Natamycin Laden Nanoparticles as Sustained Ocular Delivery Vehicles: Development, In Vitro/In Vivo Characterization and PK/PD Indices
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Purpose
Natamycin is the only approved medication for the treatment of mycotic keratitis. Current dosage regimen include one drop of natamycin suspension instilled in the conjunctival sac at hourly or two hourly intervals for several days which has poor patient compliance. The purpose of the present study was to design a corneal targeted nanoformulation in order to reduce the dose and dosing frequency of natamycin and evaluate its pharmacokinetic/pharmacodynamic indices in comparison with clinical marketed preparation(Natamet® 5%, w/v).

Methods
Poly-D-glucosamine (PDG) - polycaprolactone (PCL) nanoparticles (NPs, 1% and 5%, w/v) were prepared by nanoprecipitation method. These NPs were characterized for particle size, zeta potential, surface morphology, drug loading, mucoadhesive properties, in-vitro release and antifungal activity. The applicability of these NPs as ocular delivery vehicles was investigated by comparing the pharmacokinetic-pharmacodynamic (PK/PD) indices with Natamet®. In addition, the ocular pharmacokinetic profiles and rational PK/PD based dosage regimens in preclinical NZ rabbit model were also reported.

Results
The optimized PDG-PCL NPs formulation (natamycin to polymer weight ratio of 1:5) has a mean particle size of 217 ± 2 nm with a high positive surface charge of +43.5 ± 1.55 mV. The mucoadhesive properties were significantly higher as compared with PCL NPs. The in-vitro drug release studies indicated that developed NPs were able to prolong the release of encapsulated natamycin up to 8 h. The in-vitro antifungal activity was comparable with Natamet® (MIC90 = 3.12 mg/L). The NPs 5% exhibited significant enhancement in AUC(0–∞) (~6.38 fold), MRT (~6.17 fold) and decrease in clearance (~6.33 fold) as compared with Natamet®. The ideal dosing intervals which could maintain the natamycin concentration above tenfold of MIC90 i.e., 31.2 mg/L by NPs 1% and NPs 5% were every 210 min and 300 min, respectively as compared with every 120 min by Natamet®.

Conclusion
In conclusion, the developed mucoadhesive nanoformulations were compatible with ocular milieu and demonstrated their potential as viable alternative to marketed natamycin suspension with prolonged release and mucoadhesive properties.