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A NOVEL CORTICOSTEROID CUBOSOMES – FOR OCULAR DRUG DELIVERY

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ABSTRACT

Corticosteroid containing ocular formulation is very exigent tasks faced by the pharmaceutical industry while designing drugs acting on various ocular related diseases. Because ocular drug delivery faces various limitations like complex ocular anatomy and poor ocular bioavailability of drugs due to the high turnover rate of tears, lower corneal permeation, and rapid nasolacrimal drainage, and most important is irritation to the eye caused due to corticosteroid structure. The preferred dosage form for ocular delivery of corticosteroid is a solution or the ointment, but to sustain the level of drug at the target site during therapy is not possible so it is necessary to formulate novel drug delivery techniques. A large number of novel carrier drug delivery systems systems have been developed to overcome the above problems but among them, cubosomal drug delivery is a safe and effective technique for corticosteroid ocular drug delivery. Cubosomes are distinct, sub-micron; self assembles liquid crystalline particles having honeycomb (cavernous) structure which separate two internal aqueous channels and large interfacial area; having particle size ranges from 10-500 nm in diameter. This review briefly describes the ocular administration of corticosteroids with the cubosomal drug delivery system along with various drugs studied in ocular drug delivery, a method used for the preparation of Ocular cubosomes and its evaluation parameter. The benefits of cubosomal drug delivery will likely be applied widely in all treatment, diagnostic, and research aspects of ophthalmology in the future.

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INTRODUCTION

Cubosomes are discrete, cubic nano-structured, self-assembled particles of bicontinuous cubic liquid crystalline phase which physically looks transparent.[1] which are stable in excess water so their dispersions are less viscous than the parent cubic phase (drug and polymer mixture).[2] The Father of word "Cubosome" was Larsson since the structure resembles cubic molecular crystals[1], its internal structure was confirmed in 1967.[3] Cubosomes having particle size ranging between 10-500 nm in diameter and square-shaped structure.4 Cubosomes refer as "bicontinuous" because it is having two distinct large interfacial area (continuous, but non-intersecting) consisting hydrophilic regions separated by the bilayer.

Cubosomes is one of the unique system for the entrapment of corticosteroids for ocular dosage forms because they have great potential in drug nano-formulation including high drug load because it is having high internal surface area, high heat Stability, high thermodynamically stability[1] and able to encapsulate hydrophobic, hydrophilic and amphiphilic substances.

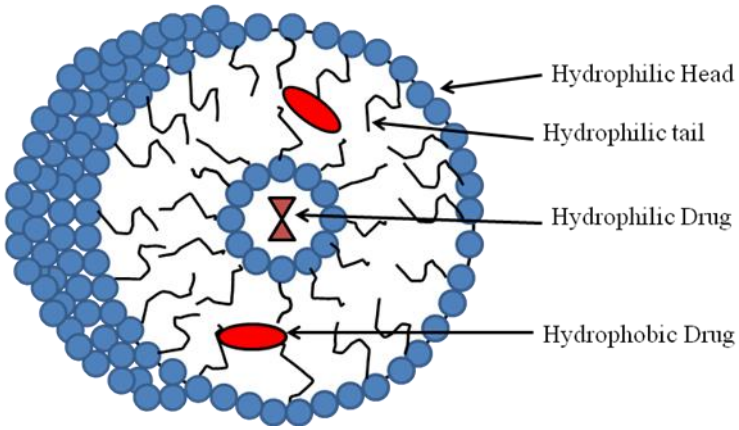

Figure 1: Honeycomb like cubosomal Structure with entrapped drug.

Generally, cubosomes are composed by simple dispersion of lipids and surfactants (polymers) with polar as well as non-polar components hence said as amphiphilic. The class of amphiphilic materials likes monoglycerides, glycerate surfactants, glycolipids, phosphatidylethanolamines, and urea derivatives having natural tendency to form non-lamellar nanostructures.[5]

The amphiphilic molecules act by hydrophobic effect into the polar solvent to impulsively identify and assemble to form liquid crystal of the nanometre scale. Then formed cubosomes are formulated into a product and applied as ocular drops, creams or gels which are absorbed/ released via diffusion. The diffusivity from eye of solubilised molecules (drug) is reduced by about 33% in bulk cubic phases because, the much smaller length scale of cubosomes makes them difficult to directly use for controlled release but Still, altering cubosome charge, viscosity, and structure can improve release kinetics .[6] Cubosomes can be modified with protein to increased stability for a longer duration of time.

The universal application for delivering drug molecule associated with various limitations is drug delivery vehicles hence bulk cubic phases designed to achieve controlled release frequently, the first patent on cubosomes was to specify its medical and controlled release applications.[1] Corticosteroids have been used in the treatment of ocular inflammatory disease for more than 40 years, first used intraocular in 1974 by Peyman et al.[2] Corticosteroids bind to the steroid receptors present in the ocular cells and show angiostatic and antipermeable properties.

Then they cause either induction or repression of the target genes and inhibit inflammatory symptoms like edema and vascular permeability.[7] So they are preferred for posterior segment diseases such as age-related macular degeneration (AMD), diabetic retinopathy, and macular edema.[8] The most preferred route for the administration of corticosteroids is the topical instillation of the formulation into cul-de-sac of an eye to treating the ocular diseases like conjunctivitis, uveitis, endophthalmitis, glaucomatous conditions and post-operative pain.

To achieve maximum biavailability of steroids a number of formulations have been developed like gels or hydrogel, in situ gelling systems, ocuserts, polymeric vehicles but each systems carries it's own side effects like.

Table 1: Various steroid dosage form along with its side effects. [9-10]

Dosage form	Limitations
Hydrogels, Ointment, suspension and emulsion.	Improper administration that is not reproducible. Blurred vision and lachrymation.
Ocusert	Revealed a sustained effect but it can cause crusting of eyelids, unintended elimination during sleep, and meddling with vision.
conventional eye drops (solutions or suspensions)	Less than 5% of eye drops actually reach the intraocular tissues poor ocular bioavailability imparts the need of frequent doses.

The main purpose of this review is to overcome this all problems associated with corticosteroid administration in ocular cavity by encapsulation of corticosteroid in cubosomes. Hence this review justify research drug delivery of is one of the challenging approaches to overcome this problem.

ABSORPTION BARRIERS FOR OCULAR DRUG DELIVERY

The human eye is a complex sensory organ having to weight about 7.5 g which is approximately less than 0.05% of the weight of the body. It has two regions: the front of the anterior segment which covers one-third portion of the eye and which involving aqueous humor, cornea, conjunctiva, iris, ciliary body, and lens and the back. While the posterior segment covers remaining two-third portion of the eye which involving vitreous humor, retina, choroid, and optic nerve.[11]

Drug delivery through anterior portion is considered as one of the most suitable non-invasive route of drug delivery system the capacity of the conjunctival sac when the lower lid is pulled away is approximately 25 ml but which reduces to approximately 10 ml when eyelid returns to its normal position, but ocular tissue absorption of administered drugs is estimated to be less than 5% due to the presence of a variety of barriers. Some of the dynamic barriers include;

- Reflex blinking (5–7 blinks/min).
- The tear turnover-The basal tear flow is 1.2 ml/min (0.5– 2.2 ml/min). Reflex stimulation might increase lachrymation 100-fold, up to 300 ml/min so the topical administered drug is easily drainage of the drug from eye after application.
- Nasolacrimal drainage.
- Pathological conditions affecting conjunctiva may limit the holding capacity of conjunctiva sac.[12]
- 2-3 ml mucus is secreted daily which covers ocular surface and becomes a barrier for drug absorption.[13]

All the above conditions significantly decrease drug availability for therapeutic effects. Furthermore the physicochemical properties of the drug such as the molecular size, shape, solubility, and lipophilicity, also act as a barrier to ocular delivery, [11] some investigations have also revealed the importance of precorneal tear film as a significant barrier to drug absorption.[14]

MECHANISMS OF PERMEATION OF CUBOSOMES THROUGH OCULAR SURFACE

The mechanism of drug transport across the biological membrane is dependent on the nature of the activity and composition of the carrier, and the anatomy and physiology of the ocular system. A mechanism involved in ocular membrane transport is in intra (Trans) and inter (Para) cellular transports. This mechanism s manipulated by using drug carriers system, in which drugs can be incorporated either in the core or as an integral part of the vesicles.

Paracellular diffusion is defined as the movement of drug molecules across a membrane by going between, or going through, two cells. Paracellular diffusion process is solely passive which dependent upon pore size of the cell, as well as the size and shape of the xenobiotic (drug molecule).

Transcellular diffusion is the movement of a drug across the cell. In intestinal absorption, the drug is exposed to the enzymes within the cell, as well as any efflux pumps that are present on the apical region of the membrane resulting in transcellular diffusion.

Transcellular diffusion may be passive, facilitated, or active. Transcellular movement is a common route of drug transport in which, the drug passes through the passage of the drug. But some drugs are too polar to pass across the lipoidal cell membrane only those drugs transported through the paracellular pathway, between the cells.

When we topically apply the cubosomal eye drops; encapsulated corticosteroid can be effectively delivered to the cornea and anterior sclera. Interactions of vesicles with the corneal epithelium may have increased the probability of transcorneal drug penetration and also enhance intraocular drug supply via the non-corneal route. Conjunctival and scleral penetration is important in delivering poorly absorbed drugs.

ADVANTAGES OF CUBOSOMES: [1,2,15] various common advantages of Cubosomes are;

1. Cubosomal drug delivery having high internal surface area and cubic crystalline structures so which resulting high drug payloads.
2. Promising vehicles for different routes of administration.
3. They can be prepared by a simple method.
4. Having lipid biodegradability.
5. They can encapsulate all 3 types like hydrophilic, hydrophobic and amphiphilic substances.
6. Targeted release and controlled release of bioactive agents.
7. Even after dilution Cubosomes retain their stability which is not possible with other liquid crystalline systems because they transform into micelles. Thus, being incorporated into formulations easily.
8. Protecting drugs from degradation, and delivering them directly to the tumor site i.e site targeting action.
9. The cubic phases of cubosomes are colloidal dispersion which is thermodynamically stable for longer time.
10. Enhances the solubility of the poorly water-soluble drug.

DISADVANTAGES OF THE CUBOSOMES: [1,2,15]

It do not offer controlled drug delivery on their own compared with polymer-based drug delivery.

1. It is very difficult to load hydrophilic active ingredients during the formation of cubosomes because we use a large amount of water for the dispersion of GMO and Poloxamer already present in it.

Industrial scale production is sometimes difficult because of high viscosity and lacks of advanced types of machinery are available by considering manufacturing techniques of cubosomes.

Table 2: Experimental Corticosteroidal Preparations formulated by various researchers prepared.

Sr No	Researcher	Drug	Dosage form	Side effects	Reference
1	Lixia Luo et. al	Dexamethasone	carboxyl-terminated poly(lactic-*co*-glycolic acid) encapsules	Stability, homogeneity and mass production	16
2	Chee Wai Wong et. al	Prednisolone phosphate and triamcinolone acetonide phosphate	liposome's		17
3	Darren J. Lee	Dexamethosone	drug delivery implants	Although small, the risk of endophthalmitis, blurred vision.	18
4	Xiaoyan Yang et. al	Hydrocortisone Butyrate	D,L-lactic-co-glycolic acid nano particles thermosensitive gel	Stability, initial burst phase	19
5	Akira Yanagawa et. al	Hydrocortisone 17-butyrate 21 -propionate	lipid microspheres	Stability, homogeneity and mass production.	20
6	Yannis A. et. al	Triamcinolone Acetonide	Intraocular injection	Endophthalmitis, Retinal and vitreous hemorrhage,	21
7	Corine R. Ghosn	Dexamethasone	Intravitreal Implant	Retinal detachment Blurred vision	22

Table 3: Currently Marketed corticosteroidal Preparations.

Drug Name	Dosage form	Brand Names	Used for treatment
Dexamethasone	Dissolving implants	Ozurdex	Prevent eye inflammation caused by disease Allergies, shingles (herpes zoster), severe acne, iritis, uveitis, eye injury, radiation, chemical burns, certain other conditions like blockage of certain blood vessels in your eyes & posterior uveitis.
	Ocular Suspension	Dexycu , *Maxidex*	
	Intraocular injection	Dextenza, Dexycu, Ozurdex	
Difluprednate	Ocular emulsion	*Durezol*	Treat anterior uveitis, inflammation that affects the front part of the eye.
Fluocinolone	Implant	Retisert	Treat Non-infectious posterior uveitis.
Fluorometholone	Liquifilm	FML Liquifilm	Bacterial, fungal, or viral infection of the eye (including herpes).
	Ophthalmic Suspension	Fluor-Op	
	Eye Ointment	FML	Eye inflammation caused by surgery, injury, or other conditions.bacterial, fungal, or viral infection of the eye (including herpes).
	Eye drops	*Flarex, FML Liquifilm*	
	Eye drops, ointment	FML®	
Loteprednol	Eye drops gel	Lotemax SM *Alrex, Inveltys,*	Inflammation caused by allergies, shingles (herpes zoster), severe acne, iritis, or certain other conditions.
Prednisolone	Eye drops	Ocu-Pred-A , pred-NIS-oh-lone	Palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides,
	Ophthalmic suspension	Econopred	
Medrysone	Ophthalmic suspension	HMS	Treatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis, and epinephrine sensitivity.
Triamcinolone	Intravitreal & ophthalmic injection	Triesence	During a certain type of eye surgery (vitrectomy).
		Trivaris	Treat inflammation caused by disease or injury.

SIDE EFFECTS OF OCULAR DRUG DELIVERY OF CORTICOSTEROIDS WHICH MAY OVERCOME BY CUBOSOMAL DRUG DELIVERY: [8, 10, 16, 17]

Corticosteroids drug delivery has various side effects which will be overcome by cubosomal vesicular drug delivery systems like normal corticosteroidal dosage forms are easily washed out from the eye due to natural blinking, induced lacrimation, normal tear turnover, rapid precorneal clearance, as well as nasolacrimal drainage while cubosomes have bioadhesive property which will overcome this effect.

Precorneal obstacles and corneal barrier together lead to a great loss for the medications instilled cubosomes are nano in size as well as they can easily cross various barrier Gels, ocular inserts, and in-situ gels are approaches used to improve the precorneal residence but have disadvantages of patient discomfort and blurred vision and long-term solution of steroids also cause cataracts and glaucoma but cubosomes are transparent in appearance and having good bioavailability so the small dose is effective. Corticosteroid eye drops are suspension in nature so irritates eye due to its complex nature but which is overcomes by incorporation of drug into cubosomal vesicles.

PREPARATION METHOD PREPARATION OF CUBOSOMES:

Various methods used for preparation of cubosomes which are; Where GMO- Glyceryl monooleate, Poloxamer 407- P407.

Top down Approach:

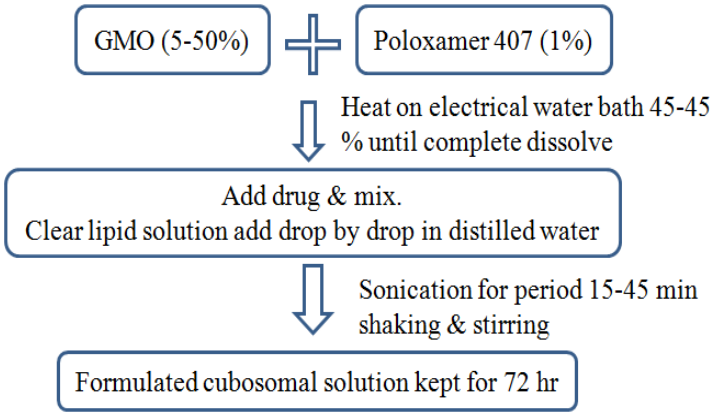

Figure 2: Top down Approach for formulation of cubosomes. [23]

Fragmentation method:

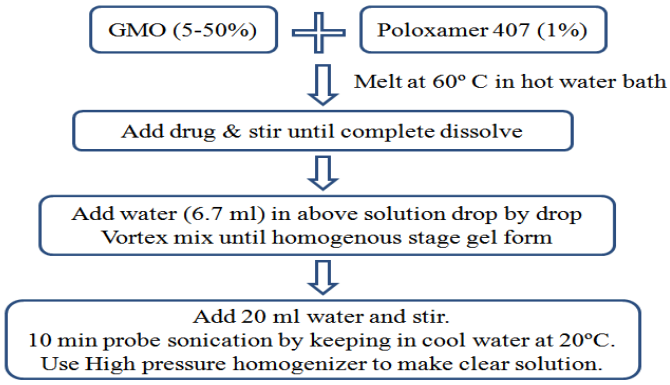

Figure 3: Fragmentation method for formulation of cubosomes. [24-25]

Adapted coarse method:

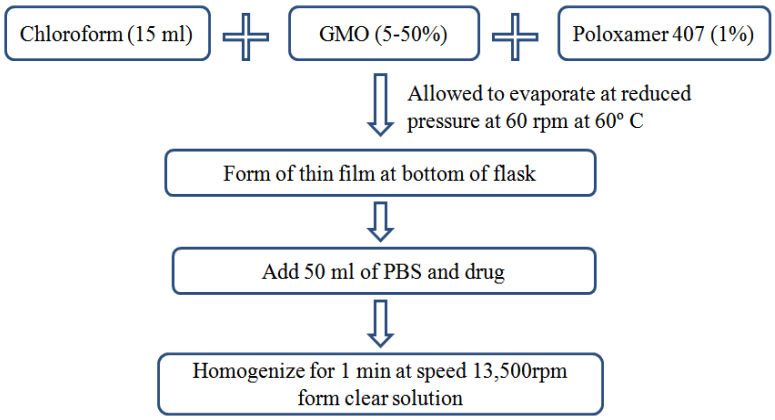

Figure 4: Adapted coarse method for formulation of cubosomes. [26]

Combine surfactant method:

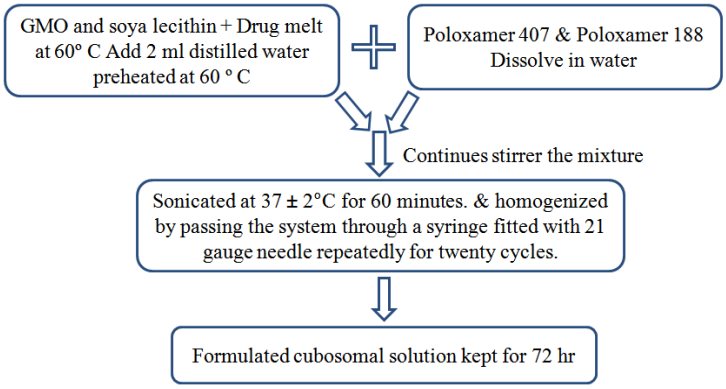

Figure 5: Combine surfactant method for formulation of cubosomes. [27]

Non aqueous method:

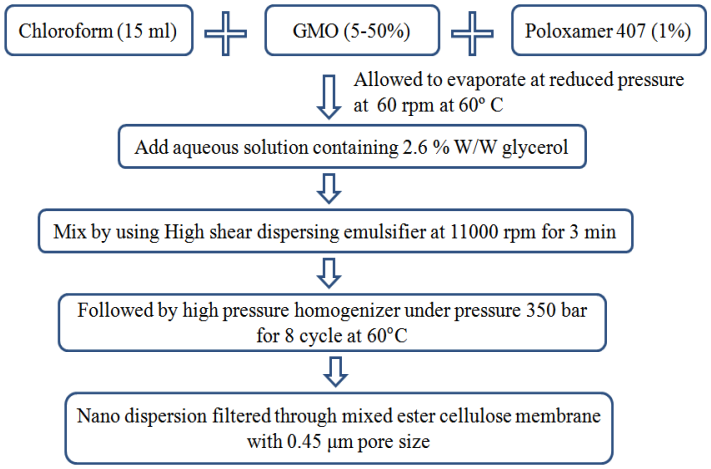

Figure 6: Non aqueous method for formulation of cubosomes. [22]

EVALUATION OF OCULAR CUBOSOMAL SYSTEM:

Thermal Analysis:

Thermal Analysis Differential scanning colorimeter is used to evaluate the physical status of the drug which entrapped within the cubosomes.GMO and Poloxamer 407 melt together in temperature at around 37ºC to 56ºC which may be resulting the plasticizing of Glyceryl Monooleate(GMO).

The thermal events related to the formulated drug's melting point are different from thermal events of the native drug (no sharp drug melting peak at around 200oC). The thermal events observed between 200ºC and 300ºC may be related to the glyceryl monooleate degradation process.[4]

Particle morphology / Transmission electron microscopy:

Particle morphology / Transmission electron microscopy: Particle morphology studied by using transmission electron microscopy (TEM) in which images were taken using a JEM 1400 JEOL instrument. Specimens were prepared by drop-casting of the cubosomes (5/ 10 mL) on a copper grid with 10% phosphotungstic acid/ 300 carbon mesh is coated with copper grid and letting the cubosomes settle for 3-5 min.

The size distribution was determined by examining an overview TEM image using software .[26, 29]

X-ray Diffraction Measurements/ Small-angle X-ray scattering:

Small-angle X-ray scattering (SAXS) measurements were carried out on a high-flux SAXS instrument operating in the line of collimation and equipped with an imaging plate (IP) as a detector. The IP with a pixel size of 42.3×42.3 μm2 was extended into a wide-angle range (the q range covered by the IP was up to 28 nm-1, $q=[4\pi\sin\theta]/\lambda$, where λ is equal to wavelength of 0.1542 nm and 2θ is the scattering angle). The liquid samples loaded quartz capillary having diameter of 1 mm exposed for 60 minutes.

The SAXS experiment helps to investigate the internal structure of the cubosome. The values of scattering vector q corresponding to the scattering peaks for cubosomes F1 and F2 (Figure 3) appeared in the ratio of q1:q2:q3 =2:4:6, which corresponded to the Miller indices, hkℓ =110, hkℓ =200, hkℓ =211, respectively. The results fit the characteristic peaks of the Im3m crystallographic space group (Q229), which contains a primitive cube phase.[26]

In vitro drug release studies:

Drug release from cubosomes is evaluated by using a dynamic dialysis method. The samples of various formulations were placed in dialysis bags (cellulose membrane), then immersed in 500 mL of simulated tear at 37±1 oC, Maintained paddle rotation speed. At predetermined time intervals, a 5 mL sample was withdrawn and immediately replaced with an equal volume of the tear. Then the concentration of the released drug is measured.[4]

For alternative methods, Franz diffusion cell was used to measure in-vitro drug release.

Particle size and size distribution:

The size distribution of cubosomes was measured using a Zetasizer Nano ZS90 (Malvern Instruments, Malvern). The samples were diluted 50-fold with water before measurement. Malvern Instruments provides software dispersion technology using that software cubosomal size was analyzed. Some alternative methods are dynamic light scattering Instruments, sometimes referred to as photon correlation spectroscopy, which non-invasive, well-established technique typically used when particle is in the submicron region. The samples were vortexed before measuring the particle mean diameter, size distribution, and polydispersity of cubosomes and temperature should maintain up to 25°C. Based on a reference from the National Institute Standard (NIST), a PI <0.05 was considered Monodispersed.[26]

Encapsulation efficiency (EE):

Cubosomal dispersion was transferred into a centrifugation tube (Remi RM-12 microcentrifuge) and was centrifuged at 15000rpm for 30 min. Then 10µl clear supernatant liquid collected and diluted with distilled water up to 10 ml estimated at 248 nm using UV-visible spectrophotometer. % EE calculated by using the following formula.

$$\%\,EE = \frac{Wa - Ws}{Wa} * 100$$

Where, W_a is the amount of drug added to the system, and W_s is the amount of drug in the supernatant. The results were repeated as the mean of three independent experiments performed in triplicate

Nonencapsulated or free drug-in-solution leaked outside the sub-tubes, making it possible to measure its concentration in solution and thus allowed the deduction of the proportion of drug encapsulated in cubosomes.

Preliminary studies conducted with known concentrations of drug from the calibration curve showed that this specific drug did not significantly bind to the membrane. Moreover, the UV molar absorptivity (ε~11,200 l/mol cm) did not change significantly for free and uncapsulated drug. That UV absorbance was used to compute the total concentration, and the UV absorbance of drug contained in filtrate after centrifuge was used to compute the Cf filtrate concentration. Thus, percent EE was calculated using same formula.[26]

Stability study:

Using standard of Chinese Pharmacopoeia 2010 (part 2, Appendix XIX C) stress testing was studied to evaluate physical stability. Freshly prepared cubosomal samples placed in a drug stability test chamber under strong light (4,500±500 lx) and high temperature (60°C) for 5 and 10 days, afterwards the appearance and particle size of the samples were checked. It was observed that after storage of trasparent cubosomal solution which will turn turbid. Also at refrigerator temperature homogenized dispersions results in the formation of white, semi-solid, ointment-like gels may be due to crystallization of the colloidally dispersed monoolein. This type of behavior is observed in monoolein/water bulk systems due to high tendency for super cooling at sub-ambient temperatures. But the crystallization in the ternary monoolein/poloxamer/water bulk system could not be observed due to addition of poloxamer which modifies the crystallization behaviour of monoolein.[4]

In vitro trans-corneal permeation study/ In vitro release analysis:[4]

To performer *In vitro* release analysis franz diffusion cell is used which contains donor and receptor compartments and freshly excised goat cornea was used as diffusion membrane.

Diffusion area was 0.64 cm2. Bicarbonate ringer solution (pH 7.4) was used as buffer medium which maintained at pH at 37ºC with constant stirring. Permeation study was continued for 240 min. Samples were withdrawn from receptor compartment by maintining sink condition and analyzed for drug content by measuring using spectrophotometer. Results were expressed as amount of drug permeated and percentage of permeation. The permeation (%) or in vitro ocular availability was calculated as follows:

Permeation % = Amount of drug permeated in receptor / Initial amount of drug in donor * 100

Evaluation of corneal hydration levels (%HL)/ In vitro corneal retention study:

After completion of permeation study experiment, the sclera tissue was removed from cornea; its epithelial surface was wiped with filter paper and weighed (Ww). The cornea was then soaked
in 1ml of methanol, dried for 12 hour at 90 ºC, and reweighed (Wd). From the difference in weight, corneal hydration (%) was calculated by using following formula:

$$\% \text{ HL} = [(W_w - W_d)/W_w] \times 100.$$

Calculation of apparent permeability coefficient (Papp) and steady-state flux (Jss)
Apparent permeability coefficient and steady-state flux were calculated using the following equations:

$$P_{app}\,(\text{cm/s}) = \left[\frac{\Delta Q}{\Delta t} \times \frac{1}{(\text{A.Co.60})}\right]$$

where DQ/Dt (mg/min) is the flux across the corneal tissue. A is the area of diffusion (cm2), Co (mg/cm3) is the initial concentration of drug in donor compartment, and 60 is taken as the factor to convert minute into second. The slop of the regression line obtained from the linear part of the curve between the amount permeated (Q) versus time (t) plot is calculated as flux across the cornea.

Ocular irritation test- Evaluation with the Draize method:

Draize method used to evaluate ocular irritation test where rabbit used as test animal. Two groups; each contains 6 rabbits are treated with eye drops (1–2 drops in the right eye) for every 30 min for 6 hour with different formulations. The left eyes served as controls which is treated with saline solution. The ocular condition was recorded at every 1, 2, 4, 24, 48, and 72 h.
Ocular irritation scores for every rabbit were calculated by adding the irritation scores for the cornea, iris and conjunctiva which was obtained by dividing the total score for all rabbits by the number of rabbits.

Table 4: Irritation was classified according to four grades:28

Sr. No	Irritation score	Scale for evaluation
1.	0–3	practically non-irritating
2.	4–8	slightly irritating
3.	9–12	moderately irritating
4.	13-16	is severely irritating (or corrosive)

Histological examination:

Histological examination was carried out to study corneal structure and integrity. To perform histological the corneas were removed from the eyes of freshly sacrificed rabbits and incubated at 37 ºC for 2 h in the cubosome formulations.
PBS and sodium dodecylsulfate (SDS) solution in PBS 0.1% (w/w) were used as reference solutions.

After incubation, remove the the corneas and washed with PBS and fixed with a formalin solution 8% (w/w) and study the histological changes in tissue.

In vivo pharmacokinetics:

To perform vivo pharmacokinetics; 25% (w/v) tropicamide eye drop is used to dilate the pupils of the rabbits. Anesthetize the rabbits (n=3) with sodium pentobarbital injection through the marginal ear vein and implant the A CMA20 microdialysis probe (CMA/AB Microdialysis, Sweden) into the aqueous humor using a 25 G needle. Slowly remove the needle and leave the probe with the dialysis membrane in the middle of the anterior chamber. Fix the outlet of probe to prevent any movement during sample collection. The probes were perfused with pH 7.4 isotonic phosphate buffer saline (IPBS) at a flow rate of 2 µL/min using the BAS microdialysis system (Bioanalytical System Inc, USA). After probe implantation, the animals were allowed to stabilize for 2hour for the restoration of intraocular pressure and replenishment of the aqueous humor originally lost during probe implantation.

After that, 100 µL of the formulation (FB, 0.2 mg/mL) was instilled into each eye and continue the instillation for 6hour. Samples were collected after every 20 min and were analyzed using HPLC.

The micro dialysis probe was perfuse at a rate of 2 µL/min with different concentrations of standard solution and collects the dialysates for 20 min after 30 min of perfusion and injected into the HPLC Column to determine the in vivo relative recovery of drugs.

A ratio of drug concentration In to dialysate (cd) : to solution in dialysis membrane (Cm) to that in the tissue (Cm) is used to calculated recovery (R) using following equation:

$$R=\frac{C_d-C_p}{C_m-C_p}$$

Where Cp is the drug concentration in the perforate and R is the value of the slope for the plot of Cd–Cp versus Cp.[28]

CONCLUSION

Formulation of cubosomes is simple dispersion and homogenization of monoolein and poloxamer 407 in water which is suitable delivery of lipophilic, hydrophilic drugs through the cornea and hence use in the treatment of various ocular disease. Similarly, the use of corticosteroid delivery systems in the case of the ocular drug delivery system has to gain lots of attention over the past couple of decades which is resulting in the development of multiple corticosteroidal formulations. But the cubosomal cortocostroidal system may have been shown to the number of advantages over conventional eye drops. Thus, future corticosteroid therapies using nanomedicine can be envisioned to specifically act on all ocular problems with minimum side effects and shows the best efficiency of controlled release drug carrier.

RECOMMEND FUTURE RESEARCH

In future; specialized studies are required to confirm this fascinating hypothesis and to better investigate the role of vesicles and cubosomes in controlling the release of the drug.

CONFLICT OF INTERESTS

Author has no any conflict of interest.

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