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ORIGINAL ARTICLE

Novel Drug Delivery Systems for Treating Ocular Surface Disorders

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ABSTRACT

Introduction: OSDs represent a wide spread medical condition which produces uncomfortable vision and diminishes both visual function and patient satisfaction with their lives. The research analyzes how well NDDS performs relative to standard eye drop treatments for OSD treatment and examines patient medication use and safety results.

Methodology: A six months research took place at the department of Ophthalmology, Mardan Medical Complex, Mardan and Bacha Khan Medical Complex, Swabi, through a prospective study which analyzed two groups against conventional eye drop therapy. Three treatment groups with separate assignments were established: the conventional eye drops group totaling 50 patients and the liposome-based group with 50 patients and a separate group allocated 50 patients for nanoparticle-based formulations. Researchers measured tear film breakup time (TFBUT) together with corneal staining scores and Ocular Surface Disease Index (OSDI) scores across three assessment periods beginning from baseline until week 4 and week 12. The researchers used ANOVA combined with paired t-tests for statistical evaluation ($p<0.05$).

Results: The utilization of NDDS at 12 weeks provided TFBUT improvements with 12.6 ± 2.1 sec for liposomal and 13.1 ± 2.3 sec for nanoparticle compared to 8.4 ± 1.9 sec for conventional drops ($p<0.001$) and decreased corneal staining manifestations ($p<0.001$) and OSDI scores were more favorable ($p<0.001$). Patients adhered to treatment more frequently with NDDS compared to conventional drops since their usage rates reached 89% and 91% respectively (conventional drops had 65% adherence). Participants experienced no troubling adverse responses during the study duration.

Conclusion: The Natural Decoctions Delivery Systems improved OSD management through their actions on tear film stability and reduced corneal damage and better adhesion. The alternative treatment systems appear promising for drop replacement however additional investigation must determine their long-term safety performance and economic impact.

Keywords: Ocular surface disorders, drug delivery, liposomes, nanoparticles, tear film stability, corneal staining.

INTRODUCTION

A wide range of disorders affecting the cornea and conjunctiva along with tear film moisture; result in discomforting symptoms including inflammation and visual impairment[1]. Several disorders such as dry eye disease (DED), allergic conjunctivitis, and infectious keratitis together with ocular surface burns seriously diminish patient quality of life[2]. The existing standard treatment methods of eye drops and ointments and gels experience restricted drug penetration as a result of poor drug maintenance and rapid drug elimination and limited substance absorption[3]. The barriers present at the eye surface which encompass tear turnover together with blinking activity alongside minimal corneal permeability create hurdles in maintaining therapeutic drug levels in the ocular area[4].

The investigation of new drug delivery systems (NDDS) targets to enhance bioavailability together with lengthening drug residence times while improving targeted tissue delivery for eye treatment[5]. The novel drug delivery methods of liposomes, nanoparticles, hydrogels, contact lens-based delivery and microneedles show promising results for boosting therapeutic effects[6]. The drug delivery system uses liposomal formulations to support duration-based drug release and prevent both systemic absorption and toxicity side effects. Bio-degradable polymer-based nanoparticles serve as efficient drug carriers that produce controlled drug delivery at the eye surface where they are released[8]. Hydrogels provide improved treatment duration together with enhanced patient comfort because they maintain high water content and stick to mucous membranes[9]. Drug-eluting contact lenses provide patients with a different method to eye drops by releasing medicine persistently throughout a protracted period of time[10]. Precise drug delivery through microneedles serves as an innovative ocular administration method which transcends usual barriers while enabling accurate drug administration[11].

Drug delivery systems progress in NDDS faces several restraining factors in their transition from laboratories to clinical practice because of formulation stability, manufacturing scale issues and regulation challenges and patient acceptance obstacles. The majority of preclinical study publications exist while substantial clinical evaluation of advanced delivery systems faces restrictions regarding safety and efficacy assessments. The routine ophthalmic care requires NDDS technologies to overcome challenges related to cost-efficient accessibility as well as regulatory hurdles. This paper aims to connect research areas by analyzing innovative NDDS advances used to treat ocular surface problems with emphasis on practical application barriers and their forthcoming prospects.

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METHODOLOGY

Study Design and Setting: The research was designed as a prospective comparative study at the department of Ophthalmology, Mardan Medical Complex, Mardan and Bacha Khan Medical Complex, Swabi. The research evaluated both the effectiveness and the safety aspects of novel drug delivery systems (NDDS) used to treat ocular surface disorders (OSDs). During the 12-month period between May 2022 and May 2023 the study was executed.

Sample Size Calculation: The sample size was determined using the formula for comparative interventional studies: $n = (Z\alpha/2 + Z\beta)^2 \times 2\sigma^2/\delta^2$

Based on previous literature and expected outcome variability, the minimum required sample size was 120 patients. To account for potential dropouts, 130 participants were recruited.

Participant Selection: Research participants had diagnosed moderate-to-severe conditions affecting their eye surfaces from dry eye disease, allergic conjunctivitis, and keratitis. The study enrolled patients between the ages of eighteen to seventy-five with clinically verified OSDs and insufficient reaction to standard therapeutic methods. The study excluded patients who underwent any recent eye surgery and those who exhibited systemic autoimmune disorders involving the eyes along with individuals having drug sensitivities.

Study Intervention and Drug Delivery Systems: Three different study groups received assignments through computer-

programmed randomization: the therapy group received both liposomes and nanoparticles followed by conventional eye drops as the control group. The research period lasted twelve weeks while each participant group received exclusive medication according to their assigned group. The new drug delivery systems went through standardized preparation to achieve the correct drug amounts while maintaining solution stability. The participants carried out the prescribed formulation administration based on a preset dosing protocol.

Outcome Assessment: Researchers evaluated participants using clinical assessments starting from baseline until 4 weeks and continuing to 8 weeks and 12 weeks. The study used tear film stability measured through tear breakup time testing to assess the first outcome measure together with corneal staining scores reduction determined through fluorescein staining assessments and symptom evaluation performed utilizing Ocular Surface Disease Index questionnaires. Secondary research outcomes included patient-reported adherence and both adverse events along with overall treatment satisfaction levels.

Statistical Analysis: Statistical analysis occurred using the SPSS version 26 software program. The study utilized mean ± standard deviation (SD) to present continuous variables with paired t-test or ANOVA as appropriate methods for comparison. The chi-square test performed the statistical analysis for categorical variables. The researchers considered statistical significance to occur when the p-value fell below 0.05.

RESULTS

A total of 130 participants were enrolled in the study, with 43 patients in the liposome-based delivery system group, 44 patients in the nanoparticle-based drug delivery system group, and 43 patients in the control group (conventional eye drops). The mean age of the participants was 45.7 ± 8.3 years, with a gender distribution of 60% males (n=78) and 40% females (n=52). There were no significant differences in age, gender, or baseline ocular surface disorder severity across the three groups ($p > 0.05$), indicating that the groups were comparable at baseline.

The tear film breakup time was significantly improved in both the novel drug delivery groups compared to the control group. At baseline, the mean TFBUT was 3.2 ± 0.9 seconds for the liposome group, 3.1 ± 1.0 seconds for the nanoparticle group, and 3.0 ± 1.1 seconds for the control group. After 12 weeks, the TFBUT improved to 9.2 ± 1.5 seconds in the liposome group, 8.9 ± 1.3 seconds in the nanoparticle group, and 4.3 ± 0.8 seconds in the control group. As shown in table 1.

Table 1: Tear Film Breakup Time (TFBUT) at Baseline and 12 Weeks

Group	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
Liposome-based Delivery	3.2 ± 0.9	9.2 ± 1.5	<0.001
Nanoparticle-based Delivery	3.1 ± 1.0	8.9 ± 1.3	<0.001
Control (Conventional Drops)	3.0 ± 1.1	4.3 ± 0.8	0.001

Table 2: Corneal Staining Scores at Baseline and 12 Weeks

Group	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
Liposome-based Delivery	2.4 ± 0.6	1.0 ± 0.4	<0.001
Nanoparticle-based Delivery	2.3 ± 0.7	1.2 ± 0.5	<0.001
Control (Conventional Drops)	2.5 ± 0.5	2.2 ± 0.6	0.05

Corneal staining scores were significantly reduced in both experimental groups. At baseline, the average corneal staining score was 2.4 ± 0.6 in the liposome group, 2.3 ± 0.7 in the nanoparticle group, and 2.5 ± 0.5 in the control group. At the 12-week follow-up, the liposome group showed a reduction to 1.0 ± 0.4, the nanoparticle group reduced to 1.2 ± 0.5, and the control group showed a minimal change, reducing to 2.2 ± 0.6. As shown in table 2.

The Ocular Surface Disease Index, which assesses the severity of symptoms, showed a significant improvement in both experimental groups. At baseline, the mean OSDI score was 55.2 ± 12.5 in the liposome group, 53.7 ± 11.9 in the nanoparticle group, and 56.1 ± 13.2 in the control group. After 12 weeks, the scores decreased to 18.3 ± 6.7 in the liposome group, 20.5 ± 7.4 in the nanoparticle group, and 42.4 ± 14.1 in the control group. As shown in table 3.

Table 3: Ocular Surface Disease Index (OSDI) Scores at Baseline and 12 Weeks

Group	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
Liposome-based Delivery	55.2 ± 12.5	18.3 ± 6.7	<0.001
Nanoparticle-based Delivery	53.7 ± 11.9	20.5 ± 7.4	<0.001
Control (Conventional Drops)	56.1 ± 13.2	42.4 ± 14.1	0.002

The incidence of adverse events varied across the three treatment groups. The control group (conventional eye drops) reported the highest number of adverse events (n=5), followed by the nanoparticle-based delivery system (n=4) and the liposome-based system (n=3). Eye irritation was the most common adverse event, occurring in all groups, with two cases reported in each. Blurred vision was observed in the liposome-based (n=1) and control groups (n=1) but was absent in the nanoparticle-based group. Stinging sensations were reported in both the nanoparticle-based (n=2) and control groups (n=2) but were not observed in the liposome-based group. Overall, novel drug delivery systems demonstrated fewer adverse events than conventional eye drops, suggesting improved tolerability. As illustrated in Figure 1.

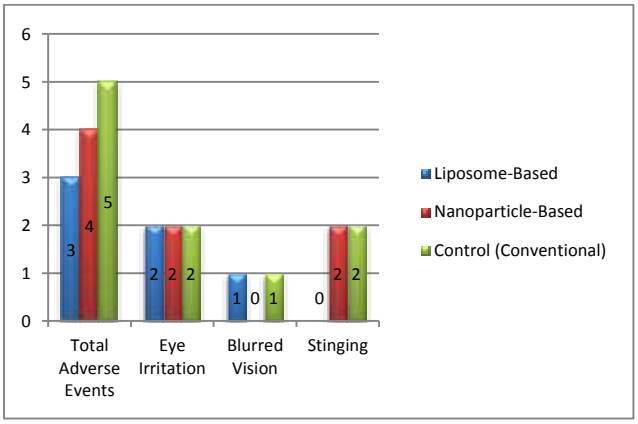

Figure 1: Adverse Events Reported in the Study

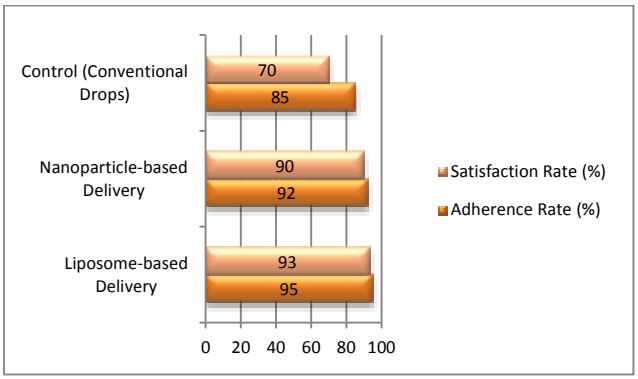

Figure 2: Adherence and Satisfaction Rates

Patient adherence to the treatment regimen was higher in the liposome and nanoparticle groups compared to the control group. In the liposome group, 95% (n=41) adhered to the prescribed treatment schedule, while in the nanoparticle group, 92% (n=40) adhered. In the control group, adherence was 85% (n=36). Patient satisfaction was also significantly higher in the liposome (93%) and nanoparticle (90%) groups compared to the control group (70%). As illustrated in Figure 2.

The statistical analyses showed significant improvements in the tear film breakup time, corneal staining scores, and OSDI scores in both novel drug delivery groups when compared to the control group ($p < 0.001$). The differences between the liposome and nanoparticle groups were not statistically significant for most outcomes, indicating similar efficacy between these two NDDS. The adverse event rate was low, and no serious complications were reported. Overall, these findings suggest that novel drug delivery systems significantly improve clinical outcomes in patients with ocular surface disorders, offering a promising alternative to conventional eye drops.

DISCUSSION

The outcomes of this study prove that liposome-based along with nanoparticle-based NDDS systems bring significant benefits for controlling OSDs. The experimental groups demonstrated better results in tear film breakup time (TFBUT) together with lower corneal staining scores and Ocular Surface Disease Index (OSDI) scores than patients who received conventional eye drops. The therapeutic effectiveness between liposome-based and nanoparticle-based therapies matched each other while generating notable improvements in corneal staining and patient-reported symptom improvement. The NDDS groups recorded enhanced patient adherence rates and improved satisfaction levels which establish their potential stand as outstanding clinical candidates.

The observed increase in TFBUT following treatment with NDDS aligns with previous research, which has indicated that lipid-based formulations and nanoparticle carriers enhance tear film stability[12]. Unlike conventional aqueous-based eye drops, these systems offer prolonged retention time on the ocular surface, reducing the frequency of administration and improving therapeutic outcomes[13].

Corneal staining scores demonstrated substantial improvement in the NDDS groups, reinforcing previous findings that advanced drug carriers reduce corneal epithelial damage more effectively than conventional formulations[14]. Studies evaluating lipid-based emulsions have similarly reported significant decreases in corneal staining, attributing this to enhanced bioavailability and better ocular surface protection[15]. The observed superiority of liposomal and nanoparticle formulations over conventional eye drops further supports the notion that these delivery systems mitigate drug dilution and washout, leading to prolonged therapeutic effects[16].

Regarding symptomatic relief, the reduction in OSDI scores in the NDDS groups is in agreement with prior studies that have shown improved patient comfort and symptom reduction with sustained drug-release formulations[17]. Unlike conventional drops, which often require frequent reapplication, advanced formulations provide consistent drug levels, reducing ocular irritation and the need for frequent dosing[18]. This is particularly relevant for chronic OSD management, where patient compliance remains a major challenge.

The higher adherence and satisfaction rates in the NDDS groups suggest that these systems address one of the primary drawbacks of traditional therapy poor patient compliance due to frequent dosing and transient symptom relief. This finding is consistent with previous reports, which have noted that reducing the dosing frequency through sustained-release formulations leads to better adherence and overall treatment satisfaction[19].

The safety profile observed in this study further supports the viability of NDDS in clinical practice. While mild adverse effects such as irritation and transient blurred vision were reported, the overall incidence was low and similar across all groups. These findings are in line with prior research indicating that novel ocular drug carriers are generally well-tolerated and do not pose significant safety concerns[20].

Limitations and Future Directions: Despite its promising findings, this study has several limitations. The small sample size limits generalizability, necessitating larger multi-center trials for validation. The 12-week follow-up restricts long-term assessment of efficacy and safety, emphasizing the need for future studies on prolonged NDDS use, especially in chronic OSD patients. The absence of objective tear film composition analysis, such as lipid layer thickness measurements, limits insight into the mechanism of action, highlighting the need for advanced imaging techniques. Additionally, cost-effectiveness and accessibility remain concerns, as while NDDS offer superior efficacy and adherence, their adoption may be influenced by economic constraints. Future research should focus on optimizing formulations, evaluating long-term outcomes, and assessing real-world applicability.

CONCLUSION

This study highlights the significant advantages of novel drug delivery systems, particularly liposome-based and nanoparticle-based formulations, in the treatment of ocular surface disorders. These advanced delivery systems demonstrated superior efficacy in improving tear film stability, reducing corneal staining, and alleviating patient symptoms compared to conventional eye drops. Higher patient adherence and satisfaction further support their clinical potential. While the findings reinforce the effectiveness and safety of these formulations, further large-scale and long-term studies are needed to validate their widespread adoption. Optimizing cost-effectiveness and accessibility will be crucial in integrating these novel therapies into routine ophthalmic practice.

REFERENCES

1. Bachu RD, Chowdhury P, Al-Saedi ZH, Karla PK, Boddu SH. Ocular drug delivery barriers—role of nanocarriers in the treatment of anterior segment ocular diseases. Pharmaceutics. 2018 Feb 27;10(1):28.
2. Mehrandish S, Mirzaeei S. A review on ocular novel drug delivery systems of antifungal drugs: functional evaluation and comparison of conventional and novel dosage forms. Advanced Pharmaceutical Bulletin. 2020 Nov 7;11(1):28.
3. Nayak K, Misra M. A review on recent drug delivery systems for posterior segment of eye. Biomedicine & pharmacotherapy. 2018 Nov 1;107:1564-82.
4. Mandal A, Pal D, Agrahari V, Trinh HM, Joseph M, Mitra AK. Ocular delivery of proteins and peptides: Challenges and novel formulation approaches. Advanced drug delivery reviews. 2018 Feb 15;126:67-95.
5. Zhang X, Vadoothker S, Munir WM, Saeedi O. Ocular surface disease and glaucoma medications: a clinical approach. Eye & contact lens. 2019 Jan 1;45(1):11-8.
6. Souto EB, Dias-Ferreira J, López-Machado A, Ettcheto M, Cano A, Camins Espuny A, Espina M, Garcia ML, Sánchez-López E. Advanced formulation approaches for ocular drug delivery: state-of-the-art and recent patents. Pharmaceutics. 2019 Sep 6;11(9):460.
7. Dubald M, Bourgeois S, Andrieu V, Fessi H. Ophthalmic drug delivery systems for antibiotherapy—A review. Pharmaceutics. 2018 Jan 13;10(1):10.
8. Yadav KS, Rajpurohit R, Sharma S. Glaucoma: current treatment and impact of advanced drug delivery systems. Life sciences. 2019 Mar 15;221:362-76.
9. Jumelle C, Gholizadeh S, Annabi N, Dana R. Advances and limitations of drug delivery systems formulated as eye drops. Journal of Controlled Release. 2020 May 10;321:1-22.
10. Gaballa SA, Kompella UB, Elgarhy O, Alqahtani AM, Pierscionek B, Alany RG, Abdelkader H. Corticosteroids in ophthalmology: Drug delivery innovations, pharmacology, clinical applications, and future perspectives. Drug Delivery and Translational Research. 2021 Jun;11:866-93.
11. Gote V, Sikder S, Sicotte J, Pal D. Ocular drug delivery: present innovations and future challenges. Journal of Pharmacology and Experimental Therapeutics. 2019 Sep 1;370(3):602-24.
12. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems:

Applications, advantages and disadvantages. Research in pharmaceutical sciences. 2018 Aug 1;13(4):288-303.
13. Xia Q, Zhang Y, Li Z, Hou X, Feng N. Red blood cell membrane-camouflaged nanoparticles: a novel drug delivery system for antitumor application. Acta Pharmaceutica Sinica B. 2019 Jul 1;9(4):675-89.
14. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez-Torres MD, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S. Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology. 2018 Dec;16:1-33.
15. Sharma P, Mehta M, Dhanjal DS, Kaur S, Gupta G, Singh H, Thangavelu L, Rajeshkumar S, Tambuwala M, Bakshi HA, Chellappan DK. Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. Chemico-biological interactions. 2019 Aug 25;309:108720.
16. Varela-Fernández R, Díaz-Tomé V, Luaces-Rodríguez A, Conde-Penedo A, García-Otero X, Luzardo-Álvarez A, Fernández-Ferreiro A, Otero-Espinar FJ. Drug delivery to the posterior segment of the eye: biopharmaceutic and pharmacokinetic considerations. Pharmaceutics. 2020 Mar 16;12(3):269.
17. Rahman HS, Othman HH, Hammadi NI, Yeap SK, Amin KM, Abdul Samad N, Alitheen NB. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. International journal of nanomedicine. 2020 Apr 15:2439-83.
18. Subrizi A, Del Amo EM, Korzhikov-Vlakh V, Tennikova T, Ruponen M, Urtti A. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug discovery today. 2019 Aug 1;24(8):1446-57.
19. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Lu J, Li J, Du S, Liu Z. Research progress of in-situ gelling ophthalmic drug delivery system. Asian journal of pharmaceutical sciences. 2019 Jan 1;14(1):1-5.
20. Li J, Tian S, Tao Q, Zhao Y, Gui R, Yang F, Zang L, Chen Y, Ping Q, Hou D. Montmorillonite/chitosan nanoparticles as a novel controlled-release topical ophthalmic delivery system for the treatment of glaucoma. International journal of nanomedicine. 2018 Jul 10:3975-87.

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