INTISARI

Bioavailabilitas obat di mata secara topikal rendah (<5%) karena adanya hambatan anatomis dan fisologis. Kornea merupakan salah satu *barrier* anatomis yang berpengaruh terhadap permeasi okular. Rendahnya permeasi obat melalui kornea akan menyebabkan rendahnya bioavailabilitas obat di mata. Adanya pergantian air mata yang tinggi, waktu tinggal yang singkat di *cul de sac*, eliminasi obat serta *drainase nasolachrymal* juga memberikan pengaruh terhadap rendahnya bioavailabilitas obat. Strategi peningkatan bioavailabilitas obat di mata dapat dilakukan dengan sistem penghantaran obat dalam bentuk *in situ gel* nanopartikel. *In situ gel* nanopartikel dapat meningkatkan waktu kontak dan permeasi obat sehingga dapat meningkatkan bioavailabilitas obat. Efektivitas sediaan *in situ gel* dalam peningkatan bioavailabilitas obat di mata salah satunya dapat digambarkan dengan uji permeasi sediaan secara *ex vivo*. Penelitian ini bertujuan untuk mempelajari permeasi *in situ gel* nanopartikel levofloksasin secara *ex vivo.*

Penelitian terdiri dari dua tahap. Tahap pertama yaitu optimasi formula nanopartikel levofloksasin beserta karakterisasinya. Optimasi formula menggunakan *D-Optimal Mixture Design* yang terdapat dalam piranti lunak *Design Expert® 7.1.5*. Tahap penelitian yang kedua yaitu formulasi dan evaluasi sediaan *in situ gel* nanopartikel levofloksasin. Nanopartikel formula optimum diformulasi dalam bentuk sediaan *in situ gel* dengan polimer natrium alginat. Evaluasi sediaan *in situ gel* nanopartikel levofloksasin meliputi uji sterilitas, osmolalitas, kejernihan, kandungan obat, kapasitas pembentukan gel, viskositas dan sifat alir, pH, uji pelepasan secara *in vitro*, uji permeasi secara *ex vivo*, uji iritasi, uji aktivitas antibakteri secara *in vitro* menggunakan bakteri *P. aeruginosa ATCC 27853* dan *S. aureus ATTC 25923.*

Hasil formula optimum nanopartikel levofloksasin menggunakan *D-Optimal Mixture Design* terdiri dari kitosan 0,03% b/v; alginat 0,05% b/v; levofloksasin 0,1% b/v dengan proporsi pada saat formulasi masing-masing 5:1:1. Ukuran partikel, PDI, zeta potensial formula optimum bernilai 295,71 ± 4,15 nm; 0,416 ± 0,009; dan zetapotensial bernilai 24,40± 1,010 mV. Sediaan *in situ gel* nanopartikel LEVH yang dikembangkan jernih, pH sediaan ± 6, proses gelasi segera, bertahan selama beberapa jam, hasil uji viskositas dan osmolalitas memenuhi syarat sediaan *in situ gel* okular . Persen pelepasan obat kumulatif *in situ gel* nanopartikel LEVH pada rentang 73,48±14,57 % - 84,88 ±7,64 dengan profil pelepasan mengikuti kinetika Korsmeyer Peppas *with T lag.* Jumlah obat yang terpermeasi selama 36 jam sebesar 31,719 ± 0,618 µg. Model permeasi *in situ gel* nanopartikel LEVH mengikuti 4 model kompartemen dengan 1 kompartemen *lag*. Prediksi *in vivo* C_{max} dalam *aquous humor* sebesar 1 µg/mL yang nilainya lebih tinggi dari MIC levofloksasin terhadap *S. aureus ATTC 25923* dan *P. aureginosa ATTC 27853. In situ gel* nanopartikel memiliki daya hambat terhadap bakteri *S. aureus ATTC 25923* dan *P. aeruginosa ATCC 27853* dalam kategori *susceptible*. Hasil uji iritasi menunjukkan bahwa *in situ gel* nanopartikel levofloksasin tidak menimbulkan iritasi.

Kata kunci : *D-optimal Mixture design*, nanopartikel, levofloksasin, in situ gel

ABSTRACT

Ocular bioavailability is low (<5%) due to anatomical and physiological barriers. The cornea is one of the anatomical barriers that affect ocular permeation. The low permeation of drugs through the cornea will lead to low bioavailability of drugs in the eye. A high tear turnover, short residence time in the cul de sac, drug elimination and nasolachrymal drainage also influence the low bioavailability of the drug. The strategy to increase drug bioavailability in the eye can be done with a drug delivery system in the form of nanoparticles-loaded in situ gel. Nanoparticles-loaded in situ gel can increase the residence time and drug permeation to increase drug bioavailability. The effectiveness of nanoparticles-loaded in situ gel in increasing the bioavailability of drugs in the eye can be described by ex vivo permeation tests. This research aims to study on ex vivo permeation of levofloxacin nanoparticles- loaded in situ gel.

The research consists of two stages. The first stage is optimizing the levofloxacin nanoparticle formula and its characterization. Formula of nanoparticle optimization using D-Optimal Mixture Design contained in Design Expert® 7.1.5 software. The second stage of the research was the formulation and evaluation of levofloxacin nanoparticle gel in situ preparations. Optimum formula nanoparticles are levofloxacin nanoparticles loaded in situ gel with sodium alginate as polymer. Evaluation of levofloxacin nanoparticles-loaded in situ gel included tests for sterility, osmolality, clarity, drug content, gel-forming capacity, viscosity and flow properties, pH, in vitro release test, ex vivo permeation study, irritation test, in vitro antibacterial activity test using P. aeruginosa ATTC 27853 and S. aureus ATTC 25923 bacteria.

The optimum formula for levofloxacin nanoparticles using D-Optimal Mixture Design consisted of 0.03% b/v chitosan; alginate 0.05% b/v; levofloxacin 0.1% b/v with the proportion at the time of each formulation 5:1:1. Particle size, PDI, zeta potential of the optimum formula is 295.71 ± 4.15 nm; 0.416 ± 0.009; and the zeta potential is 24.40 ± 1.010 mV. The developed LEVH nanoparticle-loaded in situ gel was clear, the pH was ± 6, the gelation process was immediate and lasted for several hours, and the results of the viscosity and osmolality tests met the requirements for an ocular gel in situ preparation. The cumulative drug release percentage LEVH nanoparticle-loaded in situ gel was 73.48 ± 14.57 % - 84.88 ± 7.64 with the kinetics release profile following the Korsmeyer Peppas with T lag. The drug permeated for 36 hours was 31.719 ± 0.618 µg. The LEVH nanoparticle-loaded in situ gel permeation model follows a four-compartment model with one lag compartment. The in vivo prediction of Cmax in the aqueous humour is 1 µg/mL, which is higher than the MIC of levofloxacin against S. aureus ATTC 25923 and P. aeruginosa ATTC 27853. The LEVH nanoparticle-loaded in situ gel has inhibition against S. aureus ATTC 25923 and P. aeruginosa ATTC 27853 in the susceptible category. The results of the irritation test showed that LEVH nanoparticle-loaded in situ gel did not irritate the eye.

Keywords: D-optimal Mixture design, nanoparticles, levofloxacin, in situ gel