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Developing albumin nanoparticle thermo-responsive hydrogel composite for the ocular delivery of Dexamethasone

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OBJECTIVES

- Selection of the methods to prepare the nanoparticles.
- Selection of appropriate excipients for the formulation
- Preparation of thermo-responsive hydrogel
- Physiochemical characterization of NPs and hydrogel
- To evaluate the prepared albumin NPs
- To evaluate the prepared albumin NPs loaded thermoresponsive hydrogel

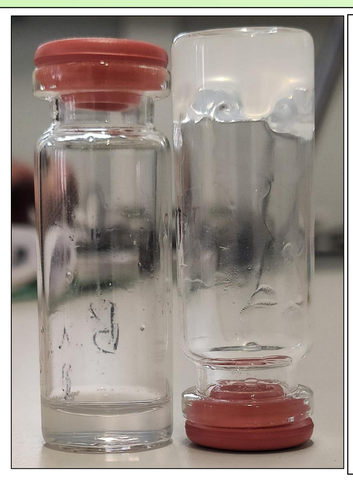
INTRODUCTION

Dexamethasone (Dex) is widely used for the treatment of various ocular diseases. However, it suffers from poor water solubility and low bioavailability, due to its hydrophobic properties,

The ocular delivery systems has been proposed to prolong its pre-corneal retention time, providing a sustainable drug release and enhancing corneal permeability

The aims of this work developing a thermo-responsive *in situ* hydrogel containing chitosan coated albumin nanoparticles for the ocular delivery of Dex.

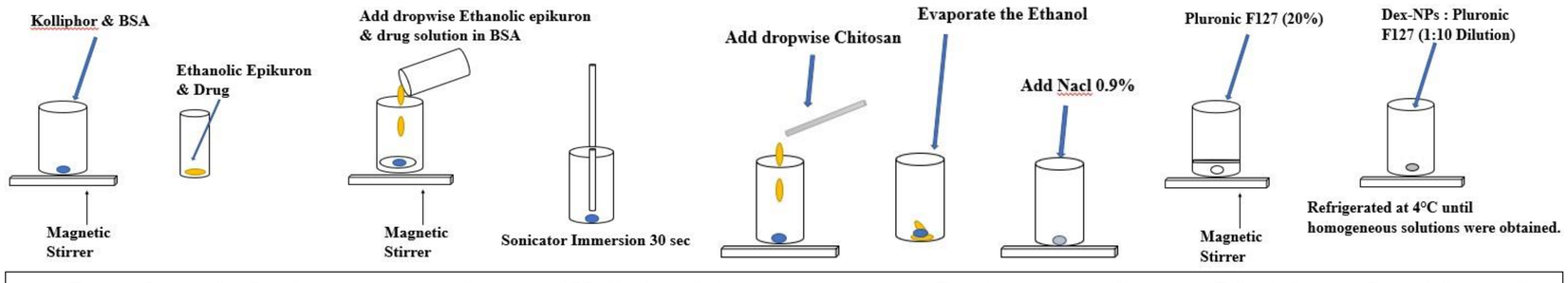
The formulation was a free-flowing liquid below 27 °C that transformed into a semi-solid gel at 34.5 °C.



Novel Ocular Drug Delivery System

- ✓ To Increase accurate dosing.
- ✓ To overcome the side effect produced by conventional system.
- ✓ To provide sustained and control drug delivery.
- ✓ To increase the ocular bioavailability of drug by increasing the pre-corneal retention time.
- ✓ To provide targeting within the ocular globe to prevent the loss to other ocular tissue.
- ✓ To overcome the protective barriers like drainage, lacrimation, and conjunctival absorption.

METHOD OF PREPARATION



Procedure:-2mL of an aqueous solution of Kolliphor 0.1% w/v containing Bovine serum albumin (BSA) 8mg/mL and 2mg of dexamethasone drug was mixed in 1mL ethanolic solution of Epikuron (1%) add dropwise under stirring condition in albumin solution. 30 second sonicator immersion at low speed.Then add 300 µl Chitosan (2.2%) at pH 4.5 dropwise under stirring condition for 1 hour. evaporate the ethanol using nitrogen reflux and add sodium chloride 500µL w/v (0.9%) under stirring condition to form Dexamethasone albumin chitosan (Dex-Bsa-Cs) Nanoparticles.

Thermo responsive Hydrogel Preparation

Thermo responsive hydrogel was prepared by using cold method, Briefly, weigh 2gm Pluronic F127 (20%) was dissolved in 10 mL of Nacl 0.9%, continuous stirring for 1.5 hour to form clear Pluronic solution and refrigerated at 4°C until homogenous solution were obtained.

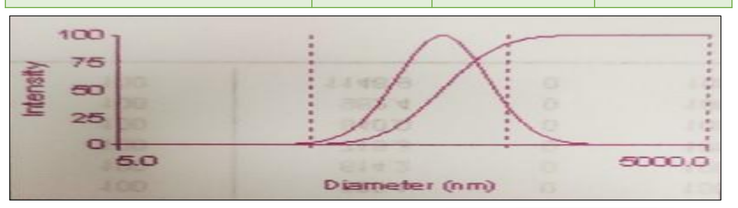
Take 1mL of Dex-Bsa-Cs NPs and 9mL of Pluronic solution (1:10 ratio) and stir for 30 minutes.

Put the Dex-Bsa-Cs NPs sol-gel in incubator at 34.5 °C for 10 minute to form thermo responsive hydrogel.

RESULT AND DISCUSSION

Particle Size

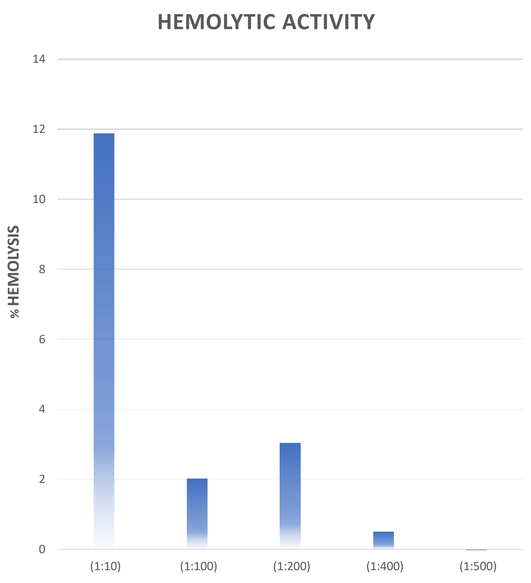
Formulations	Diameter nm	Polydispersity	Zeta Potential
Blank-Bsa-Cs NPs	180.9 ± 6.8	0.392 ± 0.007	+22.17 ± 6.55
Dex-Bsa-CS NPs	183.1 ± 6.8	0.373 ± 0.029	+22.02 ± 6.20
Blank Pluronic Gel 20% at Room Temperature	168.4 ± 2.2	0.356 ± 0.008	+8.46 ± 2.58
Dex-Bsa-Cs-NPs gel at 34.5 °C	189.8 ± 7.2	0.323 ± 0.015	+24.58 ± 8.32
Dex-Bsa-Cs-NPs solution at 4 °C	206.5 ± 4.8	0.412 ± 0.028	+22.88 ± 11.58



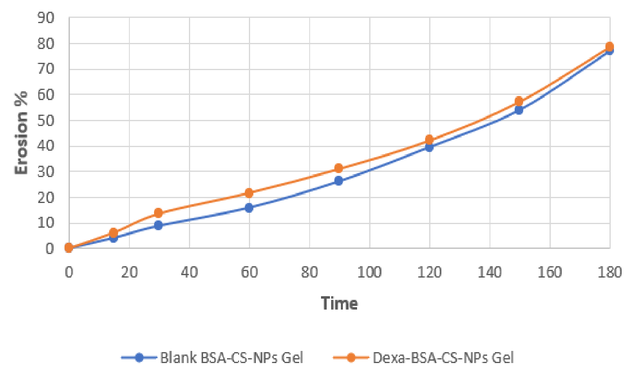
pH

Sr.no	Formulation	Temperature	pH
1	Blank-Bsa-Cs NPs	-	5.15
2	Dex-Bsa-CS NPs	-	5.20
3	Blank Pluronic 20%	Room Temperature	5.74
4	Blank Bsa-Cs-NPs gel	34.5 °C	5.70
8	Dex-Bsa-Cs-NPs gel	34.5 °C	5.30
5	Blank Bsa-Cs-NPs solution	4 °C	5.35
9	Dex-Bsa-Cs-NPs solution	4 °C	5.10

Hemolytic activity of Dex-Bsa-Cs NPs



Erosion Behavior Study



The Dex-BSA-CS-NPs Gel and Blank-BSA-CS-NPs Gel behaved similarly, demonstrating that adding BSA-CS-NPs to the gel had no influence on its structure.

78 percent of the gel had dissolved, the gel erosion profiles of both formulations were linear.

Viscosity

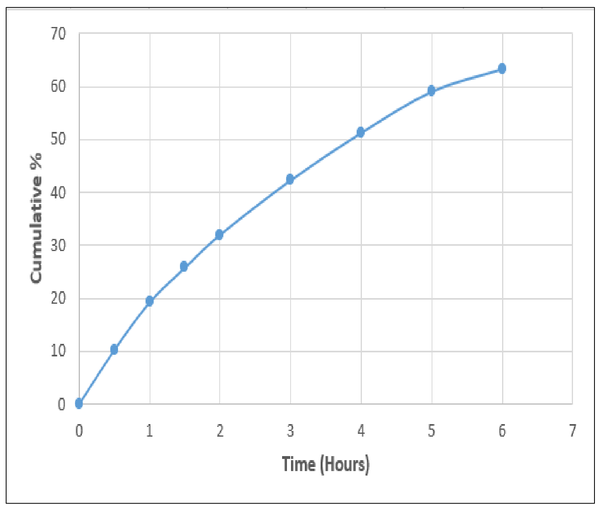
Formulations	Temperature	Viscosity
Blank Bsa-Cs-NPs gel before dilution	34.5 °C	1221.34±0.0184
Dex-Bsa-Cs-NPs gel before dilution	34.5 °C	1319.72±0.0183
Blank Bsa-Cs-NPs gel after STF dilution	27 °C	228.25±0.0215
Dex-Bsa-Cs-NPs gel after STF dilution	27 °C	313.13±0.0210

At temperatures 34.5°C, both Blank-BSA-Cs-NPs-Gel and Dex-Bsa-Cs-NP-Gel showed low viscosities, which indicates that the formulations could be instilled into the eye easily without need for storage in a refrigerator.

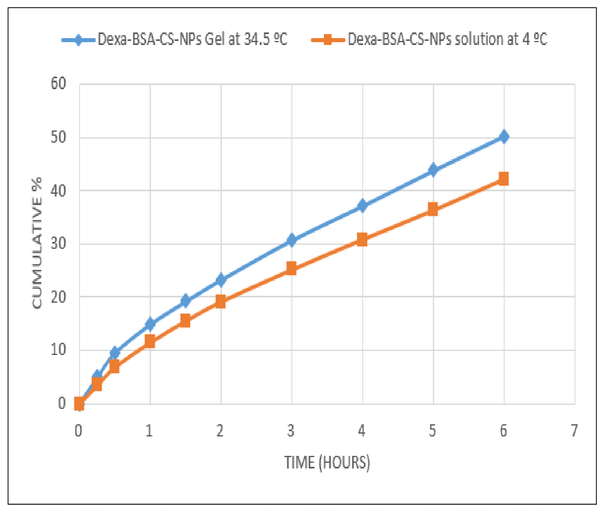
The viscosities of Blank-BSA-Cs-NPs-Gel and Dex-Bsa-CS-NP-Gel decreased after dilution with STF, but their viscosities at 34.5°C were apparently higher than those at 27°C.

This phenomenon indicates that the formulations may potentially prolong the contact time of dexamethasone in the eye.

In-Vitro release study of Dex-Bsa-Cs NPs and Dex-Bsa-Cs NPs Gel



In-Vitro release study of Dex-Bsa-Cs NPs



In-Vitro release study of Dex-Bsa-Cs-NPs Gel

In Vitro release study of Dex-Bsa-Cs-NPs was conducted 24 hours, the total percentage release was found to be 83.71%.

The cumulative percentage release study was conducted 30 hours of Dex-BSA-CS-NPs Gel at 34.5 ºC and Dex-BSA-CS-NPs solution at 4 ºC was found to be **82.87%** and **70.75%**

Drug Loading and Encapsulation Efficiency

Formulations	Drug Loading	Entrapment Efficiency
Dex-Bsa-CS NPs	21.77±0.08%	84.68±1.08%
Dex-BSA-CS-NPs Gel at 34.5 °C	0.1259±0.10%	88.16±1.22%
Dex-BSA-CS-NPs solution at 4 °C	0.1196±0.22%	83.75±1.08%

Conclusion

A thermo responsive in situ hydrogel system based on Pluronic F127 (20 %) and containing Bsa-Cs-NPs was developed for ophthalmic drug delivery. The physicochemical properties of Dex-Bsa-Cs-NPs Gel showed temperature responsive feature. This formulation which transforms into a gel when exposed to eye temperature may be applied as eye drop. The sol-gel transition temperature depend on the Pluronic F127 concentration, Increase the Pluronic F127 content decrease the sol gel transition temperature of the formulation.

In Vitro release and erosion behavior, studies showed that incorporation of Bsa-Cs-NP significantly enhanced the dissolution rate of Dexamethasone without affecting gel properties. Thus, the Dex-Bsa-Cs-NPs Gel system proposed in this work show potential for use as an ophthalmic delivery system prolonged drug residence time and improved ocular bioavailability.

References

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2. Ashaben Patel, Kishore Cholkar, et al., Ocular drug delivery systems: An overview, World J Pharmacol. 2013 ; 2(2): 47–64.