SMART GEL AND CONTACT LENSES-BASED DRUG DELIVERY SYSTEMS: NOVEL NANOTECHNOLOGY APPROACHES FOR TREATMENT OF COVID-19 ASSOCIATED CONJUNCTIVITIS

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ABSTRACT

Background: The aim of the present work is to develop advanced ocular delivery system of Naphazoline hydrochloride in ophthalmic dosage forms including thermoresponsive hydrogel, contact lenses and ocuserts.

Methods: Naphazoline hydrochloride loaded niosomes coated with chitosan (N1) were prepared via thin film hydration method, in addition, thermoresponsive gel was synthesized by cold method using poloxamer 407: poloxamer 188 in 1:3, 1:1 and 3:1 mass ratio , (G1), (G2) and (G3), respectively. The prepared niosomes (N1) were incorporated in (G3). Ocuserts were prepared from alginate and calcium chloride solutions using ionic cross-linking containing Naphazoline hydrochloride loaded niosomes coated with chitosan (F1) . Moreover, alginate based contact lens containing free drug (F2), and also readymade contact lens soaked in drug solution (F3) were prepared. Gamma radiation was adopted for the sterilization for the different formulae prior their evaluation. Niosomes were evaluated for particle size, zeta potential, entrapment efficiency and morphology using zeta sizer and SEM. Thermoresponsive gels were evaluated for viscosity, PH and gelation temperature. Thickness, elasticity and transparency of ocuserts were also evaluated. In vitro release and kinetic analysis were studied for all formulae.

Results: The obtained results revealed that niosomes' particles size increased from a value 458 nm to 680 nm upon chitosan coating, polydispersity index (PDI) was 0.257 increased to a value of 0.656, negative zeta potential value of -38.3 mV was transformed to a positive 20 mV indicating successful coating. Entrapment efficiency of Naphazoline hydrochloride was 18% due to its hydrophilicity. The prepared hydrogels showed a pseudoplastic behavior due decline in viscosity upon increased shear stress from 6 rpm to 30 rpm, at which (G1) decreased from 200 to 60 cP, (G2) decreased from 200 to 80 cP and (G3) decreased from 500 to 120 cP, noting that maximum viscosity was exhibited by (G3) due to the higher proportion of poloxamer 407 relative to poloxamer 188. A pH value of 7.4 was detected in all prepared hydrogels, however, gelation temperature varied among them, (G3) showed the desired gelation temperature at 36.5 ± 0.5 °C, while (G1) did not gel at all upon increasing temperature and (G2) gelled at 29 ± 0.5 °C. Ocuserts (F1) and contact lens (F2) showed thickness of 0.3 mm and 0.25 mm respectively. They also showed elasticity due to absence of breakage upon 200 times of folding, however regarding the transparency, (F1) was opaque while (F2) was transparent. In vitro release studies and release kinetic models showed a satisfactory controlled release pattern of the drug from the aforementioned systems as the release of formulae N1, N2, N3 was 30.34%, 29.38%, 98.73% respectively, and the release of F1, F2, F3 was 28.68%, 18.28%, 0.05% respectively.

Conclusion: These diverse systems provide enhanced targeting drug delivery and offer a promising therapeutic strategy for future ophthalmological treatments.

INTRODUCTION

Conjunctivitis is an inflammation of conjunctiva tissue of the eye, Conjunctivitis is divided into two types, irritant conjunctivitis, and allergic conjunctivitis. It is caused by an allergic reaction or autoimmune diseases which belong to Non-infectious conjunctivitis. Also, chemicals, foreign bodies as eyelashes and wearing contact lenses can cause conjunctivitis. Moreover, COVID-19 can also cause conjunctivitis as a symptom. Naphazoline is sympathomimetic alpha-adrenergic which is one of the classes used to treat conjunctivitis. Nanoparticles have shown a great potential in ocular targeting drug delivery. Niosomes are widely used as nanocarriers for their advantages over other nanocarriers, they are cheap and have high stability in addition to their ease of preparation. Niosomes are non-ionic.

surfactants which can be originated from emulsifying agents like spans and tweens. Functionalization refers to the modification of the nanoparticle's surface with functional groups or biomolecules. One of the used materials for functionalization is Chitosan which was used to make the nanoparticle positively charged and interact easily with the negatively charged cell membrane. The eye is one of the most complex organs which made it a challenging target for the pharmaceutical preparations due to its transient residence time, non-permeability of corneal epithelium, binding to the lachrymal proteins, tear production and limited corneal surface which are all problems that face conventional dosage form leading to poor bioavailability. There are alternatives for conventional ophthalmic route of administration such as thermo responsive gel and medicated contact lenses. The in-situ gel has prolonged pre-corneal residence time because of its sol-gel property. It is polymer-based gel which can be formulated by polymers such as poloxamer. Poloxamer 188 and poloxamer 407 are two of the most commonly used poloxamers. On the other hand, medicated contact lenses can be made from different polymers such as alginate hydrogel. Alginate hydrogel is a hydrophilic anionic polymer, a naturally occurring substance. Alginate has low toxicity, high flexibility, high porosity, hemostatic capability, biocompatibility, high gel-forming ability, and relatively low cost. Alginate-based Medicated contact lenses significantly increase the drug residence time in the eye and decrease the side effects compared to conventional dosage forms.

SCOPE OF WORK

To prepare Niosomes composed of Span 60 and cholesterol in mass ratio 1:1 entrapping Naphazoline using thin film hydration method and coated with Chitosan.In addition to Thermoresponsive Gel which is composed of Poloxamer 407: 188 in different mass ratio 1:3, 1:1 and 3:1 prepared by the cold method.Niosomal Naphazoline will be incorporated in the selected formula of Thermoresponsive Gel based on the best physical properties by simple mixing.

Furthermore, Niosomal Naphazoline will be also incorporated in Contact Lenses and Ocuserts composed of alginic acid and CaCl2 prepared by ionic gelation method.

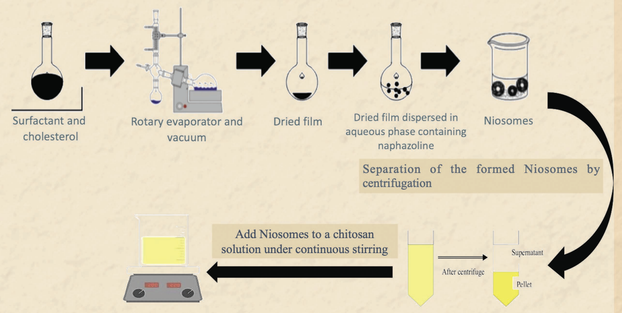
METHODS OF PREPARATION

COMPOSITION OF NIOSOMES, NIOSOMAL GEL, CONTACT LENSES AND OCUSERTS (GM)

Formulae	Composition (gm)							
	Free drug	Cholesterol	Span 60	Chitosan	Poloxamer 407	Poloxamer 188	Alginic acid	CaCl2
N1	0.5 g	2.4 g	2.6 g	0.5 g	-	-	-	-
N2	0.5 g	2.4 g	2.6 g	0.5 g	10.5 g	4.5 g	-	-
N3	0.5 g	-	-	-	10.5 g	4.5 g	-	-
G1	-	-	-	-	4.5 g	10.5 g	-	-
G2	-	-	-	-	7.5 g	7.5 g	-	-
G3	-	-	-	-	10.5 g	4.5 g	-	-
F1	0.5 g	2.4 g	2.6 g	0.5 g	-	-	0.3 g	2 g
F2	0.5 g	-	-	-	-	-	0.3 g	2 g
F3	0.5 g	Readymade Contact Lenses						

(TABLE 1)

1. CHITOSAN COATED NIOSOMES ENTRAPPING NAPHAZOLINE



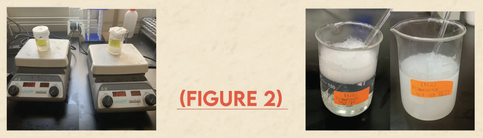
(FIGURE 1)

2. IN-SITU GEL THE COLD METHOD

P188 and P407 were added in the required calculated amount to cold phosphate buffer under continuous stirring

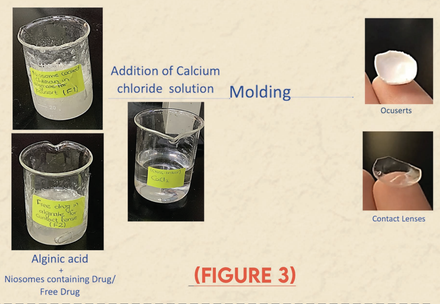
The preparation was stored at 4 °C until a clear solution of completely dissolved polymers is obtained.

The functionalized Niosomes/ free drug were added to the *In-situ* gel.



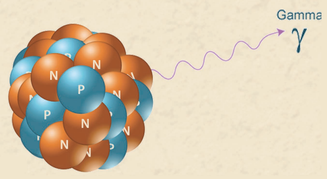
(FIGURE 2)

3. INSERTS: OCUSERT/ CONTACT LENSES



(FIGURE 3)

STERILIZATION BY GAMMA RADIATION



(FIGURE 4)

METHODS OF EVALUATION

- Entrapment Efficiency
- Particle size
- Polydispersity index (PDI)
- Zeta Potential
- Morphology
- In-vitro release
- Viscosity
- PH
- Gelation temperature
- Elactisity
- Transparency
- Thickness

RESULTS AND DISCUSSION

1- CHITOSAN COATED NIOSOMES ENTRAPPING NAPHAZOLINE

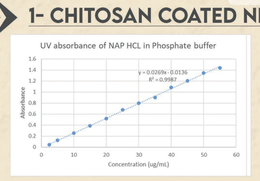


Figure 5: Calibration curve EE=18%

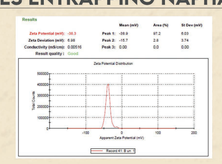


Figure 6: Zeta Potential of Uncoated Nanoparticles

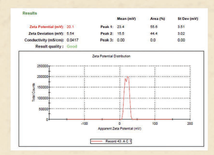


Figure 7: Zeta Potential of Coated Nanoparticles

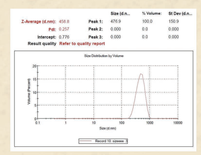


Figure 8: Particle Size of Uncoated Nanoparticles

Figure 9: Particle Size of Coated Nanoparticles

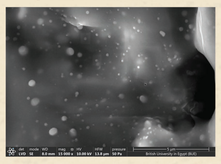


Figure 10-11: SEM of Uncoated Nanoparticles

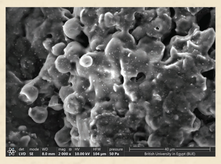


Figure 12: SEM of Coated Nanoparticles

2- IN-SITU GEL

	G1	G2	G3
Poloxamer 407: Poloxamer 188	1:3	1:1	3:1
Viscosity 6 RPM	200 cP	200 cP	500 cP
Viscosity 12 RPM	100 cP	150 cP	200 cP
Viscosity 30 RPM	60 cP	80 cP	120 cP
PH	7.4	7.4	7.4
Gelation Temperature	--	29 ± 0.5 °C	36.5 ± 0.5 °C

TABLE 2: Viscosity, pH and gelation temperature

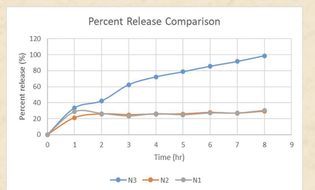


Figure 13: In-vitro Drug Release

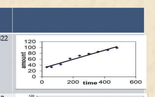
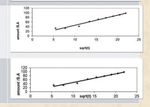
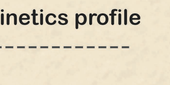
Formulae	Order	Equation	
N1	Zero	y = 0.1548x + 28.822 R² = 0.9683	
N2	Higuchi	y = 4.33x + 3.0962 R² = 0.9741	
N3	Higuchi	y = 9.692X + 2.534 R2 = 0.9727	

TABLE 3: Kinetics profile

3- INSERTS: OCUSERTS/ CONTACT LENSES

	Ocuserts	Contact Lenses
Elasticity	No breaking/no tearing Elastic	No breaking/no tearing Elastic
Transparency		
Thickness	0.3 mm	0.25 mm

TABLE 4: Elasticity, Transparency, and Thickness

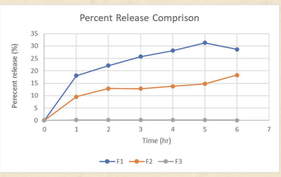


Figure 14: In-vitro Drug Release

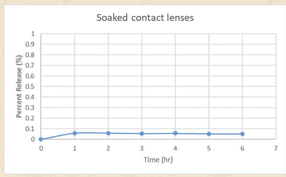


Figure 15: In-vitro Drug Release of Ready-Made Contact Lenses

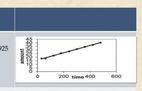
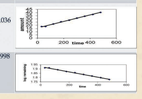
Formulae	Order	Equation	
F1	Zero	y= 3.794x + 15.925 R2 = 0.992	
F2	Zero	y = 0.0505x + 16.036 R² = 0.9969	
F3	First	y = 0.0006x+ 1.9998 R² = 0.9881	

TABLE 5: Kinetics profile

CONCLUSION

The outcomes of this study have proved that the developed chitosan coated Niosomes incorporated in thermosensitive and bioadhesive systems achieved controlled and targeted ocular drug delivery. Novel contact lenses and ocuserts composed of alginate were successfully achieved using cross-linking technique showing adequate physical characterization.

Potentially medicated contact lenses was innovatively created by soaking ready made contact lenses in saturated drug solution characterized with constant release of the drug.

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