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FORMULATION AND EVALUATION OF DEXAMETHASONE NIOSOMAL IN-SITU GEL FOR EFFECTIVE OCULAR DRUG DELIVERY

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Abstract:

The purpose of this study was to formulation and evaluation of Dexamethasone niosomal in-situ gel for effective ocular drug delivery. Dexamethasone niosomal in-situ gel, was prepared Ethanol injection and Thin film hydration technique method. Results: The particle size (average) was 2002.32nm. The DM powder being amorphous in nature was found to possess small particle size. Vesicle size of niosomes was in 0.2-0.5 µm range. The vesicles were circular in shape with uniform vesicle size distribution. The zeta value of niosomes after incorporation of drug was -44mV indicating that the stability was not affected High zeta value irrespective of charge that is positive or negative, will cause the suspended particles to repel each oher thus preventing coagulation or aggregate formation process.

Key words: Niosomal in-situ gel, Ethanol injection method & Fourier transform infrared spectroscopy.

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INTRODUCTION

A colloidal drug delivery system is an innovative approach in the field of pharmaceuticals and nanotechnology that aims to enhance the therapeutic effectiveness of drugs. It involves the utilization of colloidal particles, typically ranging in size from 1 to 1,000 nanometers, to encapsulate and deliver drugs to specific target sites within the body[1-3]. This technology has gained considerable attention due to its ability to overcome many challenges associated with traditional drug delivery methods. A colloidal drug delivery system includes liposomes, niosomes, micelles, dendrimers, in-situ gels, and so on [4-6]. It provides significant advancements in the field of ocular drug delivery, offering promising solutions (Sols) for treating various ocular disorders by overcoming numerous barriers such as corneal, precorneal, conjunctival, and formulation challenges. Niosomes have grown in prominence as the most effective drug carriers in ocular therapies. The small vesicle size of niosomes and their inability to permeate connective tissue and epithelium deliver the drug at the administration site.

However, niosomes suffer from poor precorneal retention and nasolacrimal drainage. Therefore, to overcome this problem, niosomes are being incorporated into an in-situ gel. A system known as “in-situ gel” is one that, when exposed to physiological circumstances such as variations in temperature, pH, or ion concentration, goes through a phase transition from a Sol or liquid state to a gel or semi-solid state. These systems provide controlled and sustained release of drugs for an extended period. In situ, gel formulations are predominantly based on biocompatible polymers, such as thermosensitive polymers, mucoadhesive polymers, and biodegradable hydrogels, which provide the necessary mechanical strength, stability, and biodegradability[7-9].

The potential for a paradigm shift in ocular treatments occurs with the combination of colloidal and in-situ delivery systems which overcome physiological and anatomical limitations of ocular delivery. In terms of improving solubility, stability, targeting, prolonged release, and adaptability, colloidal drug delivery methods are a promising new direction for the pharmaceutical industry. This current review provides an overview of combining in situ gel with niosomes for ocular delivery of many therapeutic agents. An in-depth review has been made focusing on various formulation, characterization, safety, and development prospects of in situ gels loaded with niosomes for ocular administration[10-12].

MATERIALS AND METHODS:

Materials

Dexamethasone was received from Sai Lifesciences, Pune, Other chemicals used were of analytical grade.

Methods

Ethanol injection method (EI)

Niosomes containing DM was prepared by EI method. Surfactant and chol in varied ratios were solubilised in methanol. Using microsyringe, the final solution was injected slowly (0.25ml/min) into DM containing Phosphate buffer (PBS) pH 7.4. Magnetic stirrer (Remi, 2MLH) was used for continuous stirring of solution where 60 °C above temperature was kept. Stirring continued for 1-1.5 h. Solvent evaporates causing vesiculation impulsively and formation of niosomes (spherical and unilamellar) takes place[13-14] .

Thin film hydration (TFH)

Accurately weighed quantity of ingredients (surfactant & cholesterol) in various concentrations (table 7.1) was solubilised in chloroform and methanol mixture in a RBF. The solvent mixture was vapourised in a rotary flash evaporator (Trident labotech, Thane) by applying vacuum (20 inches of Hg) at 25±2 ℃ temperature. In order to obtain smooth dry lipid film, the rotation of flask at 100 rpm was done. Hydration of the film with PBS pH 7.4 (10 ml) containing 25 mg DM for 45 min at 60 ℃ with shaking gently on a water bath was done. The resulting dispersion was stored at 2-8 ℃ for 24 h.

Batches of niosomes were prepared to vary in the method of preparation, the combination of surfactants, an individual surfactant in different concentrations, selection of surfactant grade and the ratio of chol and span 60 respectively. Optimization was done according to DC, EE, and vesicle size and drug diffusion study.

Drug Entrapment Efficiency (DEE)

The prepared DM niosomes were separated from unentrapped drug by rotating it at high speed (2750 rpm) for 60 min using cooling centrifuge. Cooling centrifuge (Laby instruments, India) was used as niosomes are stable and stored at refrigerated condition that is at 2-8 ° C. Absorbance of supernatant was taken after appropriate dilution at 247 nm. The settled pellets were dispersed in distilled water to get a clear solution..[15].

$$DEE\ (\%) = \frac{\text{Actual amount of drug encapsulated x100}}{\text{Theoretical drug content}}$$

In vitro dissolution:

Drug release from niosomes was studied by dialysis method. Preservative in dialysis bags were removed by soaking them in distilled water for 12 h at RT. Later they were rinsed in distilled water

before use. In vitro release of DM from niosomes was conducted by dialysis in a dialysis sac made up of cellophane membrane (Sigma-Aldrich) with phosphate-buffer pH 7.4 (100 ml) at 37°C. The dialysis bag was closed by tightly bounding the two ends with threads. The sac was suspended inside a beaker by a burette stand so that the dialysis sac with the formulation was inserted into the buffer solution. The beaker was positioned on a magnetic stirrer (Matrex) at 100 rpm at 37°C. Samples were taken out at 15, 30, 45, 60, 120, 180 min and further 1hr interval over a period of 6 hours and analysed spectrophotometrically for drug released. The fresh medium (equal volume) was replaced. The diffusion data was analyzed for calculating the quantity of drug released and percentage drug released at various time intervals[16-17].

Vesicle size distribution

The vesicle size of niosomes was examined by using principle of laser light diffraction using Nanophox NX0088. In 100 ml hexane, sample (50 mg) was dispersed and ratio of signal to noise was measured in order to eliminate error if any. The vesicle size distributions were determined at a wavelength of 750 nm and setting the scattering angle (θ) of 90..[18-19]

Polydispersity Index (PDI)

The PDI determination was done with a Zetasizer (Nano ZS, Malvern Instruments, Westborough, MA, USA) at 633 nm. The polydispersity index was calculated by

PDI = X90-X10/X50

Zeta potential

Niosomal dispersion (0.5 mL) was diluted to 50 ml by distilled water in glass beaker with constant stirring. Zeta sizer was used to evaluate the Zeta-potential of the resulting suspension (model: Nano ZS, Malvern Instruments, Westborough, MA, USA). Disposable zeta cell (small volume) was used in order to measure the electrophoretic mobility (µm/s). In-built software would convert the electrophoretic mobility measured in to zeta potential using Helmholtz – Smoluchowski equation.

Transmission electron microscopy (TEM)

TEM (CM microsocope, Philips) was utilised to evaluate the morphology and surface characteristics of niosomes. Optimized niosomal formulation's (CS17) few drops were placed on a copper grid which was carbon coated and analysed under TEM..

RESULTS & DISCUSSION

Table 1 DC, EE and vesicle size for the selection of surfactant grade for DM niosomes

Batch code	DC (%)*	EE (%)*	Vesicle size (nm)*
CS1	60.16±0.12	72.4±0.23	423±0.03
CS2	51.59±0.16	86.95±0.36	401±0.43
CS3	57.98±0.47	86.06±0.41	494±0.52
CS4	41.96±0.14	90±0.33	485±0.16
CS5	59.33±0.05	91.54±0.16	469±0.38
CSS1	54.4±0.27	87.19±0.36	356±0.26
CSS2	61.29±0.62	91.31±0.22	407±0.14
CSS3	42.12±0.29	80±0.43	396±0.49
CSS4	43.47±0.32	62.33±0.62	404±0.04
CSS5	55.57±0.38	81.61±0.04	375±0.55

Table 2 DC, EE and vesicle size for selection of chol: surfactant ratio for DM niosomes

Batch code	DC (%)*	EE (%)*	Vesicle size (nm)*
CS6	64.6±0.12	63.9±0.16	324±0.05
CS7	55.8±0.35	69.2±0.26	357±0.15
CS8	66.5±0.41	70.9±0.38	373±0.22
CS9	57±0.55	79.4±0.41	410±0.29
CS10	56.3±0.26	73.2±0.64	428±0.45
CS11	42.1±0.09	66.9±0.28	385±0.62
CS12	68±0.034	70.1±0.36	448±0.54
CS13	53.5±0.49	53.8±0.05	424±0.32
CS14	68.5±0.54	61.4±0.19	401±0.41
CS15	72.4±0.06	80±0.32	436±0.38
CS16	78.1±0.42	80.7±0.46	417±0.61
CS17	86.3±0.39	83.4±0.22	465±0.24

HLB value plays a chief role in the formation of stable niosomes. The HLB system is a ratio of hydrophilic and lipophilic contributions of the surfactant molecules is used as a parameter for niosome formation. The HLB value is 4.7 for span 60 and 4.3 for span 80 respectively. So considering the HLB value, Span 80 having lower HLB value compared to span 60 should incorporate steroid moiety more efficiently than span 60. But there is an exception. Span 80 cannot form niosomes on their own due to insufficient geometry leading to difficulty in packing properties. Double bond (high electron density) is present at C9 position in oleate moiety of span 80 results in the 'kink' structure due to adjacent hydrocarbon chain repulsion. Vesicle size of niosomal dispersion containing span 80 was less than span 60. This is related to the increased hydrophobicity. from Span 60 to Span 80. The increase in hydrophobic nature of surfactants cause decrease in surface free energy which lead to size reduction of niosomes. Since the DC of niosomes obtained by using span 80 was significantly ($p<0.05$) less due to kink in the structure than span 60, the span 60 was selected as surfactant. The results coincide with the previous study by Essa 2010 where formulation effect and processing variables effect on sorbitan monopalmitate niosomes was studied.

In vitro study

In vitro dissolution of niosomal batches was conducted by dialysis bag method. The value of t90 played a chief role in identifying the optimized niosomal batch. The purpose this study was to attain sustained drug release and hence t90 was expected to be higher for the optimized batch. The batch CS17 (chol: span 60 ratio was 1) exhibited t90 of 490 min that is the release was sustained upto 8 h of drug by this formulation (Figure 8.39 and 8.40). The change in chol: span60 ratio did not showed linear correlation either with DC, EE or drug release. The values differed randomly without showing any correlation. The niosomal batches CS1, CS15,CS16, CS17 all contained chol: span 60 ratio 1 i.e. both the ingredients were in equal quantities but still there t90 values were variable viz 112 min, 370 min, 435 min and 490 min respectively (Table 8.24). The difference in these batches was the change in concentration with respect to the whole composition. The amount of surfactant used in CS1 was ten times lesser than that used in CS17. Hence the value of t90 was shifted from 112 to 490 min. Surfactant concentrations were within the limits in accordance with safety guidelines where the surfactant amount does not exceed by 1-2.5 % w/w. In batch CS17 the amount of span is 1% w/v. The chief function of surfactant is to improve the solubility of substance but DM being water soluble, this function need not has to be achieved. The surfactants in higher concentrations act as sustained release polymers which cause the drug to release at the controlled rate. This was in agreement with findings of other studies like Tabbakhian M et.al 2006; Das k et.al 2011; Azeem A et.al 2008 indicating a more sustained drug permeation and possibly a greater drug deposition and increased drug release where drug containing vesicular systems used, as compared to a pure drug solution.

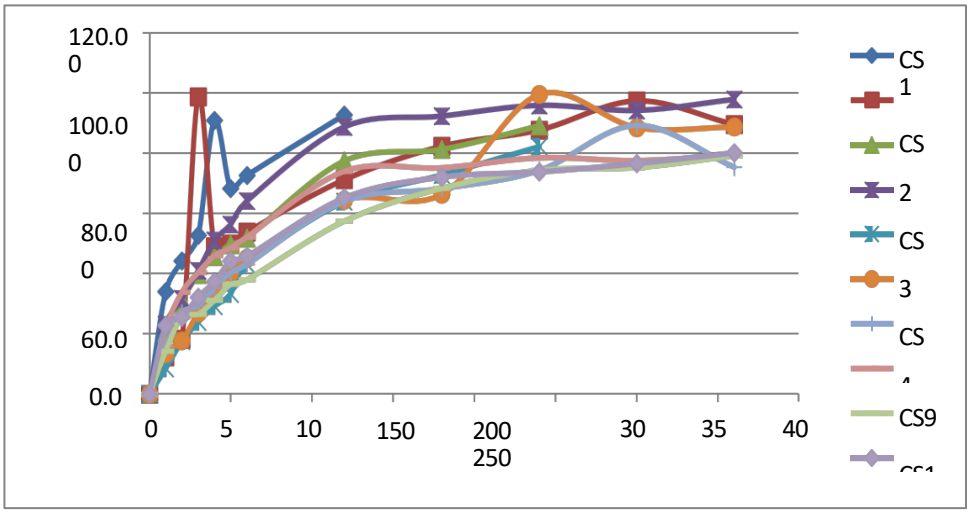

Figure 1 Dissolution drug profile of batches CS1 to CS10 for DM niosomes

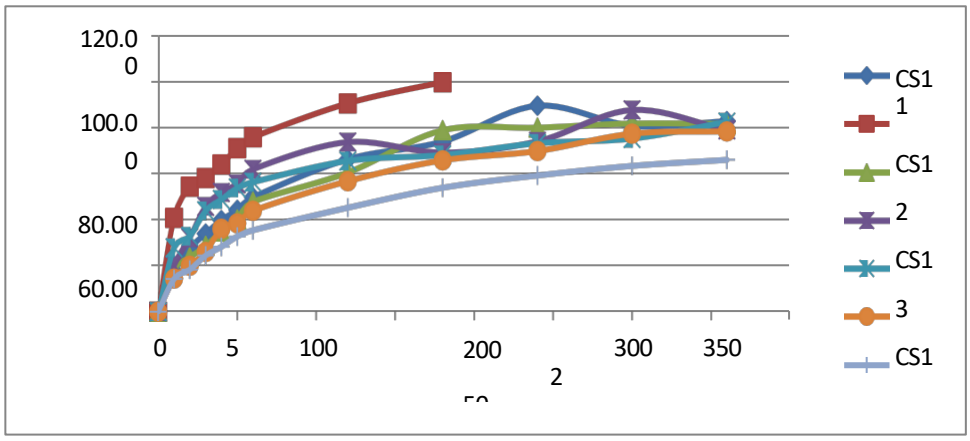

Figure 2 Dissolution drug profile of batches CS11 to CS17 for DM

Vesicle size distribution

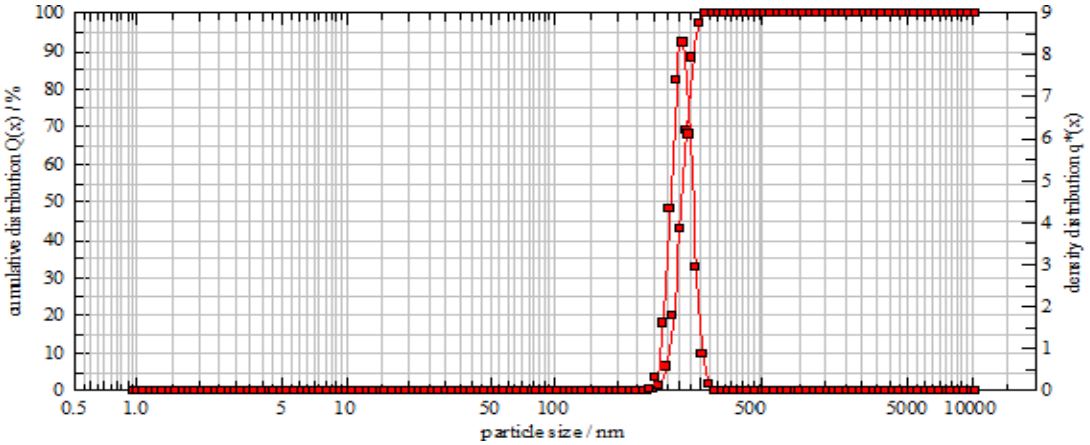

Fig 3 Vesicle size distribution of niosomes

Vesicle size of plain niosomes and drug loaded niosomal dispersion was measured by Nanophox NX0088 . Pure drug particle size was 2002 nm which was reduced to 465 nm for niosomal dispersion. Thus the particle size of drug was reduced by 4 times making the formulation feasible for ocular use to enhance their penetration through different biological barriers of the eye. The vesicle size for plain niosomes was 378 nm. The vesicle size increased for DM niosomes as compared to that of plain niosomes due to drug entrapment. According to previous studies of ophthalmological applications, the size of complex drug particles (< 10 µm) to avoid a foreign body sensation after administration [154]. For ODDS, larger particles (>1 µm) may cause ocular irritation. Particles of small size range (10 to 1000 nm) cause impoved topical entry of large molecules through the ocular barriers.

Zeta potential determination

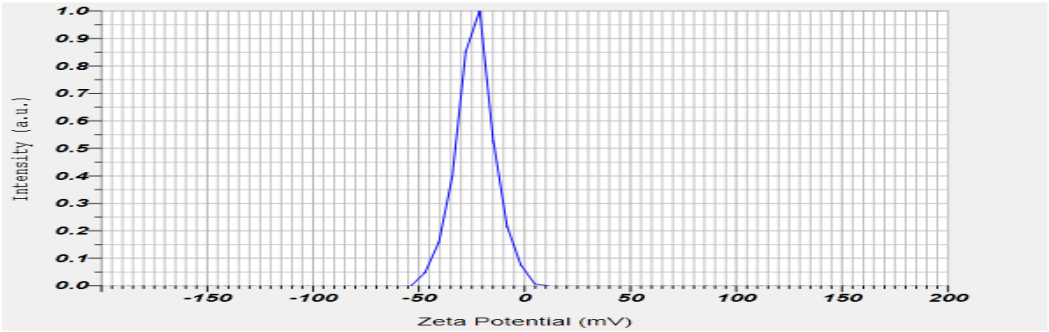

Fig 4 Zeta potential of DM niosomes

The zeta value of niosomes after incorporation of drug was -44mV indicating that the stability was not affected. It states that equimolar ratios of nonionic surfactant and chol can make the compact and well organized bilayer [157]. The zeta value denotes the colloidal system stability. High zeta value irrespective of charge that is positive or negative, will cause the suspended particles to repel each oher thus preventing coagulation or aggregate formation process. But if the value is low, the particles will come together and form aggregates thus hindering the suspension stability. The Standard limits to differentiate between stable and unstable dispersions are generally.

Polydispersity index

Table 3 PDI of plain niosomes and DM niosomal formulation

Sr.No.	Sample Name	PDI*
1.	Plain niosomes	0.795±0.038
2.	Niosomal Formulation	0.284±0.026

*(Mean± SD, n=3)

PDI values were calculated from vesicle size distribution data. The PDI value of formulation was 0.284 which was in the standard range (< 1) indicating that the formulation is monodisperse. The uniformity of the dispersed systems are expressed with the PDI values. The values < 0.7 are considered as standard measurements. Lower PDI values represent the narrow size distribution and niosomal suspension uniformity [158]. Homogeneity of niosomal dispersions was indicated by the PDI values.

TEM analysis

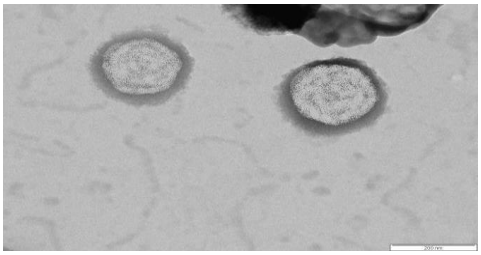

Fig 5 TEM images of optimized DM niosomal batch (CS17)

The morphology of vesicular formulations were studied by TEM analysis. TEM image of (CS17) niosomal formulation at magnification 40,000x and 45,000x (Fig 8.46) exhibited the circular shape in 2D and spherical shape in 3D view. The niosomes surface characteristics could also be studied. Vesicles were visualized as hollow vesicles. The vesicle size (432 nm) observed in TEM was found to coincide with the value obtained by vesicle size determination thus confirming the size of vesicles in the colloidal range.

CONCLUSION:

Niosomal optimized batch (CS17) could entrap DM effectively thus giving entrapment efficiency upto 83.4±0.22%. As a result, the optimised formula was further incorporated into on situ gel with desirable mucoadhesive behavior essential to achieve increased retention in eye. The DM powder being amorphous in nature was found to possess small particle size. Vesicle size of niosomes was in 0.2-0.5 µm range. The vesicles were circular in shape with uniform vesicle size distribution. The zeta value of niosomes after incorporation of drug was -44mV indicating that the stability was not affected High zeta value irrespective of charge that is positive or negative, will cause the suspended particles to repel each oher thus preventing coagulation or aggregate formation process.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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