer osigurava dovoljnu razinu hormona u krvi, nije dobro prihvaćena od strane pacijentica zbog bolne primjene. S druge strane, oralno primijenjen progesteron se metabolizira u probavnom sustavu i jetri što može biti ograničavajući parametar u pogledu učinkovitosti terapije (Nahoul i sur., 1987). Obećavajući rezultati postignuti su korištenjem vaginalne kreme s mikroniziranim progesteronom. Naime, koncentracija lijeka u plazmi nakon 24 sata bila je značajno viša korištenjem vaginalne kreme (13,9±2,3 ng/mL) u odnosu na vrijednosti progesterona izmjerene nakon oralne primjene (1,9±0,3 ng/mL) u istom vremenskom periodu (Kimzey i sur., 1991).

Vaginalne infekcije

Za liječenje vaginalnih infekcija na području Republike Hrvatske dostupno je šest registriranih proizvoda vaginalnih krema, većinom s antifungalnim lijekovima (Tablica 3). Osim tzv. „klasičnih“ antimikrobnih lijekova, u terapiji vaginalne kandidijaze djelotvornim se pokazala i vaginalna krema s eteričnim uljem biljke *Zataria multiflora*. Naime, *Z. multiflora*

sadrži karvakrol, timol i eugenol koji posjeduju antimikrobni učinak te djeluje protiv uzročnika kandidijaze (Fataneh, 1991; Mahmoudabadi i sur., 2006). Nakon sedmodnevne primjene vaginalne kreme s 0,1% eteričnog ulja *Z. multiflora* smanjeni su simptomi kandidijaze: svrbež kod 80,9% pacijentica, bol prilikom spolnog odnosa kod 92,6% pacijentica i vaginalno peckanje kod 73,9% pacijentica (Khosravi i sur., 2000).

Humani papiloma virus (HPV)

Infekcije humanim papiloma virusom (HPV) jedan su od glavnih uzročnika smrti žena diljem svijeta (Jemal i Bray, 2011) te su stoga istraživanja u ovom području od velikog medicinskog značaja. Debata i suradnici (2013) su ispitivali mogućnost korištenja kurkumina za liječenje HPV infekcija zbog antiviralnog i antitumorskog učinka kurkumina. Primjenom vaginalne kreme s kurkuminom (Vacurin) postignuta je selektivna eliminacija HPV(+) stanica, inhibicija ekspresije receptora za epidermalni faktor rasta i indukcija tumor surpresorskog gena p53. Također je ispitivana djelotvornost 5% imikvimod kreme (Aldara®) u terapiji infekcije HPV-om kod žena s intraepitelnom neoplazmom. Terapija je trajala 8 tjedana, a provedeni testovi biopsije i Papa test pokazali su učinkovitost terapije kod 76,3% pacijentica (Chen, 2012).

Tablica 3. Komercijalno dostupne vaginalne kreme na tržištu Republike Hrvatske (www.halmed.hr, pristupljeno 8.8.2019)

Zaštitno ime	Djelatna tvar	Proizvidač	Primjena
Canesten® 3	Klotrimazol	Kern Pharma	Vaginalne infekcije
Dalacin®	Klindamicin	Pfizer	Vaginalne infekcije
Linoladiol®	Estradiol	Dr. August Wolff	Vaginalna atrofija
Lomexin®	Fentikonazol	Recordati	Vaginalne infekcije
Macmiror® Complex	Nifuratel, Nistatin	Doppel	Vaginalne infekcije
Vagisan® Myko Kombi	Klotrimazol	Dr. August Wolff	Vaginalne infekcije

4.2. PJENE

Prema definiciji Europske farmakopeje, pjene su formulacije u kojma je pogonski plin (propelent) dispergiran (emulgiran) u tekućoj fazi pripravka. To su sustavi koji se sastoje od dvije ili tri faze:

- hidrofilna faza - otapalo, sredstvo za pjenjenje, stabilizator pjene
- plinska faza - pogonski plin ili propelent (n-pentan, izo-pentan, izo-butan)
- lipofilna faza - dispergirana u hidrofilnoj (Purdon i sur., 2003).

Razlikuju se dva tipa pjena, tekuće i čvrste pjene. Tekuće pjene građene su od mjehurića plina obavijenih tekućim filmom, dok čvrste pjene nastaju kada tekuća faza pjene prijeđe u gel stanje ili se taj prijelaz dogodi nakon formiranja pjene (Bauer i sur., 1999; Vaz, 2008). Takve pjene su poznate i pod nazivima suhe pjene, spužve ili kserogel, a sadržavaju najčešće antibiotike i steroide (Edwards i Panay, 2016). Također postoje i pjene koje umjesto vode koriste hidrofilna otapala poput propilenglikola, polietilenglikola (PEG) ili glicerola. Pjene su termodinamički nestabilni sustavi s velikom površinom koja ima tendenciju smanjivanja (Wilson, 1989). Naime, mjehurići unutar pjene mogu varirati u veličini i obliku ovisno o načinu izrade formulacije, odnosno o koncentraciji sredstva za pjenjenje, pH, viskoznosti i temperaturi. Oblik im varira od sferičkog do nepravilnog polihedralnog oblika. Primjerice, pri umjerenoj količini plinovite faze, mjehurići dispergirani u lipidnoj fazi biti će jednolični i sferični. Povećanjem količine plinovite faze (>0,7) nastati će deformirani polihedralni mjehurići, stisnuti jedan uz drugog i odvojeni tankim slojem koji se naziva lamela (Hansen i Derderian, 1976; Yoshimura, 1988). Tri su faze nastanka pjene:

1. otopina sredstva za pjenjenje bez inkorporiranog zraka,
2. emulzija plina - otopina uklapa zrak i nastaju mjehurići koji se pri nižim volumenima ne dodiruju,
3. pjena – polihedralni mjehurići koji se dodiruju lamelama (Arzhavitina i Steckel, 2010).

Kako bi se proizvela izdržljiva, gusta pjena potrebno je uzeti u obzir viskoznost površine (unakrsnim povezivanjem molekula surfaktanta na površini stvara se gusta pjena), elastičnost površine (sposobnost da se mala puknuća mjehurića poprave), ukupnu viskoznost i moguće odbijanje kationskih ili anionskih surfaktanata (Shinde i sur., 2013). Stabilizacija pjene postupak je kojim se sprječava promjena volumena ili visine pjene. Povećanjem koncentracije sredstva za pjenjenje, povećava se i elastičnost površine, a time i stabilnost. Također, pjene koje sadrže veći volumen plina su stabilnije. Primjenom tiksotropnih tvari poput MC, arapske

gume i sličnih, povećava se viskoznost pripravka koja sprječava odvajanje faza (Arzhavitina i Steckel, 2010).

Pomoćne tvari u pjenama

Tekućina sama ne može stvarati pjenu te je nužna uporaba sredstva za pjenjenje koje će stvoriti i stabilizirati pjenu (Arzhavitina i Steckel, 2010). To su amfipatske tvari s hidrofilnim i hidrofobnim dijelom. Hidrofilni dio omogućava topljivost u vodi, a hidrofobni dio stabilizira pjenu. Prilikom stvaranja pjene, hidrofobne molekule se raspodijele tako da smanje kontakt s vodom što dovodi do njihovog nakupljanja na površinu zrak-voda, stvaranja micela i smanjenja površinske napetosti vode (Wilson, 1989). Kombinacija više sredstava za pjenjenje može dovesti ili do ubrzanog stvaranja i veće stabilnosti pjene ili do smanjenja stabilnosti. Također postoje i tvari koje mogu ubrzati nastanak pjene, tzv. pojačivači pjene (eng. *foam boosters*). Ne smiju se koristiti u koncentracijama većim od 5% jer u suprotnom mogu uzrokovati iritacije sluznice. To su najčešće amidi masnih kiselina i alkohola primjerice dietanolamid oleinske kiseline (Arzhavitina i Steckel, 2010). Za povećanje stabilnosti mogu se koristiti i polimeri poput derivata celuloze, ksantanske gume i derivata poliakrilne kiseline. Naime, poliakrilna kiselina u reakciji s neionskim surfaktantima stvara polimer-surfaktant kompleks koji doprinosi stabilnosti pjene. Popis pomoćnih tvari koje se koriste u izradi pjena prikazan je u Tablici 4.

Tablica 4. Pomoćne tvari u izradu pjena za dostavu lijekova. Preuzeto i prilagođeno iz *Namdeo i sur*., (2013) uz dozvolu *Creative Commons Attribution License* –a.

Stabilizatori pjene	Natrij laurilsulfat, laurinska kiselina, miristinska kiselina, palmitinska kiselina, stearinska kiselina, ulje kokosa, karagenan, monoetanolamin stearinske kiseline, tragakant, alginat, želatina, natrij CMC, polivinilglikol, glicerol, sorbitol
Sredstva za pjenjenje	Stearinska kiselina, hidrogenirano ulje ricinusa, polisorbat 20, PEG-40 hidrogenirano ulje ricinusa, poloksamer F68, kokamidopropil-betain
Vodotopljivi polimeri	Ksantanska guma, agar, guar guma, HEC, HPC, HPMC, MC
Otapala	Polietilenglikol, propilenglikol, glicerol, voda, alkohol

CMC, karboksimetilceluloza; HEC, hidroksietilceluloza; HPC, hidroksipropilceluloza; HPMC, hidroksipropilmetilceluloza; MC, metilceluloza; PEG, polietilenglikol

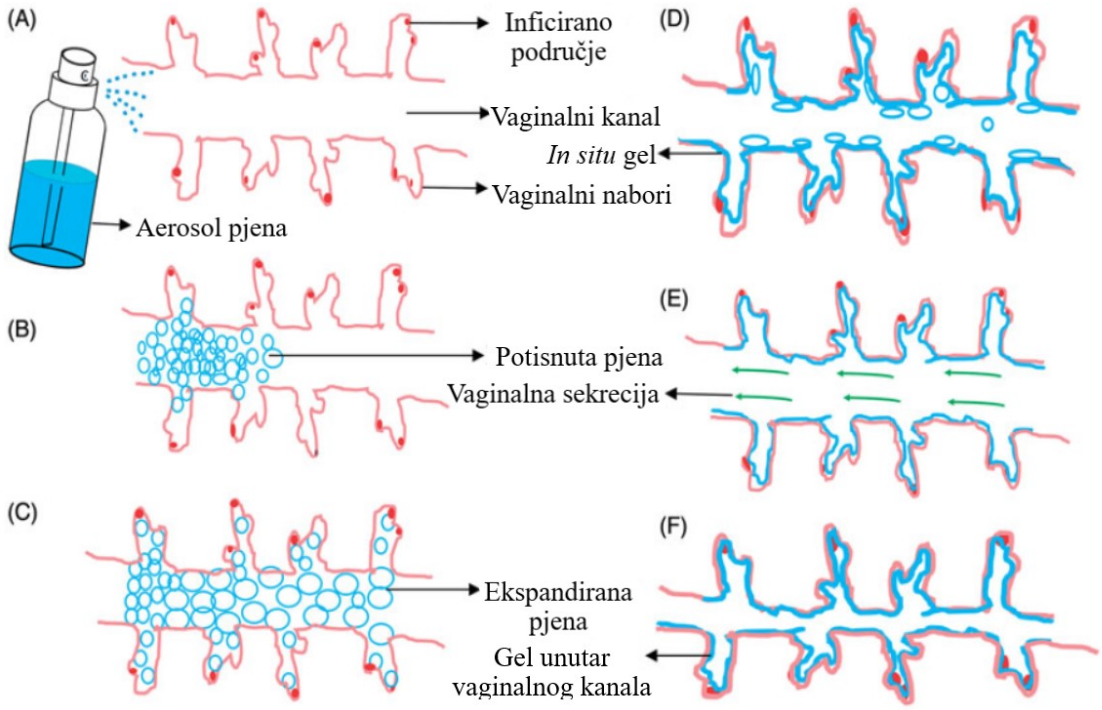
Korištenjem pjena za vaginalnu primjenu utvrđena je bolja penetracija lijeka u sluznicu nego s konvencionalnim oblicima. Naime, nakon što pomoćne tvari i otapala iz pjene ispare ili se razgrade, visoki koncentracijski gradijent lijeka osigurava brzu i efikasnu apsorpciju u sluznicu. Aerosoli pjene su prikladnan oblik za uklapanje lijekova različite molekularne mase i lipofilnosti, osjetljivih na toplinu i svjetlost (Shinde i sur., 2013).

4.2.1. Ekspanzivna termogelirajuća pjena za vaginalnu primjenu lijekova (ETGFA)

Aerosoli pjene za vaginalnu primjenu karakterizirane su izvrsnim rasprostiranjem na površini sluznice i penetracijom uklopljenog lijeka u dublje slojeve rodnice, no pripravak se relativno kratko zadržava na mjestu primjene što smanjuje efikasnost terapije. Nasuprot tome, gelovi imaju dobra mukoadhezivna svojstva te mogu osigurati produljeno oslobađanje lijeka (Mei i sur., 2017; Timur i sur., 2017; Tugcu-Demiroz, 2017). Međutim zbog visoke viskoznosti ponekad se teže rasprostiru po površini sluznice (*rugae vaginales*) (Caramella i sur., 2015). Uzevši u obzir prednosti i ograničenja aerosol pjene i gela, Mei i suradnici (2017) su razvili ekspanzivnu termogelirajuću aerosol pjenu (eng. *expansible thermal gelling foam aerosol,* ETGFA). Primjenom ETGFA terapijskog sustava bi se postiglo dobro rasprostiranje formulacije po površini sluznice i u vaginalne nabore (*rugae vaginales*) te bi pri fiziološkoj temperaturi došlo do geliranja, čime bi se omogućio bolji kontakt lijeka sa sluznicom (Slika 3).

Za izradu ETGFA korišteni su P407, P188, karbopol, čestice srebra i voda u omjeru težine 21:6,5:0,2:0,01:72,3. Takva kombinacija omogućila je postizanje optimalnih svojstva pjene, temperature geliranja (35,7±0,3 °C) i adhezivnosti. Svojstva pjene kao što su opseg ekspanzije i vrijeme trajanja pjene ovise i o izboru propelenta (pogonskog plina). Vrijeme trajanja pjene mora biti dovoljno dugo kako bi se dogodilo geliranje ETGFA prije raspadanja pjene. Trajnost pjene iznosila je 123 min, a vrijeme geliranja ETGFA izmjereno na 37 °C iznosilo je 8,7 minuta što omogućava pjeni da ekspandira do maksimalnog volumena i transformira ETGFA u gel prije nego se pjena raspadne. Adhezivna svojstva ETGFA uspoređivana su s komercijalno dostupnim vaginalnim gelom Asimi® te se pokazalo da ETGFA ima bolja adhezivna svojstva zahvaljujući karbopolu. Uspoređivana je i sposobnost oslobađanja antimikrobnih lijekova *in vitro* testovima te su oba pripravka, ETGFA i Asimi® pokazali produljeno oslobađanje. Testovi iritacije provodili su se uspoređivanjem fiziološke otopine, ETGFA bez čestica srebra i ETGFA s česticama srebra. ETGFA formulacija bez

čestica srebra pokazala je slabu hiperkeratozu vaginalnog epitela i infiltraciju eozinofila. Kod ETGFA sa česticama srebra primijećena je dodatno i infiltracija limfocita u endometriju. Antimikrobno djelovanje ETGFA posljedica je penetracije čestica srebra u bakterijske stanice (Mei i sur., 2017).



Slika 3. Shematski prikaz ekspanzivne termogelirajuće aerosol pjene tijekom ekspanzije, geliranja i zadržavanja na sluznici. (A) primjena ETGFA u obliku aerosol pjene; (B) aerosol pjena je potisnuta u vaginalni kanal pomoću repelenta; (C) pjena ekspandira i prodire do mjesta infekcije; (D) pjena pod utjecajem temperature gelira i gel prekriva inficirana područja (E) otpornost gela na vaginalnu sekreciju; (F) otpornost gela na vaginalnu kontrakciju Preuzeto i prilagođeno iz *Mei i sur.,* (2017) uz dozvolu *Creative Commons Attribution License*-a.

4.2.2. Post-ekspanzivna gel pjena s liposomima

Fosfolipidne vezikule (liposomi) imaju veliki potencijal kao nosači lijekova za vaginalnu primjenu, no tekuća konzistencija takvih nanosustava (ukoliko nije riječ u mukoadhezivnim liposomima) može biti ograničavajući parametar njihove topikalne primjene (Pavelić i sur., 2005; Mallipeddi i Rohan, 2010). Zanimljiv pristup vaginalne primjene liposoma predstavili su Li i suradnici (2012). Riječ je o post-ekspanzivnoj hidrogel (eng. *post-expansile hydrogel*

foam aerosol of propylene glycol liposomes, PEHFL) pjeni s propilenglikol (PG) liposomima. U liposome je uklopljen matrin, lijek koji ima izvrsna imunoregulatorna i protuupalna svojstva. Autori su ispitivali penetraciju matrina iz PEHFL-a i rezultate uspoređivali s onim dobivenim iz liposoma s matrinom u aerosol pjeni (eng. *propylene glycol liposomes foam aerosol*, PLFA), matrina uklopljenog u gel aerosol pjenu (eng. *hydrogel foam aerosol*, HFA) i matrina u gelu (eng. *hydrogel*, HYG). Pokazali su da PEHFL ima veliku sposobnost bubrenja koje raste porastom temperature te da takav sustav omogućuje bolju distribuciju lijeka po površini vaginalne sluznice i dulji kontakt lijeka sa sluznicom. U usporedbi s ostalim formulacijama PEHFL je pokazala najdulje vrijeme postojanosti pjene, što upućuje na povoljan utjecaj liposoma na stabilnost pjene. Penetracija matrina iz PEHFL-a u vaginalnu sluznicu je bila 2,64, odnosno 2,34 i 7, 59 puta veća od one postignute korištenjem PLFA-a HFA-a i HYG-a, te je prisustvo lijeka na površini sluznice dokazano čak 12 sati nakon primjene formulacije (Li i sur., 2012).

4.3.GELOVI

Gelovi su polučvrsti oblici za vaginalnu primjenu lijekova. To su trodimenzionalni polimerni matriksi koji sadrže mali udio čvrste tvari (polimera) dispergirane u velikoj količini vode (> 80%) (Justin-Temu i sur., 2004). Građeni su reverzibilno umreženih dugih, nepravilnih lanaca te posjeduju svojstva sličnija krutinama nego tekućinama (das Neves i sur., 2006). Prednosti gelova nad ostalim oblicima za vaginalnu primjenu lijekova su sigurnost, kompatibilnost sa sluznicom, prilagodljivost, dobro rasprostiranje po površini, visoka bioraspoloživost, brzo oslobađanje lijeka te niska cijena (Justin-Temu i sur., 2004; Vanić i sur., 2014).

Svojstva gela, kao što su hidrofilnost, viskoznost, bioadhezija i distribucija, mogu značajno utjecati na oslobađanje lijeka (Keller i sur., 2003). Stoga je, prilikom razvoja formulacije gelova za vaginalnu primjenu, važno provesti istraživanja:

- profila oslobađanja lijeka i permeabilnosti lijeka kroz vaginalnu sluznicu,
- mehaničkih svojstava (reološka i teksturna svojstva),
- toksikološkog profila i mogućnosti iritacija,
- distribucije i zadržavanja ljekovitog oblika na mjestu primjene,
- kompatibilnosti s pomoćnim tvarima, te
- mukoadhezivnosti i stabilnosti tijekom skladištenja (das Neves i sur., 2006; Vanić i sur., 2014).

Sastav gela ima veliki utjecaj na reološka svojstva. Promjenom samo jedne sastavnice gela doći će do značajne promjene u reološkom ponašanju ljekovitog oblika (das Neves i sur., 2006; Owen i sur., 2001). U pogledu viskoznosti gelova, idealnu vrijednost viskoznosti je teško definirati (Garg i sur., 2001). Često se prilikom istraživanja viskoznosti uzima u obzir samo utjecaj neotopljenih tvari u gelu, no pokazalo se da i makromolekule koje stvaraju interakcije s vaginalnim okolišem pridonose viskoznosti. Temperatura, interakcije s vaginalnom tekućinom i pH također utječu na promjenu viskoznosti. Stoga se pri formulaciji gela za vaginalnu primjenu svi ti čimbenici moraju uzeti u obzir (Owen i sur., 2003). *Texture profile analysis (TPA)* je tehnika korištena za određivanje reoloških svojstava polučvrstih oblika. Prednost metode je što se dobivaju dragocjeni podaci o čvrstoći, kohezivnosti i o adhezivnosti pripravka (Jones i sur., 2002). Reološka svojstva imaju veliki utjecaj na distribuciju i zadržavanje gela na mjestu primjene što je ključno za postizanje terapijske učinkovitosti pripravka (El-Gizawy i Aglan, 2003; Owen i sur., 2000). Primjerice, pravilan odabir viskoznosti gela omogućit će ravnomjernu distribuciju i dovoljno dugo zadržavanje gela na vaginalnoj sluznici (Di Fabio i sur., 2003; Geonnotti i sur., 2005). Osim reoloških svojstava, volumen primjene i spolni odnos također doprinose distribuciji gela na sluznici (Barnhart i sur., 2005). Dulje zadržavanje gela na mjestu primijene danas se postiže i upotrebom gelova izrađenih od mukoadhezivnih polimera. Pomoćne tvari u gelovima važne su za formuliranje gelova, no mogu pokazati toksično djelovanje na vaginalnu sluznicu. Osim što je važno dokazati njihovu sigurnost toksikološkim ispitivanjima, važno je i njihovo protektivno djelovanje na sluznicu, primjerice prilikom upotrebe iritirajućih djelatnih tvari kao što je nonoksinol-9 (Amaral i sur., 1999). Provode se *in vitro* testovi na vaginalnim epitelnim stanicama ili tkivu te svako odstupanje izloženih stanica od normalne građe može biti pokazatelj toksičnosti (D'Cruz i sur., 2004). *In vivo* testovi se također provode u ispitivanjima toksičnosti te se smatraju najpouzdanijima (das Neves i sur., 2006). Toksičnost se dokazuje nakon jednokratne ili višekratne izloženosti sluznice ispitivanom pripravku, a procjenjuje se prema nastalim promjenama na epitelu, promjenama vaginalne flore, određivanjem proupalnih citokina u vaginalnoj tekućini ili prijavom simptoma od strane žena nadležnim liječnicima, ljekarnicima i institucijama (Mauck i sur., 2004; Paternoster i sur., 2004; Patton i sur., 1999).

Pomoćne tvari u gelovima

Pomoćne tvari korištene u gelovima su omekšivači, konzervansi, promotori permeabilnosti, antioksidansi i veziva (Vanić i Jug, 2017). To su tvari koje poboljšavaju svojstva gela i time pridonose suradljivosti pacijenata što je ključno za postizanje terapijskog učinka. Toksikološki i farmakološki su inertne tvari te nemaju terapeutski učinak (Pifferi i Restani, 2003).

- **Omekšivači** su tvari koje štite od isušivanja i povećavaju distribuciju pripravka na mjestu primjene. Čine 10-20% pripravka te mogu imati i ulogu suotapala (povećava topljivost lijeka) i humektansa. To su glicerol, propilenglikol, sorbitol i etilenglikol.
- **Gelirajuća sredstva** su prirodne i sintetske makromolekule koje pospješuju stvaranje gela. Polimeri koji se najčešće koriste kao gelirajuća sredstva prikazani su u Tablici 3. Ahmad i sur. (2008) proučavali su kako polimeri utječu na oslobađanje metronidazola i klotrimazola iz ljekovitog oblika. Ispitivali su bioadhezivne polimere kao što su derivati celuloze, natrijev alginat, ksantan guma, guar guma, polikarbofil i karbopol. Istraživanje je pokazalo da se promjenom udjela polimernih komponenti može promijeniti oslobađanje metronidazola i klotrimazola za 1-5,5 sati. Gupta i sur. (2016) koristili su karbopol kako bi izradili gel koji bi imobilizirao spermije u roku 20 sekundi.
- **Konzervansi** su tvari koje osiguravaju mikrobiološku stabilnost ljekovitih pripravaka. To su parabeni, alkoholi, kvarterni amonijevi spojevi i organske kiseline. Mogu sprječavati razmnožavanje mikroorganizama (mikrobiostatici) ili trajno oštetiti mikroorganizme (mikrobiocidi). Zbog visokog udjela vode hidrogelovi su pogodni za razvoj mikroorganizama (plijesni, bakterije, gljivice) te je stoga uporaba konzervansa nužna. Kontaminacija pripravaka moguća je tijekom proizvodnog procesa, korištenjem kontaminiranih sirovina ili tvari prirodnog podrijetla (gume, sirupi), uslijed korištenja ili nepravilnog čuvanja (Vanić i Jug, 2017).
- **Promotori permeabilnosti** olakšavaju prodiranje djelatne tvari kroz sluznicu (Vanić i Jug, 2017).
- **Antioksidansi** se koriste u formulacijama kako bi spriječili oksidacijske procese. To su butilhidroksitoluen (BHT), askorbinska kiselina i tokoferol (Vanić i Jug, 2017).

Iako pomoćne tvari korištene u izradi ljekovitih oblika nemaju terapijski učinak, ponekad je važno koristiti pomoćne tvari koje doprinose terapijskom učinku lijeka. Primjerice,

hidrogelovi u čijoj izradi je korišten karagenan mogu povoljno djelovati na liječenje HIV infekcija. Naime, karagenan tvori negativno nabijen sloj koji sprječava adheziju HIV stanica na vaginalni epitel (Coggins i sur., 2000). Prije korištenja, pomoćnim tvarima potrebno je dokazati biokompatibilnost. Stoga je potrebno provesti testove na kulturama stanica pri čemu se biokompatibilnost određuje iz stupnja rasta stanica, testom proliferacije stanica, testom na nitrite i testom citotoksičnosti. Također, diferencijalna pretražna kalorimetrija (eng. *differential scanning calorimetry, DSC)* koristi se za procjenu povezanosti korištenja ljekovitog oblika na bazi polimera s narušavanjem lipidnog sloja vaginalne sluznice (Wang i Lee, 2002).

Tablica 5. Polimeri korišteni za izradu vaginalnih hidrofilnih gelova. Preuzeto i prilagođeno iz *das Neves i Bahia* (2008) uz dozvolu *Elsevier*-a.

POLIMER
Carbopol®
Želatina
Hidroksietilceluloza (HEC)
Hidroksipropilceluloza (HPC)
Hidroksipropilmetilceluloza (HPMC)
Metilceluloza (MC)
Polikarbofil
Polietilenglikol
Hijaluron polisaharid
Polivinilpirolidone
Natrijev alginat
Natrij karboksimetilceluloza (NaCMC)
Škrob

4.3.1. Termoosjetljivi gelovi

Termoosjetljivi gelovi su pripravci koji su na sobnoj temperaturi u tekućem agregatnom stanju (niska viskoznost), a porastom temperature (37 °C) geliraju. Prednost takvih sustava je što su niske viskoznosti za vrijeme prolaska kroz aplikator što im olakšava primjenu i dobro rasprostiranje po sluznici. Na mjestu primjene tekući pripravak prelazi u gel stanje čime se omogućuje dobro zadržavanje lijeka na vaginalnoj sluznici (Cook i Brown, 2018). Najvažniji parametar termoosjetljivih gelova je specifična temperatura geliranja (Tgel) koja mora biti u rasponu od 25 do 37 °C (Chang i sur., 2002). Termogelirajuća svojstva gelova posljedica su korištenja specifičnih polimera od kojih su najčešće korišteni poloksameri.

Poloksamer je generički naziv za sintetske poli(etilenoksid-propilenoksid-etilenoksid)(EO_a-PO_b-EO_a) triblok kopolimere molekularne mase 1100-14000 Da sastavljene od etilenoksida i propilenoksida u omjerima koji variraju od 1:9 do 8:2 (Ruel-Gariepy i Leroux, 2004). Poloksameri su pomoćne tvari koje se široko koriste u farmaceutskoj industriji pod nazivom Lutrol® u Europi i Pluronic® (BASF) u Americi. Nalaze na GRAS (eng. *generally recognized as safe*) listi za oralne, nazalne, rektalne, vaginalne, oftalmičke i kutane pripravke (Sandri i sur., 2011). Najčešće korišteni su poloksamer 188 (Pluronic® F68, P188) molekularne mase 7680-9510 Da i poloksamer 407 (Pluronic® F127, P407) molekularne mase 9840-14600 Da (Patel i Patel, 2009). Zbog slabih mukoadhezivnih svojstava, poloksamerni gelovi se često kombiniraju s mukoadhezivnim polimerima kao što su poliakrilna kiselina, alginati i HPMC (Ibrahim i sur., 2012).

Termoosjetljivi gelovi okarakterizirani su kritičnom vrijednosti koncentracije polimera (CMC) i temperature (CMT). Kada vodena otopina poloksamera prijeđe kritičnu vrijednost koncentracije i temperature, dolazi do agregacije molekula poloksamera u sferične micele i stvaranja gela. Sferične micele građene su od hidrofobnih blokova propilenoksida u jezgri i hidratiranih hidrofilnih blokova etilenoksida na površini (Rossi i sur., 2014). Promjenom udjela poloksamera mijenjaju se reološka svojstva gela i Tgel-a.

Chang i suradnici (2002) uspoređivali su reološka svojstva termoosjetljivih gelova pripravljenih s 15% (w/w) P407, 0,2% (w/w) polikarbofila i različitim količinama P188 kako bi mogla usporediti i mukoadhezivnost. Gelovi su također sadržavali i klotrimazol. Obje formulacije su pokazale sposobnost kontroliranog oslobađanja klotrimazola u periodu od 8 sati. Iako su obje formulacije gelirale pri temperaturi od 24-28 °C, pripravku koji je sadržavao 15% w/w P188 trebalo je duže vrijeme da prijeđe u gel u usporedbi s onim koji je sadržavao

20% w/w P188. Test otpornosti na ispiranje vaginalnom tekućinom pokazao je da jedino formulacija s 20% w/w P188 zadržava reološka svojstva gela.

Termoosjetljivi gelovi istraživani su za liječenje vaginalne kandidijaze. Kombinacijom različitih udjela P407 (15-20%) i P188 (10-20%) postiglo se kontrolirano oslobađanje ekonazol-nitrata kroz 8 sati. Također, smanjena je i toksičnost lijeka u usporedbi s kontrolom (otopina ekonazol-nitrata) (Baloglu i sur., 2011; Chang i sur., 2002). Bilensoy i suradnici (2006) proučavali su gelove s klortimazolom uklopljenim u ciklodekstrinske komplekse. Gelovi su pripravljeni s 20% (w/w) P407 i 0,2% (w/w) HPMC-a, a sadržavali su 1% (w/w) klortimazola u obliku kompleksa. Postignuto je kontrolirano i produljeno oslobađanje lijeka kroz više od 100 sati. Kim i suradnici (2010) izradili su termoosjetljivi gel s amfotericinom B uklopljenim u hidroksipropil-ciklodekstrinski inkluzijski kompleks. Pri izradi su koristili MBCP-2 (eng. *pluronic-based multiblock copolymer derivative)* sintetiziran iz poloksamera 104 i di(etilenglikol) etera. Formulacija je, osim na temperaturu (Tgel=37 °C), bila osjetljiva i na pH te se gel razgradio u kiselom mediju. To svojstvo gela omogućilo je konstantno oslobađanje lijeka kroz 3 dana na pH 5,0. Dodatno poboljšanje u oslobađanju lijeka postigli su Kang i suradnici (2010) uklopivši amfotericin B u kationske liposome koje su potom dispergirali u gel pripravljen iz P407 i P188 u omjerima 12:20 i 15:15. Tako pripremljena formulacija gelirala je na temperaturi 37-38 °C, pri čemu liposomi nisu imali utjecaja na Tgel-a. Ibrahim i suradnici (2012) pripravili su termoosjetljiv gel iz P407 i P188 za vaginalnu primjenu metronidazola. Povišenjem koncentracije P407 s 15% na 30% dovelo je značajnog smanjenja temperature geliranja s više od 40 °C na 10±1 °C. Također, pripravak je pokazao bolja mukoadhezivna svojstva i veću viskoznost pri fiziološkim uvjetima u usporebi s komercijalno dostupnim pripravkom (Tricho®). Razlog povećane mukoadhezivnosti je interakcija P188 i mukoze. Slične rezultate dobili su Aka-Any-Grah i suradnici (2010) koji su pripravili gel korištenjem 20% P407 i 10% P188. Tgel formulacije iznosio je 28 °C. Ispitivali su zadržavanje gela na vaginalnoj sluznici (otpornost gela na vaginalnu sekreciju) i profil oslobađanja metronidazola te su rezultate usporedili s kontrolnim gelom (komercijalno dostupan Tricho® gel). Korištenjem P188 i P407 postignuto je bolje zadržavanje gela na mjestu primjene (povećana otpornost gela na vaginalnu sekreciju) te kontrolirano oslobađanje lijeka tijekom 12 sati u odnosu na kontrolni gel.

Pereira i suradnici (2013) ispitivali su oslobađanje propolisa iz termoosjetljivih gelova pripravljenih ih P407 i karbopola 349P u omjerima polimera 15/0,25 % (w/w) i 20/0,15 %

(w/w). Pritom je iz gelova s omjerom polimera 15/0,25 % oslobođeno 70 do 90% propolisa tijekom 24 sata.

Liu i suradnici (2009) ispitivali su utjecaj κ-karagenana na oslobađanje aciklovira iz gela pripravljenog iz P407. Naime, pripravci s P407 trenutno su oslobađali lijek zbog brze erozije uslijed kontakta s vaginalnom tekućinom. Dodatak κ-karagenana smanjio je eroziju gela, a time i usporio oslobađanje lijeka. Potom je u pripravak dodan karbopol koji je sinergističkim djelovanjem s karagenanom poboljšao mukoadhezivna svojstva pripravka. U ispitivanju provedenom na štakorima, kompleksom karbopola, karagenana i P407 omogućeno je dobro zadržavanje aciklovira na mjestu djelovanja i 12 sati nakon primjene.

4.3.2. Kitozanski gelovi

Kitozan (CS) je mukoadhezivni kationski polimer s intrinzičnim antimikrobnim djelovanjem. Prednost kitozana je što gelira u niskim koncentracijama te je pogodan za dostavu lijekova vaginalnim putem. U formulacije se dodaje zajedno s β-glicerilfosfatom (GP) ili glicerilmonooleatom. Tako pripravljene formulacije su tekuće pri sobnoj, a geliraju pri fiziološkoj temperaturi. Naime, pri niskoj temperaturi voda je snažno vezana za polimerne lance kitozana i oni izbjegavaju međulančane interakcije. Povišenjem temperature dolazi do prijenosa protona s kitozana na β-glicerilfosfat i neutralizacije kitozana. Amino skupine kitozana reagiraju s fosfatnim skupinama β-glicerilfosfata, nastaju vodikove veze između polimernih lanaca koje smanjuju elektrostatsko odbijanje i kitozan-kitozan hidrofobne veze koje uzrokuju geliranje (Chenite i sur., 2001; Ruel-Gariepy i Leroux, 2004).

Rossi i suradnici (2014) uspoređivali su mukoadhezivna, gelirajuća i antimikrobna svojstva te sposobnost zacjeljivanja rana na dvije različite formulacije vaginalnih gelova. Usporedili su gel s kitozan laktatom i β-glicerilfosfatom (CS-L/GP) (6%/8%, w/w) i gel pripravljen s P407 i kitozan laktatom (P407/CS-L) (15/1,6%, w/w). Gelirajuća svojstva uspoređivanih gelova razlikovala su se zbog različitog mehanizma geliranja. Hidrofobne interakcije lanaca CS-L/GP gela stvarale su se već pri niskim koncentracijama dok je za stvaranje polimernih micela P407/CS-L gela bila potrebna koncentracija polimera iznad CMC). CS-L/GP gel je pokazao antibakterijska svojstva protiv *E. coli* i *Staphylococcus aureus* (*in vitro*) i svojstvo zacjeljivanja rana poticanjem proliferacije fibroblasta. Također, u odnosu na P407/CS-L gel, CS-L/GP gel je pokazao je bolja mukoadhezivna svojstva.

4.3.3. Vaginalna primjena gelova

Vaginalni gelovi kao mikrobiocidi

Brojna istraživanja u području vaginalne primjene lijekova usmjerena su na prevenciju i liječenje infektivnih spolno-prenosivih bolesti i HIV-a. Iako postoje učinkoviti oralni oblici, pokazalo se da niže doze lokalno primijenjenog mikrobiocida imaju istovjetan učinak bez sistemskih nuspojava (Sobel i sur., 1994, Wain, 1998). Mikrobiocidi se mogu primjenjivati u obliku vaginaleta, filmova i krema, no gelovi su se pokazali kao najbolji izbor. Gel, u koji je uklopljen mikrobiocid, pospješuje permeaciju istog te stvara zaštitni sloj na sluznici koji onemogućava migraciju i adheziju patogena (Mauck i sur., 2008). Također, gelovi su se pokazali i kao dobra baza za kontroliranu dostavu lijekova.

Neyts i suradnici (2000) proveli su istraživanja u kojima su uspoređivali mikrobicidni i citotoksični učinak gela s nonoksinolom-9 i vaginalnih gelova s monokaprinom (1-monoglicerid kaprinske kiseline). Gelovi s monokaprinom su izrađeni iz natrij-CMC-a i polivinilpirolidona (pH gela je iznosio oko 7), te karbomera i HPMC-a (pH gela oko 5). Istraživanja su pokazala da oba gela s monokaprinom pokazuju manji citotoksični, a veći virucidni učinak od gela koji sadrži nonoksinol-9. Također, oba gela s monokaprinom su se pokazali vrlo djelotvornima na HIV te bakterije koje uzrokuju vaginitis. Provedeni su i *in vivo* testovi na miševima u kojima se dokazalo da vaginalna primjena oba gela s monokaprinom nije uzrokovala iritacije sluznice.

Neki polimeri, osim što djeluju kao gelirajuća sredstva, mogu imati i mikrobiocidni učinak. Primjerice, gel pripravljen iz 3% (w/w) karagenana pokazao je snažan mikrobiocidni učinak *in vitro* te se u fazi I kliničkih ispitivanja pokazao sigurnim za humanu primjenu (Carraguard®, Population Council, SAD). Osim karagenana, celuloza-acetat-ftalat i karbomer također posjeduju mikrobiocidni učinak (Rohan and Sassi, 2009). Sulfatni polisaharid testiran je kao potencijalni mikrobiocid u gel formulaciji s jota-karagenanom (PC 213). Formulacija je sadržavala 2% jota-karagenana, klorovodičnu kiselinu za prilagođavanje pH vrijednosti na pH 6 i benzilni alkohol kao konzervans. Provedenim kliničkim ispitivanjem (faza I) potvrđena je sigurnost i djelotvornost gela u prevenciji HIV infekcija (Elias i sur., 1997).

Gel pripravljen iz celuloza-sulfata (Ushercell®, Polydex Pharmaceuticals, Canada) pokazao je snažno mikrobiocidno djelovanje te je prošao fazu III kliničkih ispitivanja, no zbog male učinkovitosti u sprječavanju infekcije HIV-om u odnosu na ostale komercijalno dostupne oblike, daljnja ispitivanja nisu provedena (Rohan and Sassi, 2009; Wang and Lee, 2002).

Termoosjetljivi gel pripravljen iz poloksamera u citratnom puferu (pH 4) pokazao se prikladnom podlogom za uklapanje mikrobiocida poput natrij laurilsulfat ili *n*-laurilsarkozina (Roy i sur., 2001). Kombinacijom mukoadhezivnih polimera (Carbopol® 934, HPMC) i termoosjetljivog Pluronic-a® F127, omogućeno je kontrolirano oslobađanje klotrimazola te dulji antifungalni učinak u odnosu na kontrolu (Bilensoy i sur., 2006). Termoosjetljivi gelovi istraživani su i kao podloge za lijekove uklopljene u polimerne nanočestice. U istraživanjima koja su proveli Date i suradnici (2012) potvrđeno je produljeno oslobađanje efavirenza i raltegravira te učinkovitija i dugotrajniju zaštita od HIV infekcija zbog bolje penetracije mikrobiocida u sluznicu.

Veliki broj istraživanja, u području razvoja mikrobiocida za prevenciju HIV infekcija, stavlja naglasak na primjenu dendrimera. To su polimeri pravilne, razgranate strukture koji i bez uklopljenog lijeka mogu imati antivirusni učinak. Pretkliničkim studijama pokazano je da najveći antivirusni potencijal ima SPL7013, dendrimer s polianionskom površinom kojeg je razvila Starpharma® (Melburne, Victoria, Australia). Djelovanje mu se temelji na vezanju za gp120 proteine na površini HIV-a čime se onemogućava vezanje i ulazak HIV-a u ljudsku stanicu (Rupp i sur., 2007). VivaGel® je mukoadhezivni gel koji sadrži 3% (w/w) SPL7013 u karbopolskom gelu. Blago je kiselog pH pa je u potpunosti kompatibilan s vaginalnom mikroflorom (laktobacili) te puferira alkalni pH ejakulata. Mukoadhezivna svojstva gela omogućavaju dulje zadržavanje SPL7013 na mjestu primjene. Ova formulacija je ujedno i najperspektivniji pripravak nanoterapeutika za vaginalnu primjenu te je prošao fazu III kliničkih ispitivanja (Mumper i sur., 2009; Rupp i sur., 2007). Istraživanja provedena na zdravim ženama koje su primjenjivale VivaGel® jednom dnevno tijekom sedam dana pokazala su da nema sistemske apsorpcije dendrimera te da je formulacija sigurna za primjenu. Žene u istraživanju nisu osjetile bol i pečenje u genitalnom traktu, a kolposkopski nalazi nisu pokazali oštećenje ili upalu epitela vaginalne sluznice (O'Laughlin i sur., 2010).

Zbog kiselog pH gela, karbopoli su se pokazali veoma prikladnim polimerima za izradu polučvrsith pripravaka za vaginalnu primjenu lijekova. MetroGel Vaginal® (3M Pharmaceuticals, SAD) je kiseli poliakrilatni gel (pH 4,0) s 0,75% (w/w) metronidazola namijenjen liječenju bakterijskih vaginoza (Wain, 1998). Poliakrilatni i polikarbofilni gelovi i bez uklopljene djelatne tvari (lijeka) imaju potencijala u terapiji i prevenciji recidivirajućih bakterijskih vaginoza (Miphil®, Mipharm, Italija). Prednost takvih gelova je dulje zadržavanje

na mjestu primjene (>72 sata), a kiseli pH uspostavlja prirodnu vaginalnu mikrofloru koja se narušava povišenjem pH uslijed vaginoze (Fiorilli i sur., 2005).

Mukoadhezivni gelovi pripravljeni s polimerima poliakrilne kiseline (Carbopol® 974P) ispitivani su kao podloge za primjenu liposoma s uklopljenim antimikrobnim lijekovima (Vanić i Škalko-Basnet, 2013; Vanić i Škalko-Basnet, 2014). Karbopolski hidrogelovi su se pokazali kompatibilnim s liposomima (fizička stabilnost liposoma) te su omogućili kontrolirano i produljeno oslobađanje antimikrobnih lijekova (Pavelić i sur., 2005; Pavelić i sur., 2004, Vanić i sur., 2014).

Kitozanski gelovi za vaginalnu primjenu antimikotika sve su interesantniji zbog svoje mukoadhezivnosti, biokompatibilnosti i biorazgradivosti. Rezultati ispitivanja gela s kitozanom srednje molekulske mase pokazala su dobra adhezivna svojstva gela (prisustvo gela na sluznici i nakon 24 sata), produljeno oslobađanje antimikotika i dobru antifungalnu aktivnost (Senyiğit i sur., 2014).

Vaginalni gelovi kao kontraceptivi

Vaginalni gelovi korišteni kao mikrobiocidi, također mogu imati i kontraceptivni učinak. Primjer takvog gela je Advantage-S® (Columbia Lab., SAD), kontracepcijski gel s 3,5% (w/w) nonoksinola-9 uklopljenog u bioadhezivni matriks s karbomerom i polikarbofilom (das Neves i Bahia, 2006). Međutim, danas na tržištu postoje gelovi koji su razvijeni isključivo kao kontraceptivi te uz lubrikacijska sadrže i spermicidna svojstva. Spermicidi djeluju na način da sprječavaju migraciju sjemena do mjesta začeća. Osim spermicida, na kontracepcijski učinak djeluju i reološka svojstva gela te pH. Naime povećanjem viskoznosti, povećat će se i kontracepcijski učinak zbog otežane migracije spermija (El-Gizawy i Aglan, 2003). Kiseli medij rodnice prilikom ili nakon spolnog odnosa štititi će vaginalnu sluznicu i smanjiti vjerojatnost začeća. Stoga se često kao podloge za spermicide koriste puferirani mukoadhezivni gelovi. Primjer takvog gela je ACIDFORM® gel (TOPCAD, SAD). Prednost ACIDFORM® gela je uklapanje hidrofilnih i u kiselom mediju stabilnih kontraceptiva i antimikrobnih lijekova (Garg i sur., 2001). *In vitro* studije pokazale su da ACIDFORM® gel pomješan sa sjemenom tekućinom ima izvrsna puferirajuća svojstva, a u fazi I kliničkih ispitivanja dokazana je spermicidna aktivnost i u periodu od 10 sati između aplikacije i snošaja (Amaral i sur., 2004). Sličan primjer je hidrogel BufferGel® (ReProtect Inc., SAD). To je gel pripravljen s Carbopolom®, pH vrijednosti 4 koji uz spermicidalno ima i

antimikrobno djelovanje na klamidiju, HIV i Herpes simplex virus (HSV) (Rohan i Sassi, 2009).

Među brojnim istraživanjima kontraceptivnog učinka gelova su i ona provedena s termoosjetljivim gelom pripravljenim iz poloksamera u citratnom puferu. Prednost ovog gela je sinergizam puferirajućeg djelovanja gela i natrij laurilsulfata u inhibiciji pokretljivosti spermija. Gel je pokazao veliki potencijal za uporabu kao topikalni vaginalni kontraceptiv iako je dugotrajna uporaba upitna zbog iritacijskog djelovanja natrij laurilsulfata (Haineault i sur., 2003).

Vaginalni gelovi za vlaženje rodnice

Suhoća rodnice posljedica je hormonskih promjena koje se događaju u menopauzi i uspješno se uklanja hormonskom terapijom. Zbog hidrofilne prirode, gelovi su idealni pripravci za vlaženje rodnice i dobra su alternativa za hormonsku terapiju, osobito kod žena s povećanim rizikom od razvoja tumora. Ne sadrže djelatnu tvar već su pripravljeni iz mukoadhezivnih polimera koji omogućuju dulje zadržavanje gela na mjestu primjene i velike količine vode (>90%) koja vlaži rodnicu. Najčešće je korišten polimer Carbopol® 974P koji stvara gel blago kiselih svojstava (pH 4) te povoljno djeluje na uspostavljanje prirodne vaginalne mikroflore. Replens® je prvi komercijalno dostupni pripravak koji se koristi za tegobe vezane uz vaginalnu suhoću. Pripravljen je od polikarbofila i Carbopola® 974P te ima sposobnost zadržavanja u rodnici 3-4 dana. Ukoliko je suhoća rodnice povezana s atrofijom vaginalne sluznice u postmenopauzi, tada se koriste hidrogelovi s uklopljenim solima 17-β-estradiola (Acartürk, 2009; Mauck i sur., 2008).

Vaginalni gelovi kao sredstva za poticanje trudova

Primjena prostaglandina u obliku vaginalnih gelova već se duže vrijeme koristi za poticanje pobačaja i trudova (Tylor i sur., 1999). Za izradu gelova najčešće su korišteni derivati celuloze poput HEC-a, MC-a i HEMC-a. Vaginalni put primjene prostaglandina povoljniji je za izazivanje poroda od oralnog. To je pokazano kliničkom studijom u kojoj je uspoređivana učinkovitost vaginalno primjenjenog prostaglandina E2 s oralno primijenjenim lijekom u istoj koncentraciji (Seeras, 1995). Usporedba učinkovitosti gela s prostaglandinom u odnosu na vaginalne tablete s prostaglandinom pokazala je intenzivniju cervikalnu dilataciju kod žena koje su primjenjivale gel, no nije uočena značajna razlika u ishodu trudova i porođaja (Shetty i sur., 2004). Nedostaci vaginalne primjene prostaglandinskih gelova su povećan rizik od

hiperstimulacije uterusa te niska stabilnost zbog čega se pripravak mora čuvati pri niskim temperaturama (Gregson i sur., 2005).

Ostale primjene vaginalnih gelova

Vaginalni hidrogel pripravljen iz 1% HEC-a i 1% 5-fluorouracila istraživan je za liječenje tumorskih izraslina. Rezultati su pokazali da je pripravak djelotvoran, podnošljiv i siguran za vaginalnu primjenu (Syed i sur., 2000). Gelovi su također ispitivani kao potencijalni nosači stimulirajućeg faktora granulocitno-makrofagnih kolonija (eng. *granulocyte-macrophage colony-stimulating factor,* GM-CSF) u terapiji Humanog papiloma virusa (HPV) povezanog s cervikovaginalnim predneoplastičnim lezijama. *In vivo* ispitivanja (miševi) pokazala su učinkovitost 1% (w/w) polikarbofilnog gela u stabilizaciji GM-CSF proteina i prikladnost formulacije za vaginalnu primjenu (Hubert i sur., 2004).

Rousseau i suradnici (2005) su ispitivali važnost oligosaharida (fruktooligosaharida i glukooligosaharida) u razvoju vaginalne mikroflore, posebice laktobacila. Pokazali su da oligosaharidi selektivno utječu na rast laktobacila jer nisu metabolizirani od strane patogena već ih koriste samo bakterije prirodne vaginalne flore. Vaginalnom primjena gela s glukooligosaharidom pospješeno je obnavljanje prirodne vaginalne mikroflore i uspostavljanje fiziološkog pH rodnice kod žena liječenih oralnim metronidazolom (Coste i sur., 2012).

Osim za topikalnu primjenu, gelovi su ispitivani i za sistemsku dostavu hormona vaginalnim putem. Crinone® gel (Columbia Lab., SAD) je komercijalno dostupan pripravak za liječenje neplodnosti i sekundarne amenoreje. To je mukoadhezivni gel s produljenim oslobađanjem progesterona, pripravljen od Carbopola® i polikarbofila (Cook i Brown, 2018). Han i suradnici (1995) ispitivali su vaginalnu primjenu luteinizacijskog hormona u polikarbofilnom gelu za indukciju ovulacije vaginalnim putem. U usporedbi s kontrolnim pripravkom, transvaginalna permeabilnost je bila veća, a djelotvornost istovjetna onoj postignutoj supkutanom primjenom lijeka.

Gelovi pripravljeni od polimera poliakrilne kiseline istraživani su za vaginalnu primjenu inzulina. Rezultati istraživanja na zečevima i štakorima pokazali su da je nakon vaginalne primjene, koncentracija inzulina u plazmi dosegla pik, a hipoglikemijski efekt je neprekidno trajao 30 minuta (Morimoto i sur., 1982). Kako bi postigli dulje vrijeme hipoglikemije, Degim i suradnici (2005) su pripravili kitozanski vaginalni gel s inzulinom i pri tome su koristili

dimetil-β-ciklodekstrin kao promotor permeabilnosti. Studije su pokazale da se upotrebom kitozanskog gela kao nosača inzulina postiže produljeno oslobađanje.

Tablica 6. Primjeri registriranih vaginalnih gelova u Republici Hrvatskoj (www.halmed.hr, pristupljeno 8. 8. 2019.)

Zaštićeno ime	Polimer	Djelatna tvar	Proizvođač	Indikacija
Crinone®	Carbopol® 974P i polikafbofil	Progesteron	Columbia Laboratories	Neplodnost
Prostin E2®	Silikon-dioksid	Dinoproston	Pfizer	Induciranje trudova
Prepidil®	Silikon-dioksid	Dinoproston	Pfizer	Induciranje poroda
Gynofit® hidratantni gel	HEC	-	Tentan AG	Vaginalni ovlaživač
Gynofit®	HPMC	Mliječna kiselina, natrijev laktat	Tentan AG	Održavanje vaginalne kiselosti, vaginalni ovlaživač
Multi-gyn® actigel	Ksantanska guma	2QR- unakrsni polimer galaktoarabinana i poliglukuronske kiseline	Bioclin BV	Održavanje vaginalne kiselosti, vaginalni ovlaživač
Multi-gyn® floraplus	Ksantanska guma	2QR- unakrsni polimer galaktoarabinana i poliglukuronske kiseline	Bioclin BV	Prevencija i terapija gljivičnih infekcija, prebiotik
Hyalofemme®	Karbomer	HYDEAL-D 0.2 % (ester hijaluronske kiseline)	Fidia Farmaceutici	Vaginalni ovlaživač
Multi-gyn LiquiGel®	Ksantanska guma	2QR- unakrsni polimer galaktoarabinana i poliglukuronske kiseline	Bioclin BV	Održavanje vaginalne kiselosti, vaginalni ovlaživač
K-Y®	HEC	-	Johnson &Johnson	Vaginalni oblaživač
Femigel®	Ksantanska guma	Ulje čajevca	Australian Bodycare	Održavanje vaginalne kiselosti, antiseptik
Gynaicol®	HMC	-	Medopharm	Vaginalni ovlaživač
Lactogyn®	HEC	Mliječna kiselina	JGL	Održavanje vaginalne kiselosti, vaginalni ovlaživač

HEC, hidroksietilceluloza; HMC, hidroksimetilceluloza; HPMC, hidroksipropilmetilceluloza

4.4. LUBRIKANTI

Vaginalna suhoća je učestali problem, osobito kod žena u menopauzi i postmenopauzi, a javlja se kao simptom vulvovaginalne atrofije. Lubrikanti su pripravci djelotvorni za kratkotrajno uklanjanje boli i nelagode tijekom spolnog odnosa, uzrokovane vaginalnom suhoćom. Primjenom lubrikanata smanjuje se trenje koje je posljedica suhe i tanke vaginalne sluznice. Prednost lubrikanata je ta što su prikladni za žene koje ne smiju koristiti estrogensku terapiju (Edwards i Panay, 2016).

S tehnološkog stajališta, lubrikanti su pripravci bazirani na vodi, silikonima, mineralnim ili biljnim uljima. Prednosti lubrikanata baziranih na vodi su što ne ostavljaju mrlje te u usporedbi sa silikonskim lubrikantima pokazuju manje neželjenih vaginalnih nuspojava (Herbenick i sur., 2011). Humektansi, konzervansi i emolijansi su pomoćne tvari koje se dodaju u pripravke kako bi se postigla odgovarajuća viskoznost, prevenirala bakterijska kontaminacija, no s druge strane njihova prisutnost može bitno utjecati na pH i osmolalnost pripravka (Edwards i Panay, 2016).

Zbog velikih varijacija u vrijednostima pH i osmolalnosti lubrikanata na tržištu, Svjetska zdravstvena organizacija, SZO (eng. *World Health Organization,* WHO) dala je preporuku da osmolalnost lubrikanata ne bi trebala prelaziti 380 mOsm/kg kako bi se smanjio rizik od oštećenja epitela sluznice.

U Tablici 5, koja prikazuje vrijednosti osmolalnosti komercijalno dostupnih lubrikanata, vidljivo je da većina komercijalno dostupnih pripravaka prelazi granicu od 380 mOsm/kg. Stoga je SZO odredila najvišu prihvatljivu granicu u iznosu od 1200 mOsm/kg (WHO, 2015). Provedena ispitivanja povezanosti iritacija epitela sluznice s osmolalnosti lubrikanata su pokazala da hipoosmotski lubrikant (32-316 mOsm/kg) ne uzrokuje iritacije, blago hiperosmotski lubrikant (K-Y® Jelly: 2463 mOsm/kg, Replens®: 2143 mOsm/kg) uzrokuje blage iritacije te da izrazito hiperosmotski lubrikant (Astroglide®: 5848 mOsm/kg) uzrokuje ozbiljna oštećenja tkiva i jake iritacije (Adriaens i Remon, 2008). Visoka osmolalnost može biti povezana i s citotoksičnim učinkom pripravka. *In vitro* studije na spermijima pokazale su da hiperosmotski lubrikant (>1000 mOsm/kg) uzrokuje promjene u integritetu DNA i pokretljivosti spermija (Agarwal i sur., 2008). Osim osmolalnosti i pH pripravka mora biti prilagođen mjestu primjene, odnosno za vaginalnu primjenu pH treba biti između 3,8 i 4,5, a za rektalnu 7,0. Pripravci s pH nižim od 3 nisu prihvatljivi za upotrebu na ljudskoj sluznici (Cunha i sur., 2014).

Tablica 7. Komercijalno dostupni lubrinkanti: sastav i značajke formulacija. Preuzeto i prilagođeno iz *Edwards i Panay*, (2015), uz dozvolu *Creative Commons Attribution License*-a.

Naziv	Sastojci	pH	Osmolalnost (mOsm/kg)
Astroglide®	pročišćena voda, glicerol, HEC, klorheksidin glukonat, metilparaben, glukono-delta-lakton, natrijev hidroksid	4,38	6100
BIOglide® Natural	glicerol, voda, natrijev laktat, ksantanska guma, levulinska kiselina, natrijev levulinat	4,99	>2000
Durex® Play Feel	pročišćena voda, propilen glikol, HEC, benzoična kiselina, natrijev hidroksid	5,48	1563
Intimate Organics®	voda, propandiol, celuloza, natrijev benzoat, limunska kiselina, etanol, ekstrakt biljke *Cymbopogon schoenanthus,* ekstrakt lista aloe	4,86	>2000
Intimy®	HEC, glicerol, benzalkonij klorid, limunska kiselina	6,19	1501
K-Y® Jelly	voda, glicerol, HEC, klorheksidin glukonat, glukonolakton, metilparaben, natrijev hidroksid	4,49	2007
Phyto Soya®	voda, glicerol, tekući parafin, natrijev hidroksid, karbomer, ekstrakt soje, fenoksietanol, metilparaben, propilparaben, izobutilparaben	4,94	1557
Pjur Med® Natural Glide	Voda, glicerol, ksantanska guma, benzilni alkohol, natrijev benzoat, kalijev sorbat, limunska kiselina	4,41	>2000
Ritex®	Voda, glicerol, propilenglikol, HEC, natrijev laktat, limunska kiselina	4,04	>2000

HEC, hidroksietilceluloza

Citotoksični učinak lubrikanata ne mora nužno biti uzrokovan visokom osmolalnosti već i pomoćnim tvarima dodanim u pripravak. Primjerice, parabeni koji se koriste kao konzervansi u nekim lubrikantima (K-Y® Jelly, Astroglide®, Replens®), imaju blago estrogeno djelovanje te postoje određene naznake moguće povezanosti njihove prisutnosti u formulacijama s pojavnosti karcinoma dojki. Iako direktna povezanost parabena i karcinoma nije znanstveno

dokazana, smatra se da su daljnja istraživanja u ovom području prijeko potrebna (Bledzka i sur., 2014; Harvey i Everett, 2004; Karpuzoglu i sur., 2013; Nohynek i sur., 2013).

Glikoli su humektansi u lubrikantima od kojih se najčešće koriste propilenglikol i glicerol. Njihova koncentracija je ključna u određivanju osmolalnosti pripravka. SZO predlaže da za održavanje osmolalnosti <1200mOsm/kg, koncentracija glicerola ne smije prelaziti 9,9% w/w, a propilenglikola 8,3% w/w (Edwards i Panay, 2016; WHO, 2017).

Prema preporukama SZO-a mikrobidici ne bi trebali biti prisutni u lubrikantima jer mogu uzrokovati oštećenja epitela, povećanu osjetljivost i promjene u vaginalnoj mikroflori te pojavu upala (WHO, 2012). Ranija istraživanja na lubrikantima koji su sadržavali mikrobiocid i spermicid nonoksinol-9, pokazala su ozbiljne iritacije mukoze i oštećenja stanica (Dayal i sur., 2003; Phillips i Zacharopoulos, 1998; WHO, 2015).

5. ZAKLJUČAK

Polučvrsti oblici za vaginalnu primjenu poput krema, pjena i gelova komercijalno su dostupni i dobro prihvaćeni od strane pacijentica. Inovacijama postojećih konvencionalnih oblika uklapanjem nanočestica, i/ili korištenjem termoosjetljivih i mukoadhezivnih polimera omogućuje se dobro rasprostiranje pripravaka na sluznici i zadržavanje formulacije na mjestu primjene čime se značajno povećava učinkovitost terapije. Unatoč velikom broju pozitivnih rezultata pretkliničkih istraživanja, potrebna su daljnja klinička istraživanja učinkovitosti, prihvatljivosti i sigurnosti polučvrstih pripravaka za vaginalnu primjenu lijekova.

6. POPIS OZNAKA I KRATICA

AIDS	Stečeni sindrom imununodeficijencije
BHA	Butilhidroksianisol
BHT	Butilhidroksitoluen
CMC	Kritična vrijednost koncentracije
CMT	Kritična vrijednost temperature
CS	Kitozan
CS-L/GP	Gel s kitozan laktatom i β-glicerilfosfatom
DSC	Diferencijalna pretražna kalorimetrija
E1	Estron
E2	Estradiol
E3	Estriol
EO_a-PO_b-EO_a	Etilenoksid-propilenoksid-etilenoksid
ETGFA	Ekspanzivna termogelirajuća aerosol pjena
GM-CSF	Stimulirajući faktor granulocitno-makrofagnih kolonija
GP	β-glicerilfosfat
GRAS	Generally recognized as safe
HEC	Hidroksietilceluloza
HEMC	Hidroksietilmetilceluloza
HFA	Hydrogel foam aerosol
HIV	Virus humane imunodeficijencije
HMC	Hidroksimetilceluloza
HPC	Hidroksipropilceluloza
HPMC	Hidroksipropilmetilceluloza
HPV	Humani papiloma virus
HSV	Herpes simplex virus
HYG	Hydrogel
MBCP-2	Pluronic-based multiblock copolymer derivative
MC	Metilceluloza
NaCMC	Natrij-karboksimetilceluloza
P188	Poloksamer 188
P407	Poloksamer 407
P407/CS-L	Gel s poloksamerom 407 i kitozan laktatom

PEG	Polietilenglikol
PEHFL	Post-ekspanzivna hidrogel aerosol pjena PG-liposoma
PG	Propilenglikol
PLFA	Propylene glycol liposomes foam aerosol
SZO	Svjetska zdravstvena organizacija
Tgel	Temperatura geliranja
TPA	Texture profile analysis
WHO	World Health Organization

7. LITERATURA

Abedi P, Najafian M, Yaralizadeh M, Namjoyan F. Effect of fennel vaginal cream on sexual function in postmenopausal women: A Double blind randomized controlled trial. J. Med. Life 2018; 11:24-28.

Acartürk F. Mucoadhesive vaginal drug delivery systems. Recent Pat. Drug Deliv. Formul. 2009; 3:193–205.

Adriaens E, Remon JP. Mucosal irritation potential of personal lubricants relates to product osmolality as detected by the slug mucosal irritation assay. Sex. Transm. Dis. 2008; 35:512–16.

Agarwal A, Deepinder F, Cocuzza M, Short RA, Evenson DP. Effect of vaginal lubricants on sperm motility and chromatin integrity: a prospective comparative study. Fertil Steril 2008; 89:375–9.

Ahmad FJ, Alam MA, Khan ZI, Khar RK, Ali M. Development and *in vitro* evaluation of an acid buffering bioadhesive vaginal gel for mixed vaginal infections. Acta Pharm. 2008; 58:407–419.

Aka-Any-Grah A, Bouchemal K, Koffi A, Agnely F, Zhang M, Djabourov M, Ponchel. Formulation of mucoadhesive vaginal hydrogels insensitive to dilution with vaginal fluids. Eur. J. Pharm. Biopharm. 2010; 76:296–303.

Al-Fattani MA, Douglas LJ. Penetration of Candida biofilms by antifungal agents. Antimicrob. Agents Chemother. 2004; 48:3291–3297.

Amaral E, Faundes A, Zaneveld L, Waller D, Garg S. Study of the vaginal tolerance to Acidform, an acid-buffering, bioadhesive gel. Contraception 1999; 60:361–366.

Amaral E, Perdigao A, Souza MH, Mauck C, Waller D, Zaneveld L, Faundes A. Postcoital testing after the use of a bio-adhesive acid buffering gel (ACIDFORM) and a 2% nonoxynol-9 product. Contraception 2004; 70:492–497.

Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am. J. Med. 1983; 74:14–22.

Arzhavitina A, Steckel H. Foams for pharmaceutical and cosmetic application. Int. J. Pharm. 2010; 394:1-17.

Ashok V, Manoj Kumar R, Murali D, Chatterjee A. A review on vaginal route as a systemic drug delivery. Critical Review in Pharmaceutical Sciences 2012; 1:1-19.

Baloglu E, Karavana SY, Senyigit ZA, Hilmioglu-Polat S, Metin DY, Zekioglu O, Guneri T, Jones DS. In-situ gel formulations of econazole nitrate: preparation and in-vitro and in-vivo evaluation. J. Pharm. Pharmacol. 2011; 63:1274–1282.

Barentsen R, van de Weijer PHM, Schram JHN. Continuous low dose estradiol released from vaginal ring versus estriol vaginal cream for urogenital atrophy. Eur. J. Obstet. Gynecol. Reprod. Biol. 1997; 71:73-80.

Barnhart KT, Pretorius ES, Shaunik A, Timbers K, Nasution M, Mauck C. Vaginal distribution of two volumes of the novel microbicide gel cellulose sulfate (2.5 and 3.5 mL). Contraception 2005; 72: 65–70.

Beigi RH, Wiesenfeld HC, Hillier SL, Straw T, Krohn MA. Factors associated with absence of H2O2-producing Lactobacillus among women with bacterial vaginosis. J. Infect. Dis. 2005; 191:924–929.

Berger J, Reist M, Mayer JM, Felt O, Gurny R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eur. J. Pharm. Biopharm. 2004; 57:35–52.

Biagi E, Vitali B, Pugliese C, Candela M, Donders GG, Brigidi P. Quantitative variations in the vaginal bacterial population associated with asymptomatic infections: a real-time polymerase chain reaction study. Eur. J. Clin. Microbiol. Infect. Dis. 2009; 28:281–285.

Bilensoy E, Rouf MA, Vural I, Hincal AA. Thermosensitive vaginal gel formulation for the controlled release of clotrimazole via complexation to beta-cyclodextrin. J. Control. Release 2006; 116:107–109.

Bledzka D, Gromadzinska J, Wasowicz W. Parabens. From environmental studies to human health. Environ. Int. 2014; 67:27–42.

Bradshaw CS, Morton AN, Hocking J, Garland SM, Morris MB, Moss LM, Horvath LB, Kuzevska I, Fairley CK. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. J. Infect. Dis. 2006; 193:1478–1486.

Caramella CM, Rossi S, Ferrari F, Bonferoni MC, Sandri G. Mucoadhesive and thermogelling systems for vaginal drug delivery. Adv. Drug Deliv. Rev. 2015; 92:39–52.

Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. J. Sex. Med. 2011; 8:549–59.

Chandra J, Mukherjee PK, Leidich SD, Faddoul FF, Hoyer LL, Douglas LJ, Ghannoum MA. Antifungal resistance of candidal biofilms formed on denture acrylic in vitro. J. Dent. Res. 2001; 80:903-8.

Chang JY, Oh YK, Choi H, Kim YB, Kim CK. Rheological evaluation of thermosensitive and mucoadhesive vaginal gels in physiological conditions. Int. J. Pharm. 2002; 241:155–163.

Chatsiproios D, Schmidts-Winkler IM, König L, Masur C, Abels C. Topical treatment of vaginal dryness with a non-hormonal cream in women undergoing breast cancer treatment-An open prospective multicenter study. PLoS ONE 2019; 14.

Chen FP. Efficacy of imiquimod 5% cream for persistent human papillomavirus in genital intraepithelial neoplasm. Taiwan J. Obstet. Gynecol. 2013; 53:475-478.

Chenite A, Buschmann MD, Wang D, Chaput C, Kandani N. Rheological characterization of thermogelling chitosan/glycerophosphate solutions. Carboydr. Polym. 2001; 46:39-47.

Chin SN, Trinkaus M, Simmons C, Flynn C, Dranitsaris G, Bolivar R, Clemons M. Prevalence and severity of urogenital symptoms in postmenopausal women receiving endocrine therapy for breast cancer. Clin. Breast Cancer 2009; 9:108-17.

Coggins C, Blanchard K, Alvarez F, Brache V, Weisberg E, Kilmarx PH, Lacarra M, Massai R, Mishell D, Salvatierra A, Witwatwongwana P, Elias C, Ellertson C. Preliminary safety and

acceptability of a carrageenan gel for possible use as vaginal microbicide. Sex. Transm. Infect. 2000; 76:480–483.

Cook MT, Brown MB. Polymeric gels for intravaginal drug delivery. J. Control. Release 2018; 270:145-157.

Coste I, Judlin P, Lepargneur JP, Bou-Antoun S. Safety and efficacy of an intravaginal prebiotic gel in the prevention of recurrent bacterial vaginosis: a randomized double-blind study. Obstet. Gynecol. Int. 2012; 2012:147867.

Cunha AR, Machado RM, Palmeira-de-Oliveira A, Martinezde-Oliveira J, das Neves J, Palmeira-de-Oliveira R. Characterization of commercially available vaginal lubricants: a safety perspective. Pharmaceutics 2014; 6:530-42.

D'Cruz OJ, Waurzyniak B, Uckun FM. Mucosal toxicity studies of a gel formulation of native pokeweed antiviral protein. Toxicol. Pathol. 2004; 32:212–221.

das Neves J, Bahia MF. Gels as vaginal drug delivery systems. Int. J. Pharm 2006; 318:1-14.

Date A, Shibata A, Goede M, Sanford B, La Bruzzo K, Belshan M, Destache CJ. Development and evaluation of a thermosensitive vaginal gel containing raltegravir + efavirenz loaded nanoparticles for HIV prophylaxis. Antivir. Res. 2012; 96:430–436.

Dayal MB, Wheeler J, Williams CJ, Barnhart KT. Disruption of the upper female reproductive tract epithelium by nonoxynol-9. Contraception 2003; 68:273–9.

de Araújo Pereira RR, Bruschi ML. Vaginal mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 2012; 38:643-652.

de Araújo Pereira RR, Ribeiro Godoy JS, Stivalet Svidzinski TI, Bruschi ML. Preparation and characterization of mucoadhesive thermoresponsive systems containing propolis for the treatment of vulvovaginal candidiasis. J. Pharm. Sci. 2013; 102:1222–1234.

Debata PR, Castellanos MR, Fata JE, Baggett S, Rajupet S, Szerszen A, Begum S, Mata A, Murty VV, Opitz LM, Banerjee P. A novel curcumin-based vaginal cream Vacurin selectively eliminates apposed human cervical cancer cells. Gynecol. Oncology 2013; 129:145-153.

Degim Z, Degim T, Acarturk F, Erdogan D, Ozogul C, Koksal M. Rectal and vaginal administration of insulin-chitosan formulations: an experimental study in rabbits. Drug Target 2005; 13:563–572.

Di Fabio S, Van Roey J, Giannini G, van den Mooter G, Spada M, Binelli A, Pirillo MF, Germinario E, Belardelli F, de Bethune MP, Vella S. Inhibition of vaginal transmission of HIV-1 in hu-SCID mice by the non-nucleoside reverse transcriptase inhibitor TMC120 in a gel formulation. AIDS 2003; 17:1597–1604.

Dickerson J, Bressler R, Christian CD, Hremann HW. Efficacy of estradiol vaginal cream in postmenopausal women. Clin. Pharmacol. Ther. 1979; 26.

Donders GG. Definition and classification of abnormal vaginal flora. Best Pract. Res. Clin. Obstet. Gynaecol. 2007; 21:355–373.

Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. Obstet. Gynecol. 1998; 92:757–765.

Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? Climacteric 2016; 19:151–161.

El-Gizawy SA, Aglan NI. Formulation and evaluation of metronidazole acid gel for vaginal contraception. J. Pharm. Pharmacol. 2003; 55:903–909.

Elias CJ, Coggins C, Alvarez F, Brache V, Fraser IS, Lacarra M, Lahteenmaki P, Massai R, Mishell Jr. DR, Phillips DM, Salvatierra AM. Colposcopic evaluation of a vaginal gel formulation of iotacarrageenan. Contraception 1997; 56:387–389.

Fataneh F. Anti-fungal activity of Zataria multiflora extract in vitro. Thesis of School of Pharmacy, Esfahan University, 1991.

Ferguson LM, Rohan LC. The importance of the vaginal delivery route for antiretrovirals in HIV prevention. Ther. Deliv. 2011; 2:1535–1550.

Ferris DG, Litaker MS, Woodward L, Mathis D, Hendrich J. Treatment of bacterial vaginosis: a comparison of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream. J. Fam. Pract. 1995; 41:443–449.

Ferris MJ, Masztal A, Aldridge KE, Fortenberry JD, Fidel Jr. PL, Martin DH. Association of Atopobium vaginae, a recently described metronidazole resistant anaerobe, with bacterial vaginosis. BMC Infect. Dis. 2004; 4:5.

Fichorova RN, Buck OR, Yamamoto HS, Fashemi T, Dawood HY, Fashemi B, Hayes GR, Beach DH, Takagi Y, Delaney ML, Nibert ML, Singh BN, Onderdonk AB. The villain team-up or how Trichomonas vaginalis and bacterial vaginosis alter innate immunity in concert. Sex. Transm. Infect. 2013; 39: 460–466.

Fidel Jr. PL, Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. Clin. Microbiol. Rev. 1996; 9:335–348.

Filipović-Grčić J. (2001). Praktikum kozmetologije (Skripta). Zagreb: Farmaceutsko-biokemijski fakultet.

Fiorilli A, Molteni B, Milani B. Successful treatment of bacterial vaginosis with a policarbophil-carbopol acidic vaginal gel: results from a randomised doubleblind, placebo-controlled trial. Eur. J. Obstet. Gynecol. Reprod. Biol. 2005; 120:202–205.

Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. Cochrane Database Syst. Rev. 2003. CD000218 http://dx.doi.org/10.1002/14651858.CD000218.

Foxman B, Marsh JV, Gillespie B, Sobel JD. Frequency and response to vaginal symptoms among white and African American women: results of a random digit dialing survey. J. Women's Health. 1988; 7:1167–1174.

Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. N. Engl. J. Med. 2005; 353:1899–1911.

Garg S, Anderson RA, Chany CJ, Waller DP, Diao XH, Vermani K, Zaneveld LJ. Properties of a new acid-buffering bioadhesive vaginal formulation (ACIDFORM). Contraception 2001; 64:67-75.

Garg S, Tambwekar KR, Vermani K, Garg A, Kaul CL, Zaneveld LJD, Compendium of pharmaceutical excipients for vaginal formulations. Pharm. Technol. 2001; 114–25.

Geonnotti AR, Peters JJ, Katz DF. Erosion of microbicide formulation coating layers: effects of contact and shearing with vaginal fluid or semen. J. Pharm. Sci. 2005; 94:1705–1712.

Gregson S, Waterstone M, Norman I, Murrells T. A randomized controlled trial comparing low dose vaginal misoprostol and dinoprostone vaginal gel for inducing labour at term. BJOG 2005; 112:438–444.

Gupta V, Singh S, Srivarstava M, Ahmad H, Pachauri SD, Khandelwal K, Dwivedi P, Dwivedi AK. Effect of polydimethylsiloxane and ethylcellulose on in vitro permeation of centchroman from its transdermal patches. Drug Deliv. 2016; 23:113–22.

Haggerty CL, Hillier SL, Bass DC, Ness RB. Bacterial vaginosis and anaerobic bacteria are associated with endometritis. Clin. Infect. Dis. 2004; 39:990–995.

Haineault, C. Thermoreversible gel formulation containing sodium lauryl sulfate as a potential contraceptive device. Biol. Reprod. 2003; 69:687–694.

Hajirahimkhan A, Simmler C, Yuan Y, Anderson JR, Chen SN, Nikolić D, Dietz BM, Pauli GF, van Breemen RB, Bolton JL. Evaluation of estrogenic activity of licorice species in comparison with hops used in botanicals for menopausal symptoms. PLoS One 2013; 8:67947.

Han K, Park JS, Chung YB, Jeong NJP, Park HB, Robinson J. Development of luteinizing hormone releasing hormone (LH-RH) delivery systems for vaginal mucosal route. Arch. Pharm. Res. 1995; 18:325–331.

Hansen RS, Derderian EJ. Problems in foam origin, drainage and rupture. Symposium organized by the Society of Chemical Industry, London, 1976, 1–17.

Harvey PW, Everett DJ. Significance of the detection of esters of p-hydroxybenzoic acid (parabens) in human breast tumours. J. Appl. Toxicol. 2004; 24:1–4.

Haspel AA, Luisi M, Kicovic PM. Endocrinological and clinical investigations in postmenopausal women following administration of a vaginal cream containing estriol. Maturitas 1981; 3:321-327.

Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent pretermdelivery and late miscarriage. BMJ 1994; 308:295–298.

Herbenick D, Reece M, Hensel D, Sanders S, Jozkowski K, Fortenberry JD. Association of lubricant use with women's sexual pleasure, sexual satisfaction, and genital symptoms: a prospective daily diary study. J. Seks. Med. 2011; 8:202–12.

Hernandez H, Sariego I, Garber G, Delgado R, Lopez O, Sarracent J. Monoclonal antibodies against a 62 kDa proteinase of Trichomonas vaginalis decrease parasite cytoadherence to epithelial cells and confer protection in mice. Parasite Immunol. 2004;26:119–125.

Hubert P, Evrard B, Maillard C, Franzen-Detrooz E, Delattre L, Foidart JM, Noel A, Boniver J, Delvenne P. Delivery of granulocytemacrophage colony-stimulating factor in bioadhesive hydrogel stimulates migration of dendritic cells in models of human papillomavirus-associated (pre)neoplastic epithelial lesions. Antimicrob. Agents Chemother. 2004; 48:4342–4348.

Hurley R, De Louvois J. Candida vaginitis. Postgrad. Med. J. 1979; 55:645–647.

Ibrahim EI, Fetih G, Shaaban O, Hassanein K, Abdellah NH. Development and characterization of thermosensitive pluronic-based metronidazole in situ gelling formulations for vaginal application. Acta Pharm. 2012; 62:59–70.

Issa MM, Koping-Hoggard M, Artursson P. Chitosan and the mucosal delivery of biotechnology drugs. Drug Discov. Today 2005; 2:1–6.

Jassim GA. Strategies for managing hot flashes. J. Fam. Pract. 2011; 60:333.

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J. Clin. 2011;61:69–90.

Jones DS, Lawlor MS, Woolfson AD. Examination of the flow rheological and textural properties of polymer gels composed of poly(methylvinylether-co-maleic anhydride) and poly(vinylpyrrolidone): rheological and mathematical interpretation of textural parameters. J. Pharm. Sci. 2002; 91:2090-2101.

Justin-Temu M, Damian F, Kinget R, Van Den Mooter G. Intravaginal gels as drug delivery systems. J. Womens Health (Larchmt.) 2004; 13:834-844.

Kale VV, Ubgade A. Vaginal mucosa-a promising site for drug therapy. Br. J. Pharm. Res. 2013; 3:983-1000.

Kang JW, Davaa E, Kim YT, Park JS. A new vaginal delivery system of amphotericin B: a dispersion of cationic liposomes in a thermosensitive gel. J. Drug Target 2010; 18:637–644.

Karpuzoglu E, Holladay SD, Gogal RM Jr. Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health. J. Toxicol. Environ. Health B. Crit. Rev. 2013;16:321–35.

Keller MJ, Klotman ME, Herold BC. Rigorous pre-clinical evaluation of topical microbicides to prevent transmission of human immunodeficiency virus. J. Antimicrob. Chemother. 2003; 51:1099-1102.

Khosravi AR, Eslami AR, Shokri H, Kashanian M. Zataria multiflora cream for the treatment of acute vaginal candidiasis. Int. J. Gynaecol. Obstet. 2008; 101:201-2.

Kicovic PM, Cortes-Prieto J, Milojević S, Haspels AA, Aljinović A. The treatment of postmenopausal vaginal atrophy with Ovestin vaginal cream od suppositories: Clinical, endocrinological and safety aspects. Maturitas 1980; 2: 275-282.

Kim YT, Shina BK, Garripelli VK, Kimb JK, Davaaa E, Jo S, Parka JS. A thermosensitive vaginal gel formulation with HP CD for the pH-dependent release and solubilization of amphotericin B. Eur. J. Pharm. Sci. 2010; 41:399–406.

Kimzey LM, Gumowski J, Merriam GR, Grimes GJ, Nelson LM. Absorption of micronized progesterone from a nonliquefying vaginal cream. Fertil. Steril. 1991; 56.

Kwan KW, Chlebowski RT. Sexual dysfunction and aromatase inhibitor use in survivors of breast cancer. Clin. Breast Cancer. 2009; 9:219–24.

Lamfon H, Porter SR, McCullough M, Pratten J. Susceptibility of Candida albicans biofilms grown in a constant depth film fermentor to chlorhexidine, fluconazole and miconazole: a longitudinal study. J. Antimicrob. Chemother. 2004; 53:383-5.

Lehker MW, Alderete JF. Biology of trichomonosis, Curr. Opin. Infect. Dis. 2000;13:37–45.

Lete I, Cuesta MC, Marín JM, Guerra S. Vaginal health in contraceptive vaginal ring users - a review. Eur. J. Contracept. Reprod. Health Care 2013; 18:234–241.

Li T, Wong VK, Yi XQ. Matrine induces cell anergy in human Jurkat T cells through modulation of mitogen-activated protein kinases and nuclear factor of activated T-cells signaling with concomitant up-regulation of anergyassociated genes expression. Biol. Pharm. Bull. 2012; 33:40–46.

Lindahl SH. Reviewing the options for local estrogen treatment of vaginal atrophy. Int. J. Womens Health. 2014; 6:307-12.

Liu Y, Ying Zhu Y, Wei G, Yue Lu W. Effect of carrageenan on poloxamer-based in situ gel for vaginal use: improved in vitro and in vivo sustained-release properties. Eur. J. Pharm. Sci. 2009: 37:306–312.

Mahmoudabadi AZ, Dabbagh MA, Fouladi Z. In-vitro anti-Candida activity of Zataria multiflora. Boiss. Evid. Based. Complement. Alternat. Med. 2006; 4:351.

Mallipeddi R, Rohan LC. Nanoparticle-based vaginal drug delivery systems for HIV prevention. Expert Opin. Drug Deliver. 2010; 7:37–48.

Mardh PA, Rodrigues AG, Genc M, Novikova N, Martinez-de-Oliveira J, Guaschino S. Facts and myths on recurrent vulvovaginal candidosis-a reviewonepidemiology, clinical manifestations, diagnosis, pathogenesis and therapy. Int. J. STD AIDS 2002; 13:522–539.

Martinez Oliveira J. Bacterial vaginosis and candidosis. Arq. Med. 1993; 7:194–195.

Mauck CK, Katz D, Sandefer EP, Nasution MD, Henderson M, Digenis GA, Su I, Page R, Barnhart K. Vaginal distribution of Replens® and K-Y® Jelly using three imaging techniques. Contraception 2008; 77:195–204.

Mauck CK, Weiner DH, Ballagh SA, Creinin MD, Archer DF, Schwartz JL, Pymar HC, Lai JJ, Rencher WF, Callahan MM. Single and multiple exposure tolerance study of polystyrene sulfonate gel: a phase I safety and colposcopy study. Contraception 2004; 70:77–83.

Mei L, Chen J, Yu S, Huang Y, Xie Y, Wang H, Pan X, Wu C. Expansible thermal gelling foam aerosol for vaginal drug delivery. Drug Deliv. 2017; 24:1325-1337.

Mendling W. Vulvovaginal candidosis, Theory and Practice. Berlin, Springer-Verlag 1988;1.

Mendoza-Lopez MR, Becerril-Garcia C, Fattel-Facenda LV, Avila-Gonzalez L, Ruiz-Tachiquin ME, Ortega-Lopez J, Arroyo R. CP30, a cysteine proteinase involved in Trichomonas vaginalis cytoadherence. Infect. Immun. 2000; 68:4907–4912.

Mikamo H, Kawazoe K, Izumi K, Watanabe K, Ueno K, Tamaya T. Comparativestudy on vaginal or oral treatment of bacterial vaginosis. Chemotherapy 1997; 43:60–68.

Morimoto K, Takeeda T, Nakamoto Y, Morisaka K. Effective vaginal absorption of insulin in diabetic rats and rabbits using polyacrylic acid aqueous gel bases. Int. J. Pharm. 1982; 12:107–111.

Mumper RJ, Bell MA, Worthen DR, Cone RA, Lewis GR, Paull JR, Moench TR. Formulating a sulfonated antiviral dendrimer in a vaginal microbicidal gel having dual mechanisms of action. Drug Dev. Ind. Pharm. 2009; 35:515–524.

Nahoul K, Dehennin L, Scholler R. Radioimmunoassay of plasma progesterone after oral administration of micronized progesterone. J. Steroid Biochem. 1987; 26:241.

Nappi RE, Liekens G, Brandenburg U. Attitudes, perceptions and knowledge about the vagina: the International Vagina Dialogue Survey. Contraception 2006; 73:493–500.

Neyts J, Kristmundsdottir T, De Clercq E, Thormar H. Hydrogels containing monocaprin prevent intravaginal and intracutaneous infections with HSV-2 in mice: impact on the search for vaginal microbicides. J. Med. Virol. 2000; 61:107–110.

Nohynek GJ, Borgert CJ, Dietrich D, Rozman KK. Endocrine disruption: fact or urban legend? Toxicol. Lett. 2013; 223:295–305.

O'Loughlin J, Millwood I, McDonald H, Price C, Kaldor J, Paull J. Safety, Tolerability, and Pharmacokinetics of SPL7013 Gel (VivaGel®): A Dose Ranging, Phase I Study. Sexually transmitted diseases. Seks. Transm. Dis. 2010; 37:100-104.

Owen DH, Peters JJ, Katz DF. Comparison of the rheological properties od Advantage-S and Replens. Contraception 2001; 67: 393-396.

Owen DH, Peters JJ, Katz DF. Rheological properties of contraceptive gels. Contraception 2000; 62:321-326.

Owen DH, Peters JJ, Lavine ML, Katz DF. Effect of temperature ond pH on contraceptive gel viscosity. Contraception 2003; 76:57-64.

Palmeira-de-Oliveira R, Duarte P, Palmeira-de-Oliveira A, das Neves J, Amaral MH, Breitenfeld L, Martinez-de-Oliveira J. Women's experiences, preferences and perceptions regarding vaginal products: results from a cross-sectional webbased survey in Portugal. Eur. J. Contracept. Reprod. Health Care 2014; 1–13.

Palmeira-de-Oliveira R, Palmeira-de-Oliveira A, Martinez-de-Oliveira J. New strategies for local treatment of vaginal infections. Adv. Drug Deliv. Rev. 2015; 92:105-122.

Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE. Guidelines for treatment of candidiasis. Clin. Infect. Dis. 2004;38:161–189.

Partridge AH. Chemotherapy in Premenopausal Breast Cancer Patients. Breast Care 2015; 10:307–10.

Pastorek JD, Cotch MF, Martin DH, Eschenbach DA. Clinical and microbiological correlates of vaginal trichomoniasis during pregnancy. The Vaginal Infections and Prematurity Study Group. Clin. Infect. Dis. 1996;23:1075–1080.

Patel HR, Patel MM. Poloxamers: a pharmaceutical excipients with therapeutic behaviors. Int. J. Pharm.Tech. Res. 2009; 1:299–303.

Paternoster DM, Tudor L, Milani M, Maggino T, Ambrosini A. Efficacy of an acidic vaginal gel on vaginal pH and interleukin-6 levels in low-risk pregnant women: a double-blind, randomized placebo-controlled trial. J. Matern. Fetal Neonatal Med. 2004; 15:198–201.

Patterson JL, Girerd PH, Karjane NW, Jefferson KK. Effect of biofilm phenotype on resistance of Gardnerella vaginalis to hydrogen peroxide and lactic acid. Am. J. Obstet. Gynecol. 2007; 170–177.

Patton DL, Kidder GG, Sweeney YC, Rabe LK, Hillier SL. Effects of multiple applications of benzalkonium chloride and nonoxynol 9 on the vaginal epithelium in the pigtailed macaque (Macaca nemestrina). Am. J. Obstet. Gynecol. 1999; 180:1080–1087.

Pavelić Ž, Škalko-Basnet N, Filipović-Grčić J, Martinac A, Jalšenjak I. Development and in vitro evaluation of a liposomal vaginal delivery system for acyclovir. J. Control. Release 2005; 106:34–43.

Pavelić Ž, Škalko-Basnet N, Jalšenjak I. Liposomal gel with chloramphenicol: Characterisation and *in vitro* release. Acta Pharm. 2004; 54:319–330.

Pavelić Ž. Terapijski sustavi za vaginalnu primjenu. Farm. Glas. 2005; 61:7-8.

Petrin D, Delgaty K, Bhatt R, Garber G. Clinical and microbiological aspects of Trichomonas vaginalis. Clin. Microbiol. Rev. 1998; 11:300–317.

Phillips DM, Zacharopoulos VR. Nonoxynol-9 enhances rectal infection by herpes simplex virus in mice. Contraception 1998; 57:341–8.

Pifferi G, Restani P. The safety of pharmaceutical excipients. Farmaco. 2003; 58:541–550.

Purdon CH, Haigh JM, Surber C, Smith EW. Foam Drug Delivery in Dermatology. Am. J. Drug Deliv. 2003; 1:71-75.

Ramage G, Saville SP, Thomas DP, Lopez-Ribot JL. Candida biofilms: an update. Eukaryot Cell 2005; 4:633–638.

Reichman O, Sobel J. Desquamative inflammatory vaginitis. Best Pract. Res. Clin. Obstet. Gynaecol. 2014; 28:1042–1050.

Rioux JE, Devlin MC, Gelfand MM, Steinberg WM, Hepburn DS. 17β estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 2018; 25:1208-1213.

Rohan LC, Sassi AB. Vaginal drug delivery systems for HIV prevention. AAPS Pharm. Sci. Tech. 2009; 11:78–87.

Rossi S, Ferrari F, Bonferoni MC, Sandri G, Faccendini A, Puccio A, Caramella C. Comparison of poloxamer- and chitosan-based thermally sensitive gels for the treatment of vaginal mucositis. Drug Dev. Ind. Pharm. 2014; 40:352–360.

Rousseau V, Lepargneur JP, Roques C, Remaud-Simeon M, Paul F. Prebiotic effects of oligosaccharides on selected vaginal lactobacilli and pathogenic microorganisms. Anaerobe 2005; 11:145–153.

Roy S, Gourde P, Piret J, Desormeaux A, Lamontagne J, Haineault C, Omar RF, Bergeron MG. Thermoreversible gel formulations containing sodium lauryl sulfate or n-Lauroylsarcosine as potential topical microbicides against sexually transmitted diseases. Antimicrob. Agents Chemother. 2001; 45:1671–1681.

Ruel-Gariepy E, Leroux JC. In situ-forming hydrogels – review of temperature-sensitive systems. Eur. J. Pharm. Biopharm. 2004; 58:409–426.

Rupp R, Rosenthal SL, Stanberry LR. VivaGel (SPL7013 Gel): a candidate dendrimer--microbicide for the prevention of HIV and HSV infection. Int. J. Nanomedicine 2007; 2:561–566.

Sadeghi M, Namjouyan F, Cheraghian B, Abbaspoor Z. Impact of Glycyrrhiza glabra (licorice) vaginal cream on vaginal signs and symptomes of vaginal atrophy in postmenopausal women: A randomized double blind controlled study. J. Tradit. Complement Med. 2018. https://doi.org/10.1016/j.jtcme.2019.02.005

Sahoo CK, Nayak PK, Sarangi DK, Sahoo TK. Intra vaginal drug delivery system: an overview. Am. J. Adv. Drug Deliv. 2013; 1:43-55.

Sandri G, Bonferoni MC, Ferrari F, Rossi S, Del Fante C, Perotti C, Gallanti A, Caramella C. An in situ gelling buccal spray containing platelet lysate for the treatment of oral mucositis. Curr. Drug. Discov. Technol. 2011; 8:277–285.

Schmid G, Narcisi E, Mosure D, Secor WE, Higgins J, Moreno H. Prevalence of metronidazole-resistant Trichomonas vaginalis in a gynecology clinic. J. Reprod. Med. 2001; 46:545–549.

Schmid GP. The epidemiology of bacterial vaginosis. Int. J. Gynaecol. Obstet. 1999; 67:17-20.

Schwebke JR, Barrientes FJ. Prevalence of Trichomonas vaginalis isolates with resistance to metronidazole and tinidazole, Antimicrob. Agents Chemother. 2006; 50:4209–4210.

Schwebke JR, Desmond RA, Oh MK. Predictors of bacterial vaginosis in adolescent women who douche. Sex. Transm. Dis. 2004; 31:433–436.

Seeras RC. Induction of labor utilizing vaginal vs. intracervical prostaglandin E2. Int. J. Gynaecol. Obstet. 1995; 48:163–167.

Senyiğit ZA, Karavana SY, Eraç B, Gürsel O, Limoncu MH, Baloğlu E. Evaluation of chitosan based vaginal bioadhesive gel formulations for antifungal drugs. Acta Pharm. 2014; 64:139–156.

Shetty A, Livingston I, Acharya S, Templeton A. Vaginal prostaglandin E2 gel versus tablet in the induction of labour at term-a retrospective analysis. J. Obstet. Gynaecol. 2004; 24:243–246.

Shinde N. Pharmaceutical foam drug delivery system: General considerations. IAJPR 2013; 3.

Sinha A, Ewies AA. Non-hormonal topical treatment of vulvovaginal atrophy: an up-to-date overview. Climacteric 2013; 16:305–12.

Smayevsky J, Canigia LF, Lanza A, Bianchini H. Vaginalmicroflora associatedwith bacterial vaginosis in nonpregnant women: reliability of sialidase detection. Infect. Dis. Obstet. Gynecol. 2001; 9:17–22.

Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D, Nyirjesy P, Heine MW, Willems J, Panzer H, Wittes H. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. Am. J. Obstet. Gynecol. 2001; 185:363–369.

Sobel JD. Bacterial vaginosis. Annu. Rev. Med. 2000; 51:349–356.

Sobel JD. Desquamative inflammatory vaginitis: A new subgroup of purulent vaginitis responsive to topical 2% clindamycin therapy. Inf. Dis. in Obstet and Gynol. 1994; 171:1215-1220.

Sobel JD. Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. Am. J. Obstet. Gynecol. 1985; 152:924–935.

Sobel JD. Vulvovaginal candidosis. Lancet 2007; 369:1961–1971.

Spiegel CA. Bacterial vaginosis. Clin. Microbiol. Rev. 1991; 4:485–502.

Stewart JD, Rayburn WF, Farmer KC, Liles EM, Schipul AH, Stanley JR. Effectiveness of prostaglandin E2 intracervical gel (Prepidil), with immediate oxytocin, versus vaginal insert (Cervidil) for induction of labor. Am. J. Obstet. Gynecol. 1998; 179:1175–1180.

Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 2010; 13:509–22.

Sutton M, Sternberg M, Koumans EH, McQuillan G, Berman S, Markowitz L. The prevalence of Trichomonas vaginalis infection among reproductive-age women in the United States, 2001–2004. Clin. Infect. Dis. 2007; 45:1319–1326.

Swidsinski A, Mendling W, Loening-Baucke V, Swidsinski S, Dorffel Y, Scholze J, Lochs H, Verstraelen H. An adherent Gardnerella vaginalis biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. Am. J. Obstet. Gynecol. 2008; 97:91–96.

Syed TA, Qureshi ZA, Ahmad SA, Ali SM. Management of intravaginal warts in women with 5-fluorouracil (1%) in vaginal hydrophilic gel: a placebo-controlled double-blind study. Int. J. STD AIDS 2000; 11:371–374.

Taylor SJ, Peat JK, Armour CL. An evaluation of prostaglandin E2 vaginal gel use in practice. J. Clin. Pharm. Ther. 1999; 24:303–310.

Tenore JL. Methods for cervical ripening and induction of labor, Am. Fam. Physician 2003; 67:2123–2128.

Thacker HL. Assessing risks and benefits of nonhormonal treatments for vasomotor symptoms in perimenopausal and postmenopausal women. J. Wom. Health. 2011; 20:1007-1016.

Timur SS, Şahin A, Aytekin E, Öztürk N, Polat KH, Tezel N, Gürsoy RN, Çalış. Design and *in vitro* evaluation of tenofovir-loaded vaginal gels for the prevention of HIV infections. Pharm. Dev. Technol. 2017; 23:301-310.

Tugcu-Demiroz F. Vaginal delivery of benzydamine hydrochloride through liposomes dispersed in mucoadhesive gels. Chem. Pharm. Bull. 2017; 65.

Vanić Ž, Jug M. Oblikovanje lijekova (skripta), 2017. Zagreb: Farmaceutsko-biokemijski fakultet.

Vanić Ž, Palac Z, Škalko-Basnet N. Hidrogelovi za vaginalnu primjenu lijekova. Farm. Glas. 2014; 70:813-862.

Vanić Ž, Škalko-Basnet N. Mucosal nanosystems for improved topicač drug delivery: vaginal route of administration. J. Drug Del. Sci. Tech. 2014; 24:435-444.

Vanić Ž, Škalko-Basnet N. Nanopharmaceuticals for improved topical vaginal teraphy: Can they deliver? Eur. Pharm. Sci. 2013; 50:29-41.

Verhelst R, Verstraelen H, Claeys G, Verschraegen G, Delanghe J, Van Simaey L, De Ganck C, Temmerman M, Vaneechoutte M. Cloning of 16S rRNA genes amplified from normal and disturbed vaginal microflora suggests a strong association between Atopobium vaginae, Gardnerella vaginalis and bacterial vaginosis. BMC Microbiol. 2004; 4:16.

Wain AM. Metronidazole Vaginal Gel 0.75% (MetroGel-Vaginal®): A Brief Review. Inf. Dis. in Obstet and Gynol. 1998; 6:3-7.

Wang Y, Lee CH. Characterization of a female controlled drug delivery system for microbicides. Contraception 2002; 66:281–287.

Wilson AJ. Foams: Physics, Chemistry and Structure. Springer-Verlag, Berlin/Heidelberg, 1989.

World Health Organization, Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections Overview and Estimates, 2001 (Geneva).

World Health Organization. Use and procurement of additional lubricants for male and female condoms: WHO/UNFPA/FHI360 advisory note 2012 [7 July 2015]. Dostupna na: http://apps.who.int/iris/bitstream/10665/76580/1/WHO_RHR_12.33_eng.pdf

Yoshimura AS. Foam and emulsion rheology. PhD Thesis, Princeton University, USA, 1988.

8. SAŽETAK

Polučvrsti oblici najčešće su korišteni oblici lijekova za vaginalnu primjenu. Većina ih je namijenjena postizanju lokalnog učinka (liječenje vaginalnih infekcija i spolno prenosivih bolesti, tretiranje vaginalne atrofije, induciranje poroda, kontracepcija), no dosta se istražuju i za sistemske učinke. Konvencionalni polučvrsti vaginalni pripravci imaju i nedostatke poput zbog kratkog vremena zadržavanja na mjestu primjene zbog čega nerijetko izostane željeni terapijski učinak. Stoga se velika pažnja posvećuje razvoju vaginalnih formulacija s poboljšanim svojstvima korištenjem mukoadhezivnih i termoosjetljivih polimera, inovativnim tehnologijama aerosola te nanotehnologije. Ovaj diplomski rad daje pregled trenutno dostupnih te inovativnih polučvrstih oblika za vaginalnu primjenu lijekova.

SUMMARY

Semisolid dosage forms are the most commonly used formulations for vaginal drug administration. Although most of them are intended for a topical drug delivery (treatment of vaginal infections, sexually transmitted diseases, vaginal atrophy, labor induction and contraception), they have potential for achieving systemic drug effects, too. However, the conventional semisolid formulations have some limitations such as low residence time on vaginal surface, which can lead to an unsuccessful therapy. Therefore, there is a great interest in developing an advanced vaginal formulations based on the use of mucoadhesive and/or thermosensitive polymers, innovative aerosol technology and nanotechnology. This diploma thesis provides an overview of the currently available and innovative semisolid dosage forms for vaginal drug delivery.

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Diplomski rad

POLUČVRSTI OBLICI ZA VAGINALNI PRIMJENU LIJEKOVA

Lucija Prižmić

SAŽETAK

Polučvrsti oblici najčešće su korišteni oblici lijekova za vaginalnu primjenu. Većina ih je namijenjena postizanju lokalnog učinka (liječenje vaginalnih infekcija i spolno prenosivih bolesti, tretiranje vaginalne atrofije, induciranje poroda, kontracepcija), no dosta se istražuju i za sistemske učinke. Konvencionalni polučvrsti vaginalni pripravci imaju i nedostatke poput zbog kratkog vremena zadržavanja na mjestu primjene zbog čega nerijetko izostane željeni terapijski učinak. Stoga se velika pažnja posvećuje razvoju vaginalnih formulacija s poboljšanim svojstvima korištenjem mukoadhezivnih i termoosjetljivih polimera, inovativnim tehnologijama aerosola te nanotehnologije. Ovaj diplomski rad daje pregled trenutno dostupnih te inovativnih polučvrstih oblika za vaginalnu primjenu lijekova.

Rad je pohranjen u Središnjoj knjižnici Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta.

Rad sadrži: 102 stranice, 3 grafička prikaza, 7 tablica i 182 literaturna navoda. Izvornik je na hrvatskom jeziku.

Ključne riječi: Vaginalni ljekoviti oblici, polučvrsti farmaceutski oblici, mukoadhezivni polimeri, termoosjetljivi gelovi, nanotehnologija

Mentor: **Dr. sc. Željka Vanić**, *izvanredna profesorica Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta.*

Ocjenjivači: **Dr. sc. Željka Vanić**, *izvanredna profesorica Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta.*
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Faculty of Pharmacy and Biochemistry
Study: Pharmacy
Department of Pharmaceutical Technology
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Diploma thesis

SEMI-SOLID DOSAGE FORMS FOR VAGINAL DRUG DELIVERY

Lucija Prižmić

SUMMARY

Semisolid dosage forms are the most commonly used formulations for vaginal drug administration. Although most of them are intended for a topical drug delivery (treatment of vaginal infections, sexually transmitted diseases, vaginal atrophy, labor induction and contraception), they have potential for achieving systemic drug effects, too. However, the conventional semisolid formulations have some limitations such as low residence time on vaginal surface, which can lead to an unsuccessful therapy. Therefore, there is a great interest in developing an advanced vaginal formulations based on the use of mucoadhesive and/or thermosensitive polymers, innovative aerosol technology and nanotechnology. This diploma thesis provides an overview of the currently available and innovative semisolid dosage forms for vaginal drug delivery.

The thesis is deposited in the Central Library of the University of Zagreb Faculty of Pharmacy and Biochemistry.

Thesis includes: 102 pages, 3 figures, 7 tables and 182 references. Original is in Croatian language.

Keywords: Vaginal drug delivery, semi-solid dosage forms, mucoadhesive polymers, thermosensitive polymers, nanotechnology

Mentor: **Željka Vanić**, **Ph.D.** *Associate Professor,* University of Zagreb Faculty of Pharmacy and Biochemistry

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