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Development and evaluation of Novasomal drug delivery system using natural polymer for ocular drug delivery

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ABSTRACT

Novasomes are a type of novel vesicular drug delivery system that are structurally similar to liposomes but offer enhanced stability and encapsulation efficiency. Novasomes are composed of nonionic surfactants, cholesterol, and free fatty acids, allowing them to exhibit a high degree of deformability and resilience. The purpose of this research article was to develop curcumin loaded novasomes for ophthalmic delivery. It aims to enhance drug corneal permeation and to improve its antimicrobial activity. Also, sustain release effect of the formulation is studied. Ethanol injection method was used to formulate Curcumin loaded novasomes. The researched factors were SPAN 80, CMTG and its effect on particle size (PS), Poly-dispersity index (PDI) Zeta potential (ZP), In-vitro drug release was studied. Numerical optimization by Design-Expert® software was employed to select the optimum formula. Additional evaluation of stability studies, drug permeation and anti-microbial activity studies were also performed. Zone of inhibition were observed around E.coli and S .aureus each having the diameter 2.90 cm and 3.24 cm respectively indicates that the formulation has good antibacterial activity. The study indicated Curcumin retained its antimicrobial activity when formulated as a curcumin loaded novasome forming ophthalmic system against both selected S. aureus and E. coli. Hence, the developed formulation is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release.

Keywords: *Novasomes, Curcumin, ocular drug delivery, Carboxymethyl tamarind gum*

1. INTRODUCTION

Ophthalmic medicine distribution is one of the most exciting and challenging issues facing pharmaceutical chemists. The eye is extraordinarily resistant to external substances due to its anatomy, physiology, and biochemistry. Formulator encounters incredibly difficult to avoid causing permanent tissue damage while getting around the eye's defences. The most common and widely-accepted mode of administration for many eye ailments is topical therapy administered to the eye. However, very little ophthalmic medication is absorbed because of the eye's strong defence mechanisms. Blinking, baseline and reflex lachrymation, and drainage effectively flush out foreign substances, including medicines, from the surface of the eye. Additionally, the anatomy, physiology, and barrier properties of the cornea all prevent rapid drug absorption[1]. Numerous eye drop instillations are necessary to maintain a therapeutic medication level in the tear film or at the site of action. However, repeated use of highly concentrated solutions may result in toxic side effects and cellular damage to the surface of the eye. To maximize the amount of active material reaching the target tissue or having a local effect in the cul-de-sac, the drug's residence time in the tear film should be prolonged. Additionally, it is anticipated that once-daily formulations will increase patient compliance[2].

Drug administration injections must enter the eye, first through the cornea and then through non-corneal channels. These non-corneal routes, which seem to be particularly relevant for, include drug diffusion over the conjunctiva and sclera, for medications that the cornea has a difficult time absorbing[3]. The medicine enters the corneal membrane through the precorneal gap. As a result, the effectiveness of drug absorption into the inner eye is directly influenced by the mixing and kinetic behaviour of drug deposition in tears. The majority of ophthalmic drugs are effectively absorbed across the corneal membrane by a diffusional mechanism. The effectiveness of the absorption process is determined by the rate and volume of transport activities. The physiology of pre-corneal fluid drainage or turnover also affects how much the transport or absorption process occurs. The novasome is a liposome or niosome with better structure [4]. A region of aqueous solution can be contained inside the hydrophobic membrane core of liposomes, which are spherical vesicles with a membrane made of a phospholipid and cholesterol bilayer. Lipid-soluble drugs can also be inserted between the two lipid layers. Niosomes are non-ionic surfactant vesicles that can develop in aqueous conditions with or without the inclusion of lipids like cholesterol. Due to the presence of non-ionic surfactant molecules, it can also entrap drug molecules with superior intrinsic activity, both hydrophilic and hydrophobic[5]. The novasome is a liposome or niosome with better structure. A region of aqueous solution can be contained inside the hydrophobic membrane core of liposomes, which are spherical vesicles with a membrane made of a phospholipid and cholesterol bilayer. Lipid-soluble drugs can also be inserted between the two lipid layers. Novasomes with the intention of enhancing the drug's corneal penetration and its antifungal effectiveness[6,.] The rationale behind the study was to prepare an effective drug delivery system for ophthalmic targeting using novasomes [7,8]. Curcumin was used as antibacterial drug to trat various infections of eyes[7]. In this study natural polymer carboxymethyl tamarind gum was used since due to natural origin more compatible to eyes. The objectives of study was to to formulate and evaluate curcumin loaded novasomes using various natural polymers like CMTG [9,10].

2. MATERIALS AND METHODS

Materials

Curcumin was purchased from Yucca Laboratories, Mumbai. Span 80 and cholesterol were from Loba Chemicals. Pvt. Ltd, Mumbai of laboratory grade. Carboxy methyl tragacanth was from Hindustan gums Pvt. Ltd, Mumbai of analytical grade. All other chemicals and solvents were of analytical grade and were consumed as obtained.

Experimental design

Design expert software: Design Expert® Version 10 was used. 3^2 Factorial design was applied. Three levels of -1, 0, +1 were kept and two independent and dependent variables were chosen. Span 80 and CMTG were the independent variables and particle size and drug entrapment efficiency were the dependent variables.

Formulation of Curcumin loaded novasomes

Ethanol injection was used to formulate Curcumin loaded novasomes. Curcumin, Span 80, cholesterol and CMTG were weighed accurately and taken in a beaker. They were dissolved in 10 ml ethanol and then kept in a water bath at 60 °C. Afterwards, the ethanolic solution was injected gradually into a four-fold greater volume of phosphate-buffered saline (PBS, pH 7.4) magnetically stirred at the same temperature until total vaporization of ethanol. The sudden turbidity indicated the formation of novasomes[11], the resulted novasomal dispersions were sonicated for 15 min at 25±2 °C for size reduction and stored till further use at 4 °C.

Characterization of formulated Curcumin loaded novasomes

Particle size(PS), Polydispersity index (PDI) and Zeta potential (ZP)

The resulted dispersions were diluted 10 times with distilled water in order to clarify their PS, PDI, and ZP. The determination was completed using SZ–100, HORIBA Instruments, Japan particle size analyser.

Percent Drug Entrapment Efficiency

Percent entrapment efficiency (EE %) of curcumin was calculated by indirect measurement of free curcumin (unentrapped curcumin). Briefly, 1 mL of resulted formula was exposed to centrifugation via a cooling centrifuge at 21,000 rpm for 1 hour at 4 °C. The clear supernatant was isolated and diluted. The concentration of unentrapped curcumin was spectrophotometrically assessed (V-1800, Shimadzu, Japan) at λmax 423nm. The sample batch was filtered using Whatman filter paper and centrifuged at -40°C at 12000 RPM. 10 ml supernatant was decanted, and 1 ml was pipetted into a 10 ml volumetric flask. The volume was increased to 10 ml using PBS (pH 7.4). The specimen was tested for absorbance at 423 nm using a UV spectrophotometer. The observed absorbance was converted to concentration in mg using a standard calibration curve of curcumin in PBS. The obtained concentration was entered into the following formula, and the percent entrapment was calculated.

Table 1: Optimization of formulation using 3^2 factorial design.

3^2 Factorial design			Actual values			
Run code	**Coded values**		**CMTG (mg)**	**SPAN 80 (ml)**	**Drug (mg)**	**Cholesterol (mg)**
F-1	-1	-1	0.125	3	1	60
F-2	-1	0	0.125	6	1	60
F-3	-1	+1	0.125	9	1	60
F-4	0	-1	0.250	3	1	60
F-5	0	0	0.250	6	1	60
F-6	0	+1	0.250	9	1	60
F-7	+1	-1	0.375	3	1	60
F-8	+1	0	0.375	6	1	60
F-9	+1	+1	0.375	9	1	60

Percent Entrapment Efficiency = Total drug - Free drug X 100 Total drug

Total amount of curcumin is the real weighed quantity, total amount of free curcumin (quantity of curcumin in supernatant)

Drug content

To determine the drug content of curcumin, 1 ml of the solution (ophthalmic formulation) corresponding to 100 mg was taken and diluted in 100 ml of PBS to achieve a concentration of 20 g/ml. According to the beer's range, the final dilutions were prepared with PBS. The drug concentration was determined spectrophotometrically by measuring the absorbance at 423 nm using a UV spectrophotometer. The drug content was determined using the linear regression equation derived from the calibration curve. The research was carried out in triplicate.

***In-vitro* drug release studies**

In vitro release of curcumin from the formulated curcumin-loaded novasomes was determined using dialysis bag method. The dialysis bag approach was used to quantify in vitro drug release. 2 ml of the formulation was mixed with 2 ml of Phosphate buffer saline (PBS of pH 7.4) which was then put into a dialysis bag with the mouth closed with a thread at both ends. The bag was then submerged in 100 ml of the dissolution medium, and placed in the centre of the beaker. The medium in the beaker was swirled at 50 rpm and removed with a micropipette at regular intervals while the temperature was maintained at 37± 0.5 ^{0}C. 1 ml of the sample was removed and replaced with 1 ml of new medium. The absorbance of the samples was measured using a UV spectrophotometer at a wavelength of 423 nm after appropriate dilution[13].

***Ex vivo* permeation study**

The *ex vivo* permeation of drug through isolated cornea of Goat, from formulation BNO4 was carried out using Franz diffusion cell [14]

Antimicrobial activity study

The antimicrobial activity of the formulation was checked. Zone of inhibition were observed around E.coli and S. aureus each having the diameter 2.90 cm and 3.24 cm respectively. Indicates that the formulation has good antibacterial activity [15].

Stability studies

According to the study, the formulation was physically and chemically stable because, after a six month of storage at the circumstances of 25°C 2°C / 60% 5% RH, no significant changes in any of the measured parameters were seen.

There are many important aspects which controls stability of a suspension solid phase particle size, zeta potential measurement and physical appearance. After 6 months, there were no changes in physical appearance of the suspension. The particle size was also checked and it did not show any significant change from the initial values, indicating the stability of the formulation. The zeta potential was also checked and it did not show any significant changes from the initial values, thus indicating the stability of the formulation.

3. RESULTS AND DISCUSSIONS

Particle size

Particle size has a profound effect on many formulation properties. Dynamic light scattering is used to determine particle size (DLS). The factorial batches shown improved results than trial batches only two batches were failed to show desired results. It can be noticed that the batches with lower polymer concentration have lowest particle size i.e., in range of 1 to 20 nm.

Table 2: Particle size of factorial batches

Batch no.	Particle size (nm)
F-1	271.4
F-2	256.2
F-3	160.50
F-4	109.6
F-5	153.4
F-6	124.6
F-7	323.65
F-8	286.6
F-9	206.10

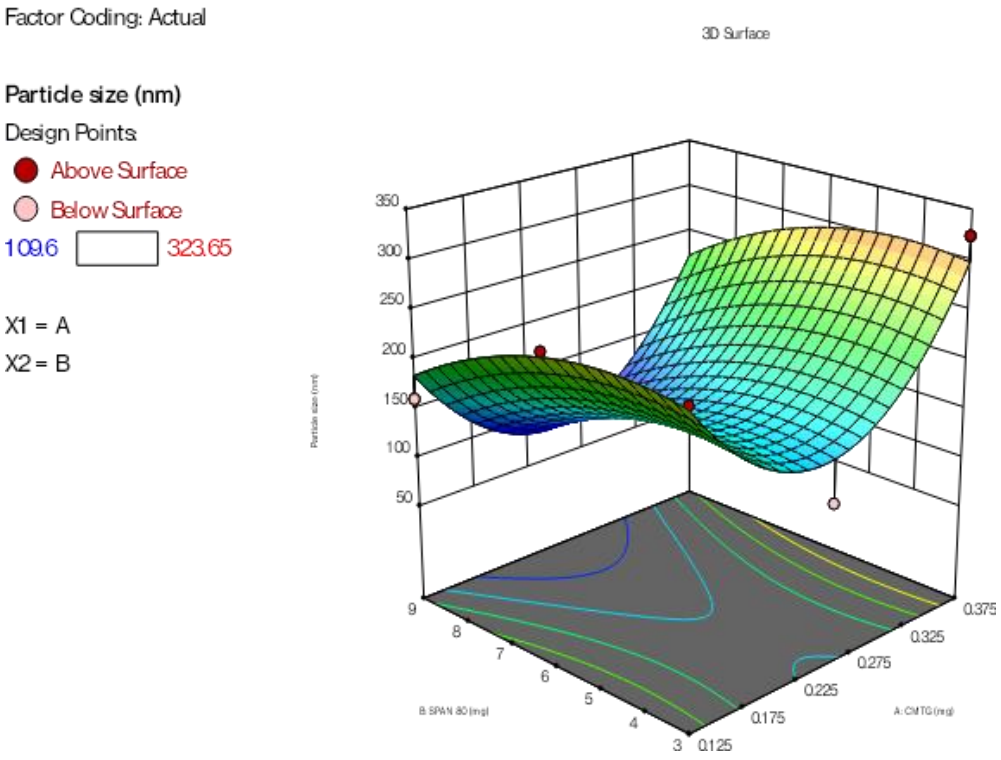

Fig 1: 3D surface plot of Particle size

In the above figure it is observed that as the concentration of the polymer CMTG is increased, the particle size also increases. Whereas, when the concentration of Span 80 is increased, the particle size decreases.

Thus, from the quadratic equation it can be inferred that there is a positive effect of factor X1 (Concentration of CMTG) and negative effect of factor X2 (Concentration of Span 80) on particle size.

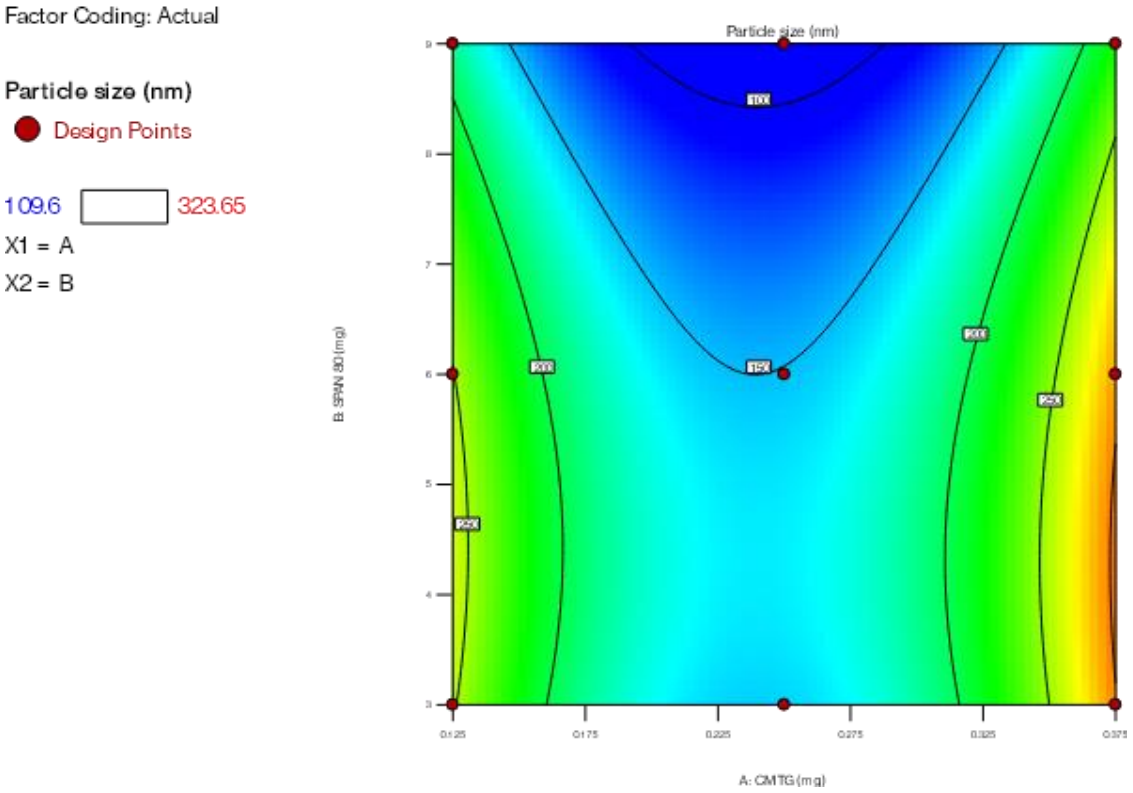

Fig 2: Contour plot of particle size

Zeta potential

Table 3: Zeta potential of factorial batches

Batch no.	Zeta potential (mV)
F-1	+6.7
F-2	+13.6
F-3	+ 15
F-4	+35
F-5	+42.6
F-6	+29.5
F-7	+29
F-8	-44.2
F-9	-64.2

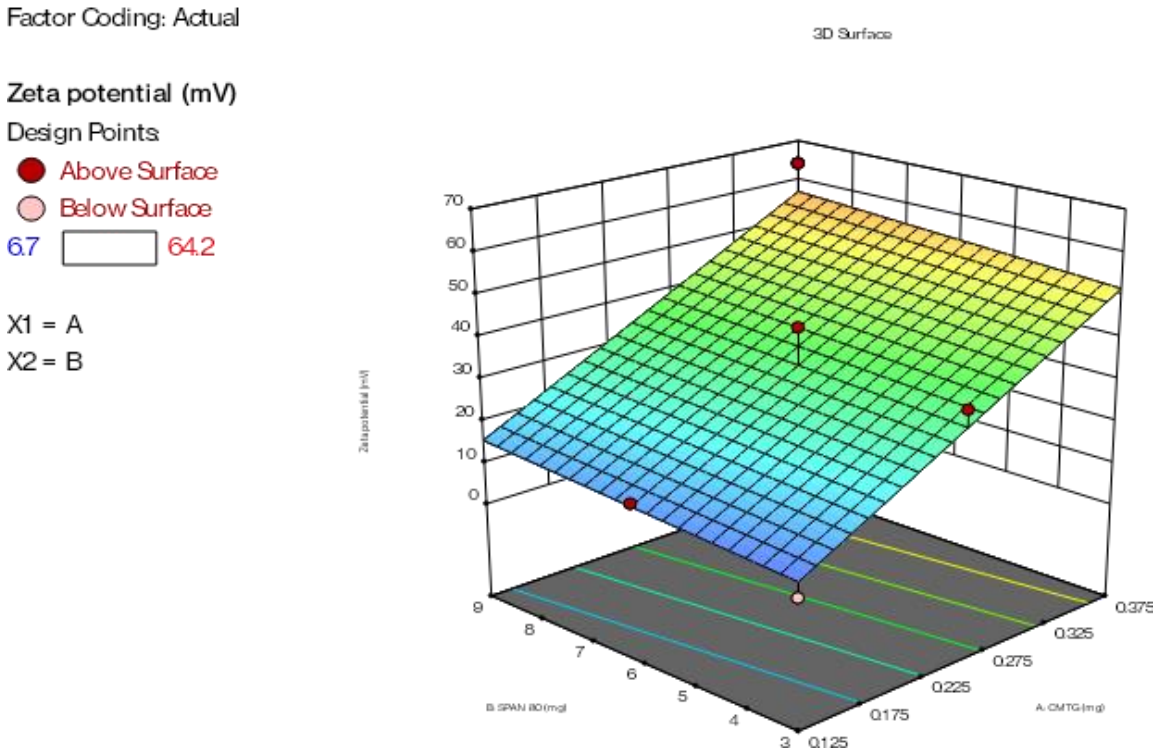

Fig 3: 3D surface plot of Zeta potential

In the above figure it is observed that as the concentration of the polymer CMTG is increased, the zeta potential also increases. Whereas, when the concentration of Span 80 is increased, the zeta potential increases.

Thus, from the quadratic equation it can be inferred that there is a positive effect of factor X1 (Concentration of CMTG) and positive effect of factor X2 (Concentration of Span 80) on zeta potential.

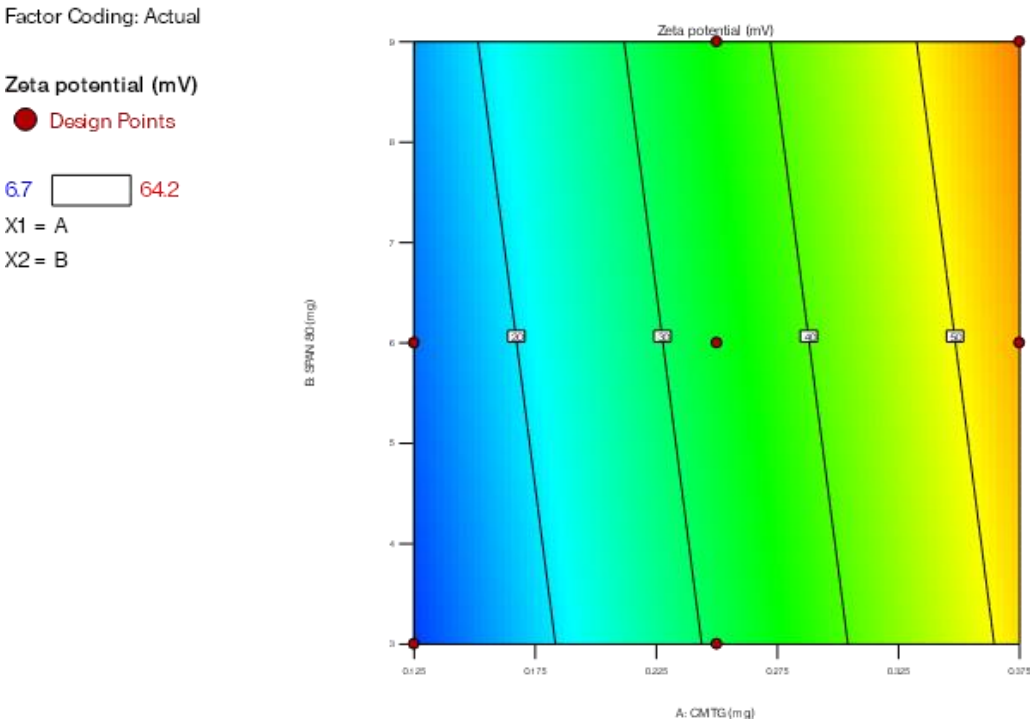

Fig 3.4: Contour plot of zeta potential

Drug entrapment efficiency

The entrapment efficiency of the factorial batches was determined by UV spectroscopy method. F4 batch was having highest entrapment efficiency [12] followed by batch 5 and batch 6.

Table4: Drug entrapment efficiency of factorial batches

Batch no.	Drug entrapment efficiency (%)
F-1	50
F-2	74.25
F-3	73.3
F-4	89.9
F-5	83.5
F-6	81.56
F-7	73.3
F-8	77.57
F-9	83.1

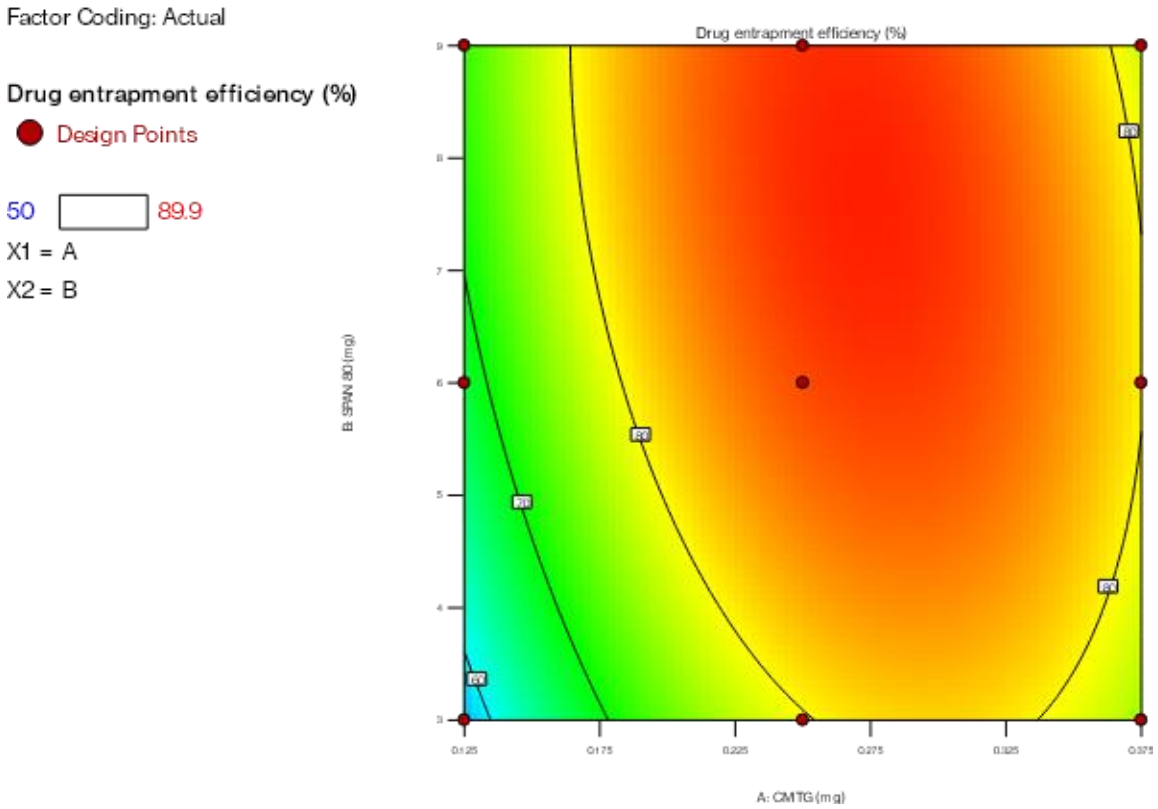

Fig 5: 3D surface plot of drug entrapment efficiency

In the above figure it is observed that as the concentration of the polymer CMTG is increased, the drug entrapment efficiency decreases. Whereas, when the concentration of Span 80 is increased, the drug entrapment efficiency increases.

Thus, from the quadratic equation it can be inferred that there is a negative effect of factor X1 (Concentration of CMTG) and positive effect of factor X2 (Concentration of Span 80) on drug entrapment efficiency.

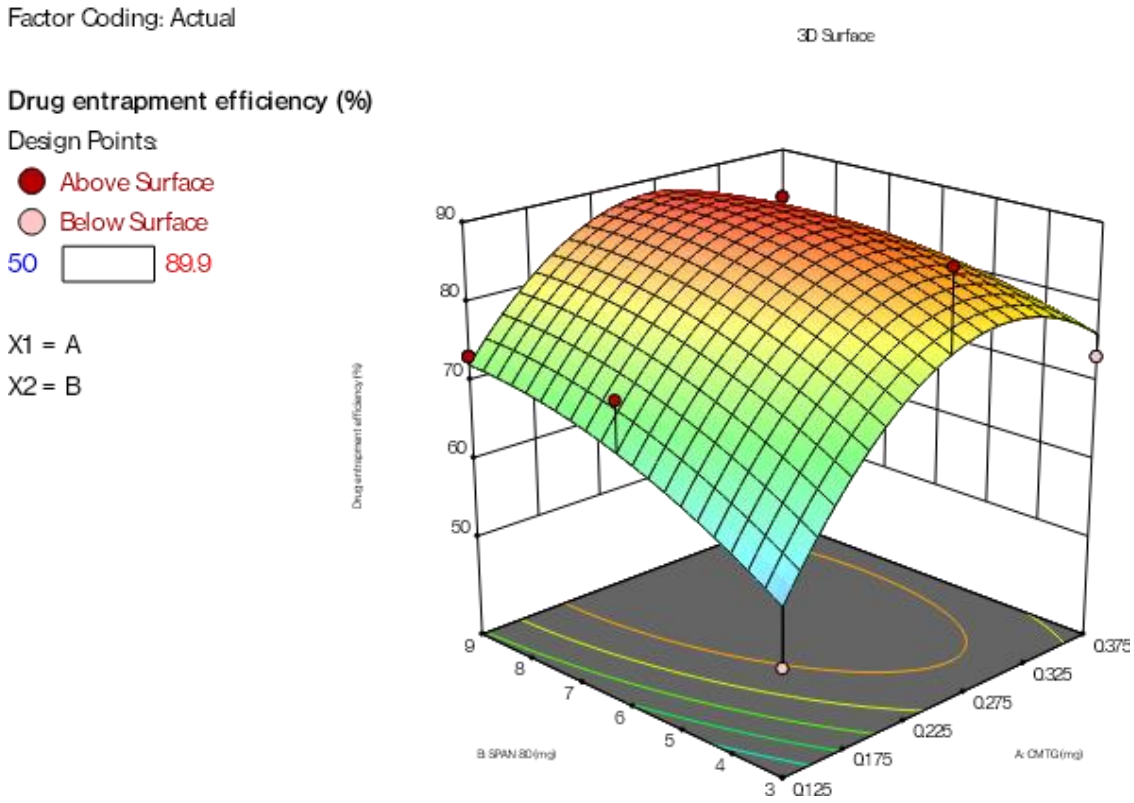

Fig 6: Contour plot of drug entrapment efficiency

Drug content

The drug content of the batch F4, F5 & F6 were determined as these batches qualified all the parameters tested above. Drug content of F4 batch was found to be highest followed by F5 and F6 respectively.

Table 5: Drug content

Batch No.	Drug content
F-4	97.88 %
F-5	94.00 %
F-6	93.35 %

***In-vitro* drug release study**

The % drug release of all the nine batches was carried out. The following figure below shows the % drug release of all the nine batches in a cumulative way. Batches: F4, F5 and F6 showed maximum drug release. The drug release profile of F4, F5 & F6 formulation combined for the comparison which concluded that BNO4 retains drug into formulation slightly more than other two formulations until 7 hours. It can be concluded that all three formulations show less than 12 % release in 1 hr. and less than 90% release in 8 hr. of dissolution which confirms all three batches are sustained release formulation.

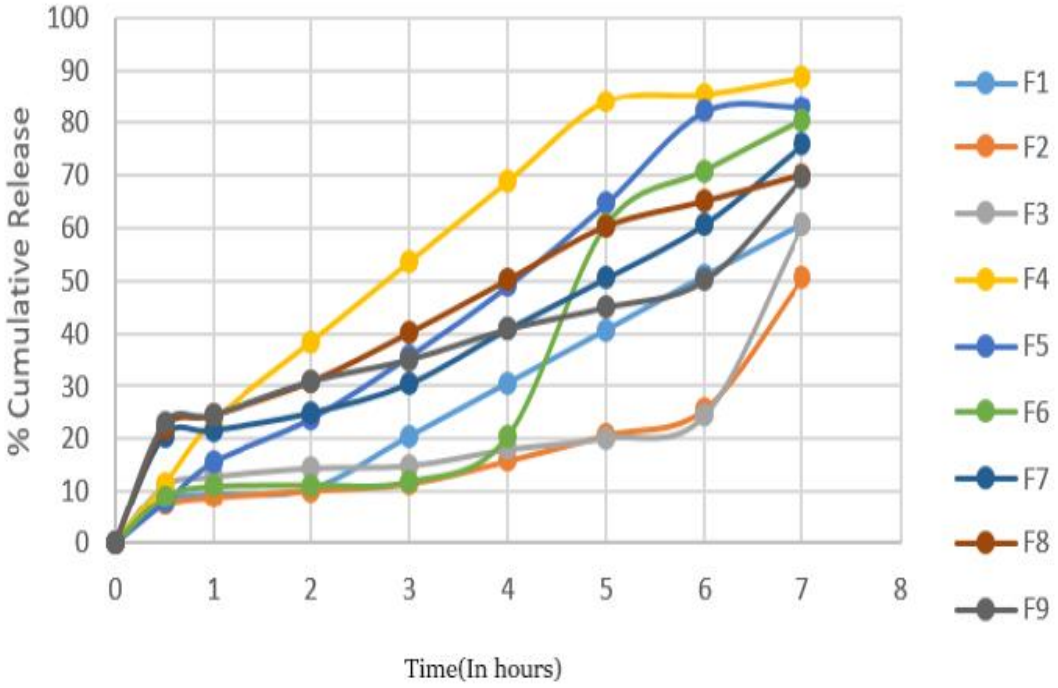

Fig3.6: In vitro cumulative drug release of all batches of Novasomes

***Ex vivo* permeation study**

The in vitro permeation of drug through isolated cornea of Goat, from formulation F4 was carried out. In vitro permeation of novasome batch F4 was 64.57 % at 8 hrs and 99.77% at 24 hrs which indicates a good permeation profile. Thus the F4 formulation shows good permeation profile.

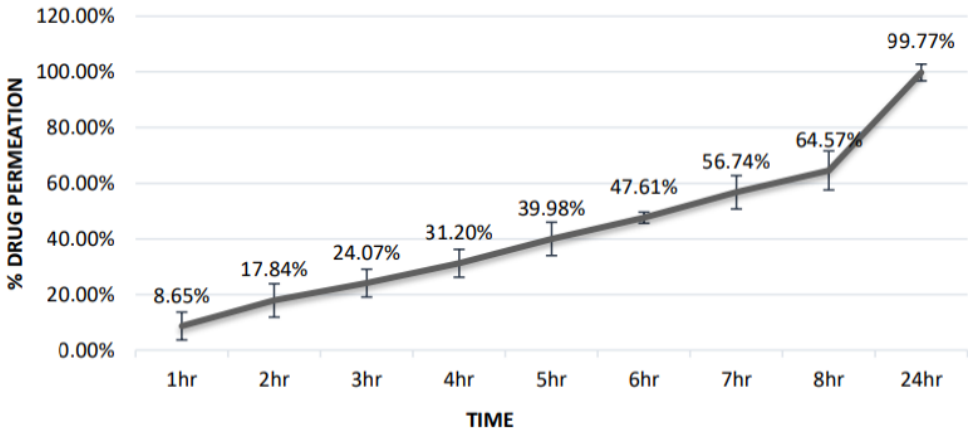

Fig 6.30: Ex vivo drug permeation study

Antimicrobial activity study

The antimicrobial activity of the formulation was checked.

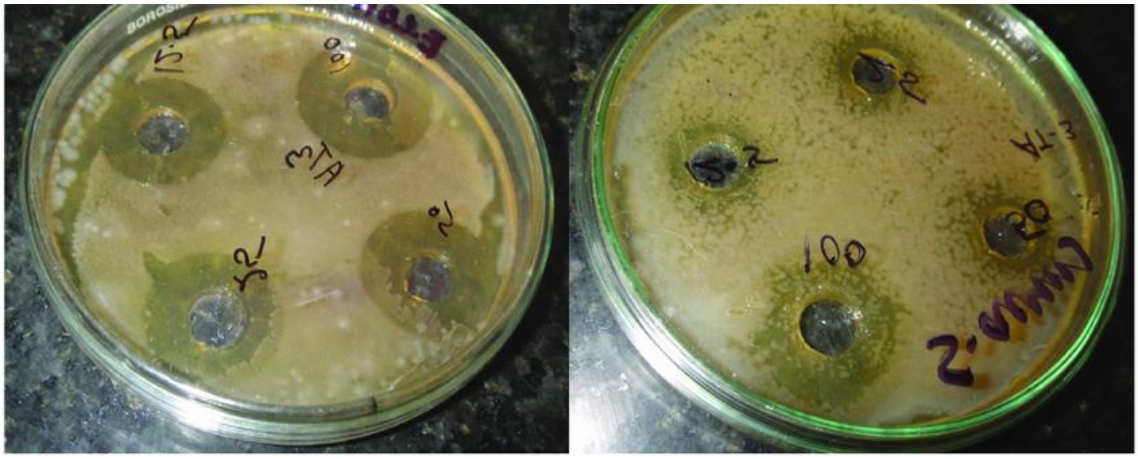

Fig 3.8 Antimicrobial activity study

From the figure it can be observed that the zone of inhibition test: Zone of inhibition were observed around E.coli and S.aureus each having the diameter 2.90 cm and 3.24 cm respectively. Indicates that the formulation has good antibacterial activity.

Stability studies

According to the study, the formulation was physically and chemically stable because, after 6 month of storage at the circumstances of 25°C 2°C / 60% 5% RH, no significant changes in any of the measured parameters were seen.

There are many important aspects which controls stability of a suspension solid phase particle size, zeta potential measurement and physical appearance. After 6 month, there were no changes in physical appearance of the suspension. The particle size was also checked and it did not show any significant change from the initial values, indicating the stability of the formulation. The zeta potential was also checked and it did not show any significant changes from the initial values, thus indicating the stability of the formulation.

Table 6: Stability studies

Batch no.	Physical appearance	Particle size	Zeta potential
F-4	White yellowish (No change observed since 1 month)	109.6 nm	+35 mV

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