"FORMULATION AND EVALUATION OF CYCLOSPORINE LOADED WAFER FOR THE TREATMENT DRY EYE SYNDROME"

A thesis submitted to

NIRMA UNIVERSITY

In Partial Fulfilment for the Award of the Degree of

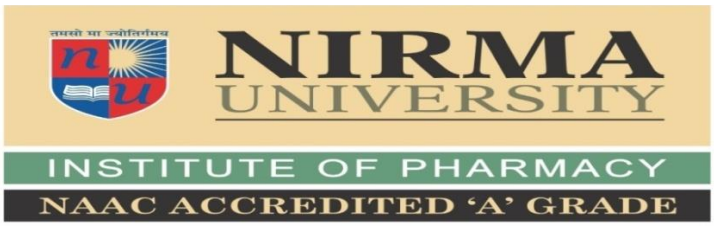
MASTER OF PHARMACY
IN

PHARMACEUTICS
BY

NIDHI ADITYA (18MPH108), M. PHARM

UNDER THE GUIDANCE OF

DR. TEJAL SHAH



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MAY 2020

CERTIFICATE

This is to certify that the dissertation work entitled ***"FORMULATION AND EVALUATION OF CYCLOSPORINE LOADED WAFER FOR THE TREATMENT DRY EYE SYNDROME"*** *submitted by* ***NIDHI ADITYA with Regn. No.(18MPH108),*** *in partial fulfilment for the award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy Nirma University under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.*

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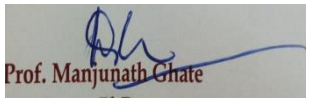

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DECLARATION

I, hereby declare that the dissertation entitled ***"FORMULATION AND EVALUATION OF CYCLOSPORINE LOADED WAFER FOR THE TREATMENT DRY EYE SYNDROME"*** *is based on the original work carried out by me under the guidance of Dr. TEJAL SHAH, Head of the Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submittedin part or full for any other degree or diploma to this or any other university or institution.*

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CERTIFICATE OF ORIGINALITY OF WORK

This is to undertake that the dissertation work entitled "Formulation and evaluation of cyclosporine loaded wafer for the treatment of dry eye syndrome" Submitted by Nidhi Aditya (18mph108) in partial fulfillment for the award of Master of Pharmacy in "M.Pharm. Programme" is a bonafide research work carried out by me at the "Name of Department", Institute of Pharmacy, Nirma University under the guidance of "Name of a Guide and Co-guide". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my Knowledge.

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Special gratitude and love towards ***my Parents*** *the bottom of my heart for giving me more than what I deserved. They always let me know that they are proud of me,*

Regards

Nidhi Aditya

FORMULATION AND EVALUATION OF CYCLOSPORINE LOADED WAFER FOR THE TREATMENT OF DRY EYE SYNDROME

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INDEX

CHAPTER-1

Table . List of Materials used

Materials	**Company/Make**
Cyclosporine	Sun Pharma ,Vadodra
HPMC k 100	Colorcon Asia Pvt. Ltd, Goa
PEG 400	Central Drug House Ltd., New Delhi
Ethanol 95%	Central Drug House Ltd., New Delhi
PVP K-30	Sisco Research Laboratories, Mumbai
Propylene glycol	Central Drug House Ltd., New Delhi

Table List of Equipments used

Equipments	**Company/Make**
Magnetic Stirrer with hot plate	EIE Instrument Pvt. Ltd., Ahmedabad
Sonicator bath	Trans-o - Sonic D- Compact,Ahmedabad
UV-Vis Spectrophotometer	Jasco V- 570, Japan
Lyophilizer	Delvac
Digital balance	CitiweighTejas Exports, Ahmedabad

INTRODUCTION

INTRODUCTION:

Dry eye disease is the commonly growing disease across the world. Dry eye is basically caused by the loss of moisture and lubrication at the surface of the eye this may result many symptoms of dry eye includes fatigued eye, sore eye, itchy eye, aching sensation, etc. it can cause by the immune disorder and metabolic disorder. For the treatment of the dry eye syndrome many eye drops are available in the market like osmodrops eye, moistane drops eye etc. because of the low bioavailability and the low therapeutic(1) effect it has less patient compliance and has less efficacy. To overcome with this issue cyclosporine loaded wafers are developed for the treatment of dry eye syndrome this assist in the improvement in the convenience and efficacy. Wafers are thin rectangular shaped membrane for the sustained and controlled release of drug for long duration. Wafer shows more therapeutic and bioavailability compare to the conventional drug delivery system it can introduced on surface of the eye by the help of tip of the finger it can remain in direct contact with the surface of the eye. It can be applied in such a way that a reservoir of that the loaded drug facing towards the surface of the eye. At the end the cyclosporine loaded wafer dissolves (2)

Wafers are applied by the help of the tip of the finger to the anterior part or surface of the eye and it is applied as such that the reserviour or drug loaded are direct contact with the surface of the eyes and at last if get dissolved itself on the ocular surface and vanishes. Wafers formation for dry eye syndrome is a new concept to treat the disease it increase the residence time at the site of action and also provide the controlled release of cyclosporine for a prolong duration in a controlled manner, this may also increase the

therapeutic effect of the drug to cure the disease as compared to the conventional drug delivery.

SYMPOTMS:

- Burning sensation
- Itchy eyes
- Aching sensations
- Heavy eyes
- Fatigued eyes
- Sore eyes
- Dryness sensation
- Red eyes
- Photophobia
- Blurred vision

Dry eye disease caused by 2 major problems:

1.Aqueous deficient (Reduce tear production)

2. Hyper evaporative (increase evaporation of tear film)

1.1 HYPER EVAPORATIVE

All over the world around 10% of the of the patient are suffered from dry eye syndrome because of the aqueous defiecent. Hyperevaporative disorder mainly caused by the malfunction of the meibomiam gland, and combinedhyperevaporative and aqueous deficient are above 80% of cases. Hyperevaporative is the excessive evaporation of lachrymal fluid from the anterier part of the eye cause reduction in lubricants in the eye due to which dryness and irritation occur in the eyes.(3)

1.2 AQUEOUS DEFICIENT:

Aqueous deficient dry eye syndromes are the type of dry eye syndrome which is cause by deficient or lack of lachrymal fluid in the anterior part of the eye. Aqueous deficient is also a condition when the lachrymal gland fail to produce lachrymal fluid this may cause irritation burning sensation, itchy eyes. These are the main and important symptoms of dry eye syndromes.(4)

PATHOPHYSIOLOGY OF KERATOCONJUCTIVITS SICCA (DRY EYE SYNDROME)

Mechanism of dry eye symdrome (keratoconjuctivitssicca) caused by dryness or hyperosmolarity stress on the ocular surface.(5) Dry eye syndrome due to hyperosmolar stress can be cause by many

reason like lachrymal gland damage; due to disease like sjogren syndrome age related degeneration of lachrymal gland, meibomiam gland; caused during the referactive surgery it may damage the sensory nerves and conjectivitis. Systemic medication and many reasons theat the production of eyes tear get reduced. The etiology of dry eye syndrome, chronic inflammation is espically caused by the hyperosmolarity and T-cell mediated immune responses are the common immortalize agents. During inflammation nuclear factor kB and mitogen activated protein kinases (MPAK) increases on the surface of the ocular. These MAPK mitogen activated protein kinase activated and triggers the interlukin -1β and tumor necrosis factor α secreated as inflammatory meadiators which in turn triggers and activates the T-cell and dentrictic cell on the ocular surface. Now from the T-cell these inflammatory mediators are released along with the hyperosmolarity and may cause cellular damage and damage to the epithelial layer and cells of goblet which now in turn damage the tear film and cause inflammation on the surface of the eye. (5)Because of These inflammation it can cause irritation on the surface of the eye, itchiness, dryness and shows many symptoms and sign caused due to the instability of the tear film and damage of the epitilial cell layer andgloblet cell layer damage. This may results in loss hoemeostatsis that leads to the dry eye syndrome.

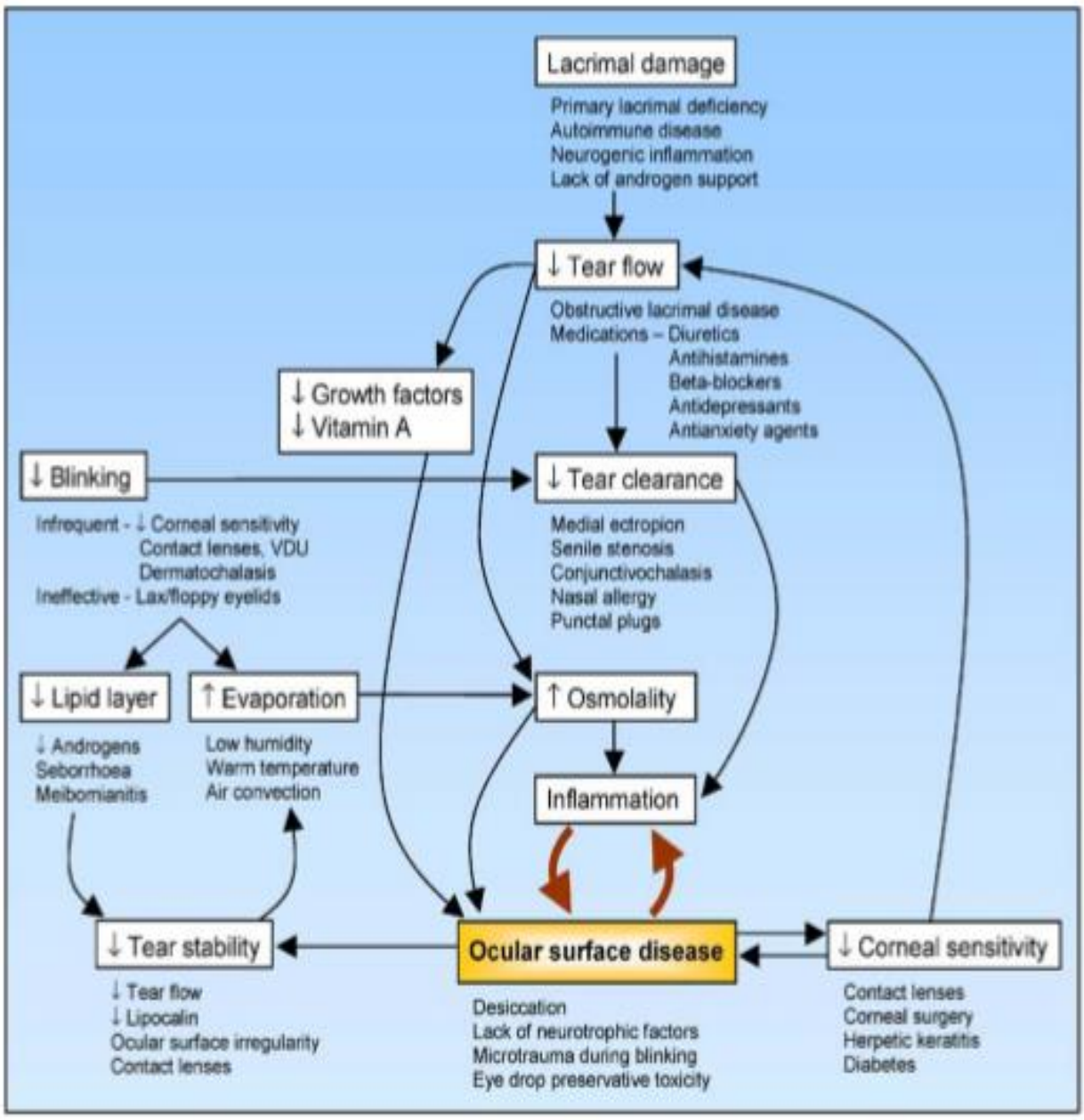


Fig.1. aetiology and pathology of DES

TEAR FILM THICKNESS AND STRUCTURE

Tear film on the precorneal surface of the eye consist of three layer structure they are:(1)

1. Watery aqueaous phase
2. Thin mucous phase

3. The uppermost layer is coating of lipid

In the early times it was believed that the thickness of the tear film was appraised by some invasive tests those are:

1. Placing glass fibre against the cornea.
2. After instillation of fluorescein measurement of fluorescence.
3. And by the absorbent paper applied on the ocular surface.

From these three invasive test the estimation of the ocular film thickness was found to be the 4µm-8µm for the humans. (6)Afterwards by using instruments like canfocal and interferometry the thickness of human film was found to be 40µm but the authors were unable to describes these studies previously it was cleared that these are the denser and deeper layer of mucus layer, below the mucus layer. Moreover the very recent study of the tear film was found to more lesser than it was estimated before by using instruments like electron microscopy is 2µm-6µm in rat and human tear film tear was found approximately 3µm thick.

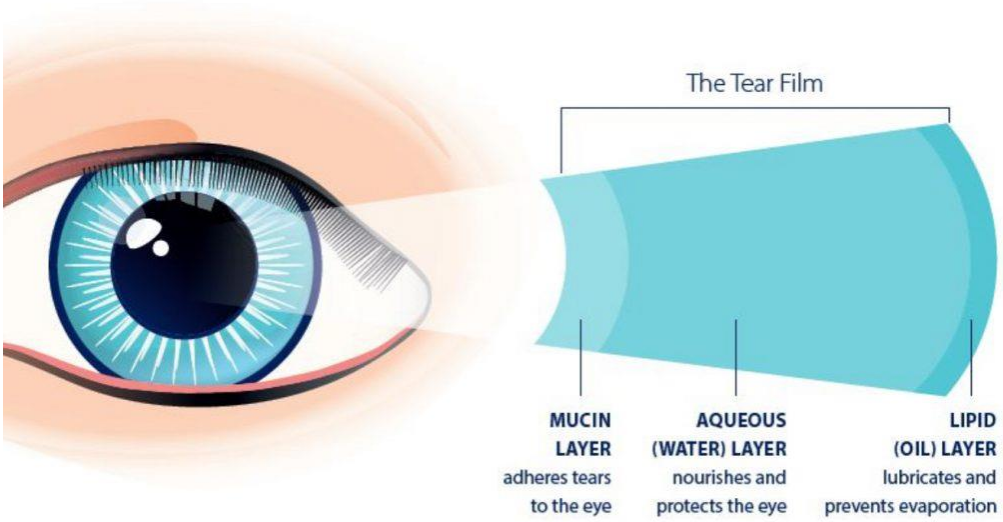


Fig.2. Layers of thin film

STRUCTURE OF TEAR FILM

The uppermost layer of tear film fluid is tear lipid film. The thickness of tear lipid film is about 50–100 nm. Meibomiam gland rooted in the eyelid region where tear lipid film rises. This gland is also called as meibum. Meibum has a tendency to contain both polar and nonpolar that in case arranged itself in such a manner that it forms a double film like structure. These thin polar layer facing in the direction of the aqueous layer and thicker layer of non polar facing outside by covering the polar aqueous layer. (1)

Under the tear lipid layer the structure of tear film is arranged in such a way that it covers the anterior part of the ocular. Tear film is consist of aqueous fluid layer and the main component of aqueous fluid layer is lacrimal gland which is secreted on

the layer of epithelial cell. The aqueous layer of the tear fluid arranged in such a pattern that it forms a cluster of tear films which in turns provides nourishment to the avascular cornea by conveying oxygen and nutrients along with the chemical signals to the envelop. The chemical signals such as electrolytes which are included in the tear fluid composition helps to steady the ph , temperature of the tear fluid and also help to determine the osmolarity of the tear fluid. The aqueous layer helps to protect the anterior portion of the eye from the unwanted things in the ocular surface and also protect from the antimicrobial and antioxidants elements as it contain growth factors which are harmful for the anterior surface of the eye. As they have the growth factor that can cause problem to the ocular conservation and healing.

The goblet cells of conjunctiva produces solubllised and viscous gel forming mucin which forms as cluster layer by layer and increase the concentration on the side of tear layer which helps to provides lubricants on the ocular surface so that it make easier the blinking action of eye.Mucin is present on the ocular surface which helps to provide lubricancy to the uppermost surface of the eye which in turn provide the smooth and complete surface that helps in easier action of blinking of eyelid. Mucin protect the cells of cornea by forming the enclosing debris in the surface of the eye for the harmless elimination at the site of caruncle through blinking. These aqueous and mucin gel combines and form a matrix of transmembranemucin which in embedded or attached to the layer of epithelial cells of cornea and conjunctiva. These combine layer are called as glycocalyx. Glycocalyx promotes the hydrophilicity and also increases the ocular surface protection.

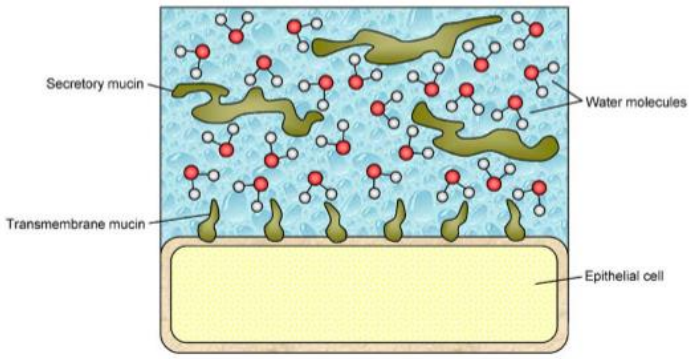
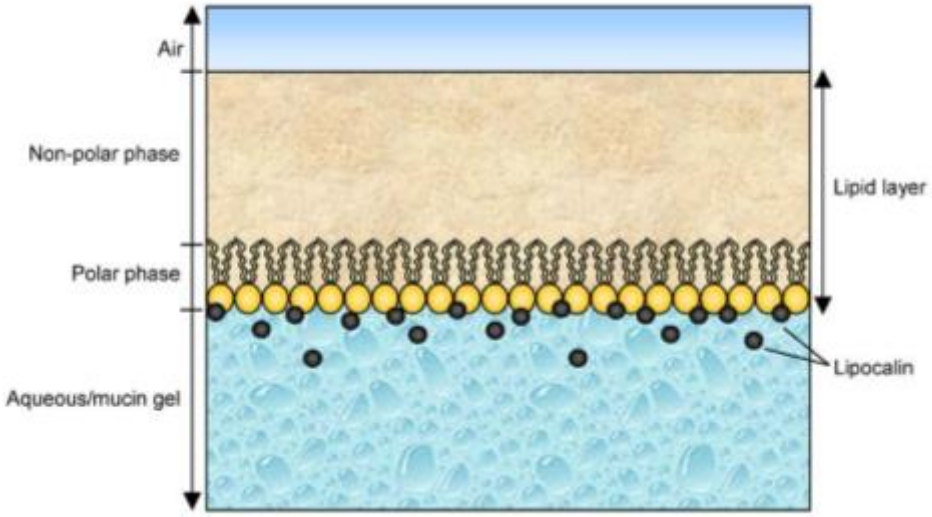


Fig. 1. Water molecules effectively compete for polar mucin attractions, preventing firm adherence of mucins in the tear film to other tear mucins and the underlying glycocalyx.

During the blinking of eye tear, eye blinks and tear film replenishes its elements and reform its film. After blinking of the eye the lipid layer of the eye is present in the compressed manner which is then stretched on the opening of eyes at interperable area. And between the blinking of the eyes tear film form thin layer and disrupted. Changes of the interfacial tension can cause impurity amongst the layer of the eyes which may cause dry spots and this may leads to the breaking of the tear film. To escape from breaking of tear film and destabilized tear film complete blinking is necessary.



Tear film's lipid layer has biphasic structure. The outer layer is more thick than the inner one and consist of nonpolar lipids whereas the inner layer consist of the polar phospholipid. The nonpolar layer in the uppermost part are tend to retard the aqueous phase while inner polar phospholipid layer are tend to facilitate interaction with aqueous layer.

TEAR FLOW:

The lack of tear supply on the surface of eye can cause release of abnormally lacrimal gland, disease of lacrimal gland and also include water production reduction or reduced lacrimal secretion reduces the tear elements which plays an important role to growth, health and healing of the ocular superfacial layer. Also provide protein to the ocular surface which in turns helps in stabilized the lipid layer.(1)

OCULAR SURFACE HYPOETHASIA:

Ocular surface hypothesia may leads to the numbness on the surface of the eyes which is generally caused by the lacrimal gland, lacrimal gland produces tear that is controlled via reflex loop. Nerves stimulates to the nasal mucosa and the stimulation of the eye surface that sends signals to the centre of the brain through the nerve called trigeminal nerve which in turn produces response signals to the nerve fibre passing to lacrimal gland with expressive stimuli that is stored into this reflex loop. There are two methods applied if the aqueous production is not in reflex origin. They are basal tear and stimulated tear. Though they are cognitively useful and synthetic tear probably. This may leads to the reduction of the sensitivity of eye surface and the ocular inflammation. Ocular surgeries like diabetes, herpetic keratitis idiosyncratic and contact lenses are trigger to β blocker and further lower the formation of aqueous tear by the lacrimal gland. Added to that the inducing tear production, neurotrophic substance which is important for epithelial substance is released by corneal cell. Lower innervation of corneal decreases the supportive factor obtainability this may lead to disease of the surface of ocular.

MEDICATION

Medication like both systemic and topical medication affect the tear production some common drugs that reduces the formation of the aqueous tear include

- Anti-muscarinic
- Anti- histamine
- β blocker
- Anti-depressent

- Anti-allergic

These are the some medication that are generally effects the tear production, all these effect the production of tear is because it can resist the transmission of impulses of cholinergic pathway.

LACRIMAL DEFICIENCY:

An autoimmune disease of exocrine system that affects the lacrimal as well as salivary gland caused by the syndrome called sjorgen syndrome. Whereas non-sjorgen is lack of tear production this also includes congenital alarimal and lacrimal deficiency this non-sjorgen syndrome is because of the steady (7)desruption of the gland of lacrimal and round cell filteration of ductal tissues. (6) The pathophysiology is not found yet but the ageing and harmonaldisbalance stimulates and immune mechanism is included. The significance of this improbability As a result of this unlikelihood, primary acquired lacrimal deficiency. The reasons for secondary procured lacrimal deficiency includes lacrimal organ infilteration, by sarcoid granulomata, lymphomas, and neurofibromas; inflammation of the lacrimal organ related with HIV contamination disease; nutrient A deficiency has been accounted to cause tear deficient added to this it also shows adverse effect on the production of mucus.

TEAR CLEARENCE

Tear clearence alludes to the rate of tear movement and is an element of tear formation and tear removal. Substance of the tear film postponed and also build the resident time, consisting poisonous cell waste items, ecological antigens, and proinflammatory cytokines, for example, interleukin (IL)- 1 and tumor necrosis factor-alpha (TNF-an) as needs be, deferred tear clearence may initiate or potentiate inflammation of ocular surface.Lessened tear formation prompts a decrease in tear rate by an inadequately comprehended mechanism.

BLINKING

Decreased tear elimination, and therefore delayed tear clearance, may emerge from rare or incapable squinting blinking or flashingis actuated by an motor part of the face (VII) nerve, intervened by nearby neuronal reponses worked by tangible nerves providing the exterior partof the eye and ocular pathway, and improved by supranuclear focuses. The essential segment of flickering of the eye is based on corneal reflex that is subject to corneal affectability, perhaps started by eye surface cooling brought about by the latent heat of the tear film as it evaporates It follows that rare flickering can result from lessened corneal affectability Infrequent fickering of eye can likewise happen with dermatochalasis because of exertion to hoist the brow invalidating the blink reflex Ineffective blinking may happen because of eyelid laxity, typically because age-related degenerative changes, however may introduce following injury or in floppy eyelid disorder. Different reasons for rare and ineffectual flickering incorporate facial paralyses, lagophthalmus, proptosis, and concentrated visual assignmentsStrengthening to their horrible consequences for tear clearence, inconsistent and inadequate

blinking may cause increase evaporative tear by increasing the interblinking periods and diminishing lipid layer thickness, the last inferable from decreased "milking" activity on meibomian organs Rare flickering can, as talked about above, be engaged with the advancement of DES. Be that as it may, the opposite circumstance of expanded flicker rate is likewise every now and again noted in Dry eye syndrome where it apparently shows the reduction of stability of tear.

TEAR FILM STABILITY:

Stability of tear is an important part as it plays a vital role for the reducing evaporative loss of tear and also helps to sustain the tear layer on the surface of the eye. In case of dry eye disease the tear film break-up. (1)In normal condition the surface of the eye in between blinking of the eye shows the slight wettability.

But in case if ocular surface does not shows the wettability this may causes many issues, for this unwettability ocular surface several hypothetical theories were proposed They were:

- Earlier it was believed that the layer of lipid is diffused and engross in between the layer of aqueous-mucus layer. Although this theory was found to be unclear or inexact as the lipid layer shows the higher diffusivity and low solubility which can easily pass to the sheet of the tear film this is uncertain if the lipid crosses the tear film and lipids present in very sufficient it get absorb with in the sort of break-up of tear film times.also, the model neglects to clarify the seriously decreased separation times seen clinically with mucus and eye surface variations from the abnormalities.
- An elective system of tear film burst proposes that separation is started by high range ofapolar van der Waals powers that is the root of breaking of

the mucous layer sheet at its most slim point, permitting the aqueous layer of the eye in direct exposure to the patch with uncovered patches of epithelium.

- The tear film instability mainly are caused by the lack of tear formation, by lowering the amount of the lipid layer, changes of the elements of the tear fluid, inflammation on the superfacial part of the eye, and also occur with the non-uniformity of the ocular surface.
- As it was discussed earlier single procedure was not followed for the instability of the tear fluid as it assistant decreasing of the lipid binding ability to the protein called lipocalin. Mucinlooses its property when it get dehydrated and also increases the menisci's curvature. Tensile strength of the thinner lipid layer was reduced.(15) By increasing the rate of the evaporation lipid layer abnormally enhance the tear thinning and also because of the ocular squamous metaplasia cause inflammation of the eye surface reduces the stability of the tear film. Deprive of the cell of goblet and also glycocalyx results in the non-uniformity of the surface of the eye this may cause enchancing the thinning of the tear film and modification of composition of tear fluid

TEAR OSMOLALITY;

Osmolality &osmolarity are properties of solution that identify with the quantity of osmotically active functioning particles osmolality contains, no. of quantity of osmoles of solute per solvent & volume of solution whereas osmolality also termed the tonicity of the eye. Osmolality is equal to the sum of the concentration of solute that can contain the osmotic force around the

membrane of the eye. Tonicity of the eye changes by crossing the different layer as the barier property of surface of epithelial not remain constant.Osmolality is considered as the improved way to explain the tear film In case of dry eye syndrome the tear film's hyperosmolarity is found to be the gold standard for the treatment of outstanding sensitivity and also specificity. The dry eye syndrome is mainly caused by the excessive evaporation of the tear fluid. They have a additional time to function when the volume is low, it reduces the percentage of water from volume of the tear fluid and it happens more faster when the lipid layers barrier function is low or it has the unstable tear film. As a result of absorption of water in the lacrimal duct the osmolality of the tear fluid secreation is increased at low rates and are originating from the lacrimal gland. This increase in osmolarity can cause inflammation and damage the surface of the eye.

INFLAMMATION OF LACRIMAL GLAND:

Lacrimal duct inflammation the lacrimal gland of numerous patients with extreme tear deficient Dry Eye Syndrome have indications of immune system sickness, confirm by infiltration of lymphocyte and immune mediated devastation of the secretory architecture and nerve fibres innervating the lacrimal gland and also the autoantibodies present on the environment such as anti-nuclear antibody Ro/SS-An, and against La/SS-B). Sjogren disorder is mainly caused by the autoimmune disorder of the lacrimal as well as salivary gland. This may cause as the primary abnormality and secondary to the rheumatoid arthritis but it can also caused by the systemic autoimmune connective tissue disorder.

WAFER:

Wafers are the type of drug delivery through which release of drug in a sustained manner for the prolong period of time wafers are consist of small reserviour in which drug is stored and releases for long duration of time. Basically wafers re the slim film like structure which employs water dissolving polymer and also have bioadhevise polymers.(8) This may cause very rapid hydrate, stickiness and also dissolved at the at the site of action. Wafers are easily dissolve and disintegrates which in turn release of drug for from the swell matrix in a controlled release of drug for a long period of time. Therefore the wafers shows the lower patient compliance and improved bioavailability compared to the conventional drug delivery methods. Wafers are the small size, shape and thickness in about 2×3cm.

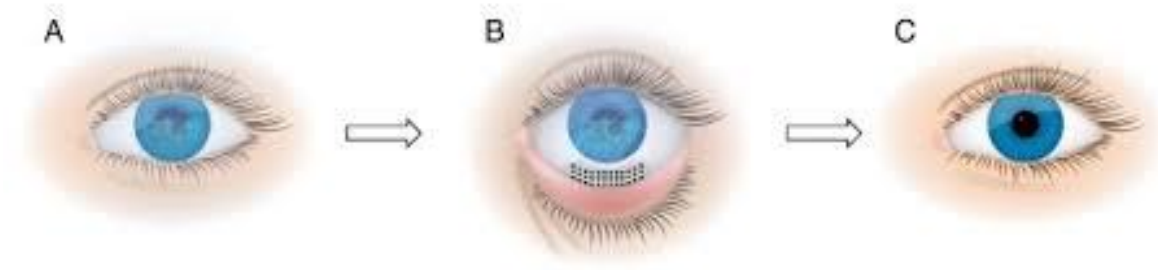


Fig3: images of wafer at precorneal site

Formulation consider

- Active pharmaceutical ingredient. (API)
- Wafer forming polymers
- Plasticizer

These are the important ingredient used for the formulation of the wafer. In case of oral wafer sweetening agent, colouring agent, flavouring agent are also used to mask the bitterness of the drug but for the application of eye API, Polymer and plasticity plays an vital role.

PLASTICIZERS:

Plasticizer plays an important role for the formulation of the wafer as its tensile strength and the mechanical property of the wafer enhanced by the addition of plasticizer on wafer. Its properties are affected by the concentration of the plasticizer. Some plasticizers which are commonly used to enchance the plasticity of the wafers are glycerol polyethylene glycol, dibutypthalateetc(9).

POLYMER

Polymers are the another important factor it can be used in the combination of the polymer or alone. Combination polymers are mainly help to enhance the hydrophilicity, flexibility and also increase the solubility of the wafers. Various types of polymers are used some of them affect the formulation of the wafers properties like hardness smoothness etc. polymers like PVP used wafer are brittle in nature however for the preparation of the flexible fast disintegrating of wafer cross povidone are used in the combination of the poly vinyl pyroolidone. Polymers like microcrystalline cleelulose are used to make the wafer non sticky and smooth surface of the wafer. But it is also used as it enchances the dissolution of the drug and minimizes the disintegrating time the drug.(8)

- Methyl cellulose A-6 and A-15
- Pullulan*
- Gelatin
- Sodium Alginate
- Hydroxy propyl cellulose

RATIONALE

- Wafers can improved therapeutic effectiveness, safety profile and prolong drug stability at the room temperature.
- Reduces the administration frequency as compare to the other ophthalmic drug delivery.
- Increases the residence time of drug and simultaneously bioavailabitilty
- Wafer technology reduces the dose as compare to the eye drops.
- Wafers are biodegradables that completelty the dissolves and fades away biodegradable wafers no need of removal from the ocular sufaces.
- Texture of the wafers should be soft, uniform, and stretchy in nature so that in can simply introduced on the ocular surface.
- Wafer can ingest exudates and promptly rise to turn into a gel.
- In case of non-biodegradable after change to gel, the gel must be sufficiently thick to cling to the injury surface all through the dressing time period and be anything but can easily remove without pain.
- In case of medicated wafer, drug and the other therapeutic excipient is release from matrix in a sustained manner for prolong period of time.
- Wafers should not cause harm and irritancy at the site of the action.(2)

ADVANTAGES:

- Wafers does not have pass first pass metabolites.
- Wafers provides controlled drug release.
- This may provide improved bioavailability.
- Wafers reduces the side effect.
- Wafers are detached and are easily application.
- Wafers gives the better compliance than other conventional drug delivery.

• Wafer are thin membrane which makes patient convenient to apply
• Available in different size and shapes
• Fast breaking down and Rapid discharge
• The medication to be consolidated ought to have low portion up to 40 mg.
• The medications with littler and moderate atomic weight are best.
• The medication ought to have great solidness and solvency in water just asinspit.

DISADVANTAGES:

- Packaging is expensive.
- Incorporation of the high dose cannot be incorporate.
- Extreme bitter drugs are not feasible in case of oral wafers.
- Unstable PH of the drugs are not administered.
- Drug has the irritant property and cannot be administered.
- It ought to be incompletely unionized at the pH of oral hole.
- It ought to be able to penetrate oral mucosal tissue.

TYPES OF WAFER:

1. Flash dissolved
2. Melt away wafer

3. Sustained release wafer
4. Flash dispersed wafer

A. FLASH DISSOLVED

- Size –2-8 cm^2.
- Thickness–20-70 µm.
- Dissolution–60 s maximum.
- Single layered structure.
- Soluble excipients are used.
- Highly hydrophilic polymers are required.
- Drugs are dispersed in solid solution phase.
- It is applied on upper palate of the tongue.

B. MUCOADHESIVE MELT-AWAY WAFERS

- Size–2-7 cm^2.(4)
- Thickness–50-500 µm.
- Dissolution–1-3 min.
- Single or multi-layered structure.
- Soluble excipients are used.
- Hydrophilic polymers are required.
- Drugs are dispersed in solid solution or suspension.
- It is applied to the gingival or buccal region.

C. MUCOADHESIVE SUSTAINED RELEASE WAFERS

- Size –2-4 cm^2.(10)
- Thickness–50-250 µm.
- Dissolution–8-10 h.
- Multi-layered structure.
- Excipients with low solubility are used.
- Non-soluble polymers are used.
- Drugs are dispersed in solid solution or suspension.
- It is applied to the gingival or oral cavity.

POSITIVE ASPECTS OF WAFERS AS ORAL FAST DISSOLVING FILMS

- Attractive measurements structure with new dynamic fixings.
- Improvement of set up items.
- Access to another sign by methods for another absorption profile in any event, for existing dynamic fixings.
- Optimization of bioavailability

APPLICATION OF WAFERS:

- Wafers are used in the ocular surface for glaucoma.
- Wafers are used in oral dispersion for fast dissolving medicine
- Wafers are manufactured for the disintegrating intestinal wafers.

- Wafers are used for the wound healing.

MARKETED AVAILABILITY TILL DATE

US allowed the permission for the import to the laboratory of Ranbaxy, Gliadel(polifeprosan 20 and carmustine implant) wafer these are the FDA approved product. Biopro a pharmaceutical company bonded with USA to indore the Gliadel wafers marketed in India. (11)This wafers are used to cure the malignant gliomas high graded and giloblastomamultiforme. India has very restricted data of the brain tumour and the CNS tumour in India around two to five new cases are found per 1,00,000 in a year.

Table 1 Comparison of Emulsion and Aqueous Formulations of Cyclosporine A

Formulation	Composition	Advantages	Limitations
Approved Formulations			
Emulsion	Anionic oil in water emulsion 0.05% (Restasis®)[10,21,22]	• Improved some subjective symptoms, corneal staining, anesthetized Schirmer's score and tear breakup time at 6 months compared with vehicle[21,22] • Can readily spread over the ocular surface on instillation[13]	• Ocular bioavailability of CsA from emulsion is low[16] • High incidence of ocular discomfort and patient dissatisfaction[22]
Emulsion	Cationic emulsion 0.1%, 1 mg/mL (Ikervis®)[23–25]	• Improved corneal staining, global symptom scores from baseline at 6 months[25] • Increased residence time and ocular tissue bioavailability of CsA compared with anionic emulsion[13] • Once-daily administration[23]	• Ocular bioavailability of CsA from emulsion is low[16] • Proportion of patients achieving meaningful improvement in OSDI scores and corneal staining were not statistically significant compared with the vehicle group[24,25] • High incidence of ocular discomfort and patient dissatisfaction[25]
Aqueous nanomicellar	OTX-101 0.09% (CEQUA™), aqueous nanomicellar solution[27,29,30]	• Improved corneal staining at 4 weeks and conjunctival staining at 6 weeks compared with vehicle, with improvement persisting throughout the study[29,30] • Improved Schirmer's test scores compared with vehicle at 3 months[29,30]	• Effect in severe forms of KCS is unknown[29,30]

Fig4. Some of the marketed product of the cyclosporine

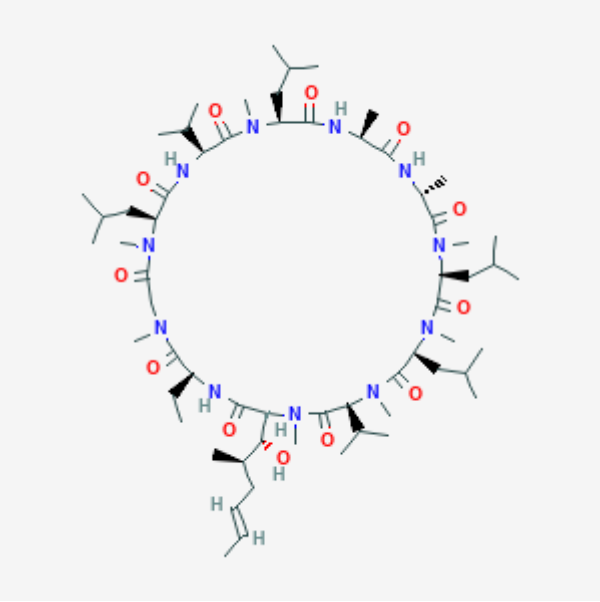
TREATMENT FOR THE DRY EYE SYNDROME:

Some available treatment for the dry eye syndromes are artificial tears which provides lubrication on the surface of the eyes and eye drops are used. But the main drawback of this treatment is that it will not provide the more bioavailability and therapeutic effect as compare to the nanowafers. Eye drops and artificial tear has to be applied twice or thrice in a single day or sometimes 5-6 times in a day for its maximum efficacy. (12)Whereas wafers can be applied once in a weak and can easily vanishes itself on the ocular surface as it contain biodegradable polymers. And also provides maximum therapeutic effect and bioavailability in a sustained manner.

Approaches used to treat dry Eye syndrome includes:

- Reduction cornea inflammation by eyedrops.
- Eye inserts that act as artificial tears
- Tear stimulating drugs
- Eyedrops made from your own blood
- Closing your tear ducts to reduce tear loss.
- Using special contact lense
- Blocking oil glands
- Using light therapy

DRUG PROFILE:

PROPERTIES	DESCRIPTION
PHYSICOCHEMICAL PROPERTIES	
Chemical name	Cyclosporine
Chemical formula	
Structural formula	$C_{62}H_{111}N_{11}O_{12}$

Molecular weight	1202.6 g/mol
Appearance	white powder.
Log P	7.5
Melting point	148-151 °C
Solubility	Slightly soluble in water very soluble in methanol, acetone, and diethyl ether
PHARMACOLOGY	
Mechanism of action	Pharmacological action of cyclosporine was found when cyclosporine molecule binding the receptor cyclophilin-1 present on the surface of the intercellular obtain the complex of the cyclosporine-cylophillin. This cyclosporine-cyclophillin complex resist the release of calcineurin. This calcineurin inhibits desphosphorylation and nuclear factor activation. i.e, Activated of T cells (NF-AT). Transcription factor NF-AT is then regulates and produces proinflammatorycytokinnins like IL-2, IL-4 TNF- alpha and interferon gamma. The dire need for the inhibition cascade is dependent on the particular inhibition of IL-2 because of the importance of interlukin on the stimulation and proliferation of Tcell. On the other side the resistance of NF-AT even generates lack of other aspects relating to T helper cells variation, T cells acceptance, thymocyte improvement. Some prediction also show NF-AT on innate immunity providing cyclosporine a controlling activity on the adaptive and innate responses.(7)

Drug warnings	In a situation of high dose, two hours after intake of drug forced emesis and gastric lavage are noticed. Carrying on the high dose intake transient hepatoxicity and neprotoxicity are noticed. Eventually 150mg/kg are permitted in minor clinical circumstances. Significant intoxication testified on the overdose in premature neonates. On high dose of cyclosporine dialysis and charcoal hemoperfusion are not effective method.
PHARMACOKINETICS	
Absorption	Absorption of the cyclosporine are basically from the small intestine. Recent dosage of the cyclosporine drug was found to be improved bioavailability, AUC and Cmax than the oil based formulation. Though they have only narrow absorption and give 30 percent of the bioavailability. Cyclosporine shows the peak of

	concentration later then 1-8 hr of primary intake with 2nd peak. This 2nd peak of concentration is because of the increased absorption due to the parallel intake of meal because bile increases the absorption of cyclosporine.
Distribution	The relative volume of distribution of cyclosporine is 4-8 L/kg.
Metabolism	Metabolisation of the drug cyclosporine is I the intestine and by the CYP-450 isoenzyme group of the liver. They don't have any particular metabolic pathway of cyclosporine metabolism. Cyclosporine drug are found to be in 30 different meatobloties from which the most lively metabolite are appear to be 10-20 percent of its activity in contrast of parent compound, which are synergistically inactive. The utmost metabolites outcomes from the oxidation process at 1β, 1-b 9-gamma, and 4-N-demethylated positions, respectively.
Route of	It is believed that after cyclosporine sulfate conjugation as a major aspect of the metabolic pathway, this

elimination	compound can stay in the bile where it is debased to the first compound and re-assimilated. The disposal profile is essentially biliary with just 6% of the portion (parent medication and metabolites) discharged in the pee while 90% of the regulated portion is wiped out in the bile. Structure the discharged extent, under 1% of the portion is discharged as unaltered medication.

LITERATURE REVIEW

J.S. BOATENG et al.

Medication discharge physical qualities of lyophilized wafers and dissolvable films arranged from sodium carboxymethyl cellulose explored & examined about. Dissolution studies by in-vitro were implemented utilizing a trade cell and medication discharge was estimated 272 nm by the help of UV spectroscopy utilizing distilled water. According to this study. The dissolution profiles of hydrochlorothiazide from the wafers and film- were thought about by deciding the rate of medication discharge, assessed from the % discharge versus time profiles and claculating their distinction (f1) and similitude (f2) factors. The impacts of drug loading, polymer substance and measure of glycerol (GLY) (films) on the medication discharge attributes of the two definitions were examined. Both the wafers and films indicated continued sort discharge profiles that were best clarified by the Korsmeyer–Peppas condition. Changes in the grouping of medication and GLY (films) didn't altogether modify the discharge profiles while expanding polymer content fundamentally diminished the pace of medication discharge from the two definitions. The rate of discharge was quicker from the wafers than the comparing films which could be credited to contrasts in the physical microstructure. The outcomes show the capability of utilizing the two definitions in different mucosal medication conveyance applications.

- ***Terry .G. Coursey et al.***

As indicated by terry.g. coursey et just for the treatment of dry eye sickness in the course of recent decades, challenges despite everything stay in conveying thr therapeutic drug degrees of antinflammatory drugs at an convinient dosing schedule and ideal tissue fixations. This examination assessed the nanowafers drug delivery method to deliver the drug on the surface of the eye. The dexamethasone nanowafer are capable to increase the diffusion of the corticosteroid on the ocular surface and are help to keep up a smooth, health corneal surface and with undamaged barrier function in mice experimentally actuated to dry eye. Added to this dexamethasone nanowafers shows and successful effects in suppressing the inflammatory mediator for providing the lubricants on the ocular surface and removal of the dryness of the cornea. Mouse eye was shown the good tolerant during the administration of the dexamethasone nanowafer only twice a day whereas the administration of the topical eye drop of the dexamethasone. The less dosing of the dexamethasone nanowafer will progress the convenience to patient and increases the compliance to the patient of the dry eye syndrome. Moreover the discharge of dexamethasone drug from the nanowafer adjusted to decrease the concentration and to reduce the toxicity of concentration, this can cause the disease of eyes like glaucoma and cataract at higher concentration of the drug. This confirmed that nanowafers drug delivery system provides the therapeutic efficacy and the translation potential for the treatment of dry eye syndrome. This study conclude at last that dexamethasone nanowafer are used to treat the dry eye syndrome simple and successful than the conventional eye drops for the dry eye syndrome.

- ***Amelia M. Avachat&Pooja J. Takudage:***

Thisstudies indicates that thewound therapeutic formulation that of the lyophilized liposomal wafer for the treatment of wound curing. These lyophilizes liposomal wafer made for chronic wound. Formulation and development liposomal wafer are found to be more effective as it shows discharge of drug in a exact and controlled way & also for long duration at the site of wound as the wafers discharge the liposomes from the matrix of the wafer. Swelling of the matrix of the wafers moist the surface of the wound for faster healing. GTX concentration at targeted site is achieved. Lyophilized wafers should be smooth, flexible and swelling and better adhesion. From the overall studies lyophilized liposomal wafer is used for the chronic wound and GTX incorporation in the wafers gives the good therapeutic effect on the targeted site for the controlled and sustained release.

- ***Daniela C. Marcano, Crystal S. Shin***

This indicates the metabolic disorder named corneal cytosis generally cause by the acculumation the cysteine crystal which may cause opacity to the coraneal and make the person blind. For the cure of the corneal cystinosiscysteamine eye drops are available, that need to be introduced for six to twelve times in a day for whole period of time. Because of this many ocular side effects are observed that is eye inflammation or eye pain. Outcome of this treatment and compliance are compromised. To overcome with these issues cysteaminenanowafer are introduced which

are easily to application simply with the tip of the finger and after that it will dissolve slowly and vanishes on the ocular surface. Cysnanowafer are the stable for 4month as compared to the cysteamine eye drops as it freezes on storing of eye drop In the refrigeration and after that it will stable for only 1-3 weeks. Nanowafers helps in increasing the therapeutic effect and safety profile and stability at room temperature.

- ***SelinSedaTimura,SelinYüksela***

This studies is for the ocular cavity from the local drugs delivery are observed far better compared to the systemic administration for the oral infection treatment of the oral infection. This articles tells about film and wafers with the monolayer and bilayer formulation with the local delivery of the drug. This study uses the chitosan, HPMC, cefuroximeaxetil (CA) for the formulation. Some of the properties of the mechanical strength, water uptake and the smooth surface and in vitro adhesion and disintegration time for proper release of the formulation were examined. Moreover the antimicrobial action was examined under the E.coli and S.aureus. for the disintegration time more than 30 in HPMC were used in the formulation with chitosan which can remain on the surface about 6hours. Considerably for the higher dose of medication discharge was attained from the wafer formulation than the drug release from the film formulation. Activity of the Antimicrobial enhanced by chitosan and HPMC are used for the action of bilayered wafer formulation with the backing layer of chitosan and drug release from the matrix HPMC for controlled and long period of time. Which some properties like mechanical strength

and adhesive property and advised the promising drug delivery system.

- ***IssacAvensu Et Al.***

This indicates the lyophilized wafer made from the chitosan for the protein drug delivery from the buccal mucosa. Preparation of the lyophilised wafer from the aqueous gel consisting of mannitol, cryoprotectant with various concentration of the glycerol .these wafer formulation for the phyico-mechanical property were characterized for their optimization. In the formulation of optimization mininmum 6.5 mg each and plasticizer and cryoprotectant. These plasticizer and cryoprotectant are then loaded to the serum of bovine and lyophilizes and non lyophilized annealing. Lyophilisation cycle was determined by the differential scanning methodand was further evaluated by thermal event before feeze drying and possible separation of phase of bovine serum from after the freeze drying, properties like texture analysis was evaluation in vitro muco-adheive property of the by the tensile mode, moisture content of the wafer was evaluated by the thermo-gravimetric, and the drug release study was done by the phosphate buffer saline of 0.1 M further its crystalinity of the formulation was examined by the electron microscopy and also from the X-diffreaction method. As a result wafer shows that successful delivery for buccal mucosa transfering of protein contatined drugs

- ***Micheal E. Johnshon Et Al.***

This article studies on dry eye syndrome (DED) this is basically a diseases of the ocular surface with multiple aetiology of the dry eye disease. The main cause of this is due to thebreaking of the tear film or abnormal tear film. These tear film idiosyncrasies may cause by the lack of tear production,and insufficient formation of tear or supply of tear, irregular composition of tear. Dry eye syndrome destroys the haemostasis of tear film layer and its side layer of eye. Dry eye syndrome and also effect the capability to achieve the important function to the layer of epithelial cell. Pathogenesis of the dry eye syndrome has stimulation the therapeutic effect. This studies main goal is to achieve the dry eye disease development and contribution assembly, manufacturing and function of the dry eye syndrome.

- ***Shiow-Fern Ng***

The wafers are defined as the described as the gas dispersed on the solid matrix which contain the interlinked hole. Wafers are manufactured from the lyophilizer method. Over last 20 years this found an intresting for the formulation of wafer for the treatment of the wound. Specifically wafers are formed from the biopolymers such as cellulose derivatives, alginate, chitosan are used commonly as they contain less toxicity and also provide better mechanical property than others polymers and also has biodegradable property so that it can easily degrade on the site of action. Lyophilised wafer has vast prospective as a recent dressing method as it provides moisturiser at the surface of the wound and heal the wound. The wafers penetrate the exudate of the injury and converts the matrix into the gel, this gels

provide moisture to surrounding of the wound. Wafers contain biopolymer and active ingredients important for the curing of wound. Biopolymers wafers having drugs are act as a sustain discharge of the drug in a organised way from the matrix gelation of wafer. But the wafer's mechanism is not identified. Single and the main factor that influence the release of drug from the wafer is cross-linkage of hydrogel. The cross-linking method of the hydrogels may be physical and chemical in nature. Earlier the cross-linking of hydrogel are known as physical gel. The total work are held together by the by the chemical forces like hydrogen bonding, hydrophobic forces. On the other hand, substance gels are produced when they are covalently cross-connected, and ordinarily they can be framed with or without the option of cross-linkers.Drugloaded intohydrogels may reside in thesolvent pockets held with in the cross-linkages Endless supply of water (in light of lyophilisation), the medications become related with polymer chain cross-linkages. Consequently the communications of medication with the cross-linkages are thought to assume an indispensable job in controlling medication discharge.

- ***Kenneth Sall, MD,Onex Dara Stevenson, MD et al***

  Taking everything into account, this investigation exhibited that details of topical Cyclosporine A ophthalmic drug delivery of emulsion were very much endured and successful in the therapy of moderate to extreme dry eye illness. This was apparent through upgrades in both goal and emotional measures. The upgrades found in the abstract proportions of covered eye and the utilization of artificial tears confirm that the progressions found in the target

signs came about in significant benefits that changed the requirement for patients to utilize palliative medications. On the other hand the upgrades in two of the target indications of dry eye exhibit that CsA treatment isn't simply palliative in nature and that it along these lines speaks to the first helpful treatment specifically for dry eye malady and a significant advancement in the administration of this normal and disappointing condition.

- ***Nafishajumaat et al.***

In this study lyophlised wafer are successfully attain the antimicrobial activity with using different derivative of cellulose like methyl cellulose and sodium carboxy methyl cellulose. Both these derivative wafers are formulated contain properties like wafer flexibility smoothness, texture white colour and has odour acceptable NACMC/NC contain high uniformity of the drug in the wafer and also contain the high drug release rate. NACMC/NC wafers shows higher rate of the resistance gram positive and gram negative bacteria.

- ***Juliana Souza RiberioCoasta:***

This articles studies about the patient facing difficulty in swelling capsule tablet or having the fear of taking drug from the parentral route. To overcome with this problem many buccal and oral dispersion tablet dosage form this make easier for the patient compliance. Other than this no requirement of intake of water,

swallowing of tablet capsule, or needle are the dosage form allowed drug release modulation. Oral dispersion dosage form are also contain lyophilisation of wafer. Which have the faster releasing and disintegration rate compared to the conventional drug. Lyophilisation wafer stick on the surface of the mucosa and release of the drug in a sustained manner for long period of time. According to the recent study and research highlighted on the process of lyophilisation of wafer, formulation feature and treatment of the disease. This also comprise CQA (control of quality attribute) and CPP (control processing parameter) and also debated and experimental example. Added to this product of immediate release of medication contain biopolymers matrixes and formation method. Concluded to this wafers has capable for the sustain release of drug and also the stability of the drug. This assembled result of development of the new wafers for many disease and molecule of dug.

- ***Ramesh Y, GundalaPraveena, Gobinath M***

Medicated Wafers as novel medication conveyance system having a superior patient consistence and may offers to improve biopharmaceutical properties, improved adequacy and better security contrasted and the customary measurement structures. The Flash discharge wafer is promising because of the accessibility of

present day advances joined with all around manufactured market acknowledgment. Future opportunities for enhancements in quick dissolving drug conveyance framework are splendid. The current report presumes that Flash discharge oral Wafer is generally worthy and precise oral measurements structure which sidestep the hepatic structure and show progressively healing reaction. Quick dissolving Wafers have a few points of interest over traditional dosage form and quick dissolving tablets. Oral Wafers can displace the over-thecounter (OTC) medications, nonexclusive and name brand from showcase because of lower cost and consumer consistence.

- ***Joshua S. Boateng and Isaac Ayensu***

This examination includes the turn of events and functional characterization of a thiolated chitosan (CS) framework for potential buccal delivery of proteins to the patient. Thiolated CS was processed by conjugating CS with thioglycolic acid and dialyzed to evacuate overabundance acid. Measure of thiolweight immobilized on CS was resolved utilizing L-cysteine alignment bend. The weight normal weight of CS and thiolated CS were observed utilizing gel permestion chromatography. Overlaid wafers were gotten by pouring gels (containing bovine- serum albumin); BSA, various measures of glutathione as protein

inhibitor and mucin to mimic salivary state) of the thiolated CS into molds recently fixed with impenetrable ethylcellulose (EC) movies and freeze-dried. The subsequent plans were dissected utilizing lessened absolute reflectance Fourier change infrared (FTIR) spectroscopy, round dichroism (CD) and examining electron microscopy (SEM). The plans were additionally described for utilitarian buccal mucosa execution utilizing hydration, growing, mucoadhesion and in vitro medicate disintegration contemplates. FTIR indicated fruitful thiolation of CS's amine usefulness, CD affirmed that BSA compliance stayed unaltered all through the gel plan and freeze-drying process, while SEM demonstrated a permeable microstructure of the wafers and a uniform EC film cover with no obvious pores or splits. The practical description considers indicated that glutathione effectly affected hydration, mucoadhesion and in this way sedate disintegration and discharge qualities, while mucin influenced the mucoadhesive properties of the wafers. It was presumed that BSA-loaded wafers containing 10% w/w glutathione as chemical inhibitor was the detailing decision for potential buccal delivery and ought to be chosen for additional examinations.

- ***Kamal Singh Rathore1, Dr. Rajesh Kumar Nema***

Most of eye infections are treated with topical eye drops. The small bioavailability and advantageous answer displayed by these ordinary eye drops because of quick precorneal disposal of the medication might be overcome by the utilization of in situ gelling frameworks that are ingrained as drops into the eye and experience a sol-to-gel change in the circular drive. As of late, expanded consideration has been given to the improvement of new frameworks for the conveyance of visual prescription. Various visual conveyance frameworks extend the degree of medication activity by upgrade of corneal assimilation; these incorporate suspension, solvent gels and emulsions, hydrophilic visual supplements, particle pair affiliations, liposomes, niosomes, nanosuspension, nanoparticles and prodrugs. Other conveyance frameworks enrich with a controlled arrival of medications, consequently maintaining a strategic distance from the beat section with which symptoms are related. These frameworks can be founded on any of a few unique components, and incorporate both erodible and nonerodible lattices, wafers. Timolol maleate was the first β-blocker to be utilized as an antiglaucoma specialist and to date stays as the standard since none of the more up to date beta blockers were seen as progressively successful. Timolol maleate has the longest record of wellbeing and adequacy to bring down IOP and is regulated by means of eye drops at least one times each day. The basic advance is to build up a plan for timolol maleate that prompts continued conveyance for long time.

- ***Kenneth Sall, MD, Onex Dara Stevenson***

In summarizing of this study it is found to be critical to remember that there is presently no helpful treatment for dry eye sickness. The main medicines

accessible are palliative in nature and give insufficient alleviation to numerous patients, especially those with interminable moderate to extreme ailment. These patients are at expanded danger of visual surface harm and visual disease, just as being exposed to incessant visual uneasiness and visual difficulties. The information introduced here show upgrades in objective and abstract proportions of dry eye illness that are past what can be normal with other existing medications and along these lines are clinically significant. In addition, the adjustments in target measures propose the likelihood that treatment with topical CsA may likewise result in clinically significant changes in the movement of the illness and its sequel. All in all, this investigation exhibited that novel plans of topical CsA ophthalmic emulsion were all around endured and powerful in the treatment of moderate to extreme dry eye illness. This was apparent through enhancements in both target and emotional measures. The upgrades found in the abstract proportions of obscured vision and the utilization of artificial tears confirm that the progressions found in the target signs came about in significant benefits that adjusted the requirement for patients to utilize palliative medicines.

- ***Stephen C Pflugfelder Fang BianCintia S de Paiva***

Dry eye and tear brokenness are regular visual issue that cause cornea hindrance interruption bringing about an inadequately greased up and sporadic cornea epithelium, eye bothering and obscured vision. It influences a large number of individuals worldwide and is one of the most successive conditions for which patients look for eye care.Aging and female sex are noteworthy hazard factors for dry eye which increments in pervasiveness

around the fifth decade,with further increment consistently thereafter. Prevalence of dry eye changes from 2%to 50%, contingent upon the populace considered and the indicative models for dry eye(symptom survey versus objective signs).There is rare data about the regular history of dry eye, yet there is a perceived detachment among signs and indications; patients will in general be increasingly suggestive at early stages. Dry eye causes corneal anomaly and diminishes practical vision by modifying contrast affectability and, along these lines, diminishes personal satisfaction with a critical weight on the person just as the societyA meta-investigation of distributed examinations indicated expanded chances proportion for wretchedness and uneasiness in patients with visual Sjögren condition (SS). There is expanded proof that dry eye is an incendiary disease,and this survey will concentrate on grid metalloproteinases (MMPs) and their job in the pathogenesis of dry eye.

- ***Stefano Barabino***

The tear film, lacrimal gland , corneal and conjunctival epithelia and Meibomian organs cooperate as a lacrimal fluid unit (LFU) to save the intigrity and capacity of the ocular surface. The trustworthiness of this unit is important for the wellbeing and ordinary capacity of the eye and visual framework. Anxious associations and foundational hormones are notable factors that keep up the homeostasis of the visual surface. They control the reaction to interior and outside stimuli. According to the' investigations show that immunological components likewise assume a vital job in directing the visual surface condition. Our investigations exhibit how mitigating elements, for example, the declaration of vascular endothelial development factor receptor-3 (VEGFR-3) in corneal cells, juvenile corneal inhabitant antigen-

introducing cells, and administrative T cells assume a functioning job in ensuring the visual surface.

Dry eye disease (DED) influences a huge number of individuals worldwide and impacts the personal satisfaction for patients. In its most serious structures, DED may prompt visual impairment. The etiology and pathogenesis of DED remain to a great extent indistinct. Regardless, in this survey we sum up the job of the disturbance of afferent and efferent immunoregulatory components that are liable for the chronicity of the malady, its side effects, and its clinical signs. We delineate current calming medicines for DED and suggest that anticipation of the interruption of immune regulatory instruments may speak to a promising remedial methodology towards controlling visual surface aggravation.

- ***Henry D. Perry, MD; Renee Solomon***

Our investigation exhibits that in patients who have dry eye side effects and are obstinate to standard counterfeit tear treatment, cyclosporine may lighten signs and indications of the illness. Shockingly, the best suggestive advantage happened in the gentle patient gathering. Past examinations have concentrated for the most part on patients with moderate to extreme dry eye disease.4,8,11 Patients with serious dry eye are the most hard to treat and have the most issues enduring any eye drop medicine, including cyclosporine. We didn't discover any distinctions in results concerning the utilization of punctalplugs.The focal point of this examination was the adequacy of a Food and Medication Administration–endorsed sedate in patients with mellow,moderate, and extreme dry eye malady. There were no

articles in the friend audit writing assessing cyclosporine in patients with gentle or moderate dry eye infection. There was no requirement for a benchmark group in this examination to decide whether the medication was protected or successful, as wellbeing and viability contemplates were acted in stage 1, 2, and 3 investigations for the Food and Drug Administration. This was a postmarket investigation of the adequacy of cyclosporine in a patient populace with less serious infection than those recently examined. One of the impediments of the investigation is reasoning that the dynamic fixing and not the vehicle was answerable for the improvement. In any case, enlistment standards included just those patients who were inert to fake tears treatment. In this way, it is less likely that our outcomes are because of the impacts of the vehicle. The qualities of this examination are that it was forthcoming, enlisted an enormous number of patients, had a generally low quiet dropout rate, had suggestive OSDI testing at each visit, and had cautious consecutive assessment of indications of dry eye malady at each visit. The base time of follow-up was the period of time that it normally produces cyclosporine to take results, yet it would have been exceptional if the least follow-up had been a half year for all patients.

- ***Lade Milind S , Payghan Santosh A***

Wafers as novel drug delivery systems have morepatient compliance and could deliver much better Biopharmaceutical qualities, much better effective and better harmlessness contrast to standardised oral dosage structures.

Coming times, Flash release wafer will have potential assurance because of the accessibility of modern technologies integrated with well-developed market acquisition. Upcoming chances for improvisations in quick

dissolving drug conveyance method are bright. By the current information has been drawn that Flash release oral Wafer is more convincing and exact oral dosage type which goes past the hepatic system and has shown much therapeutic reaction. Quick dissolving Wafers have a number of benefits over standardised dosage forms and quick dissolving tablets. The pharmaceutical companies favor this dosage form because of both patient compliance (chiefly pediatric and geriatric) in addition to industrial admissibility. Oral Wafers can put back the over-the-counter (OTC) drugs, generic and name brand from market due to cheaper cost and consumer‘s conformation.

EXPERIMENTAL WORK

MATERIAL AND METHOD

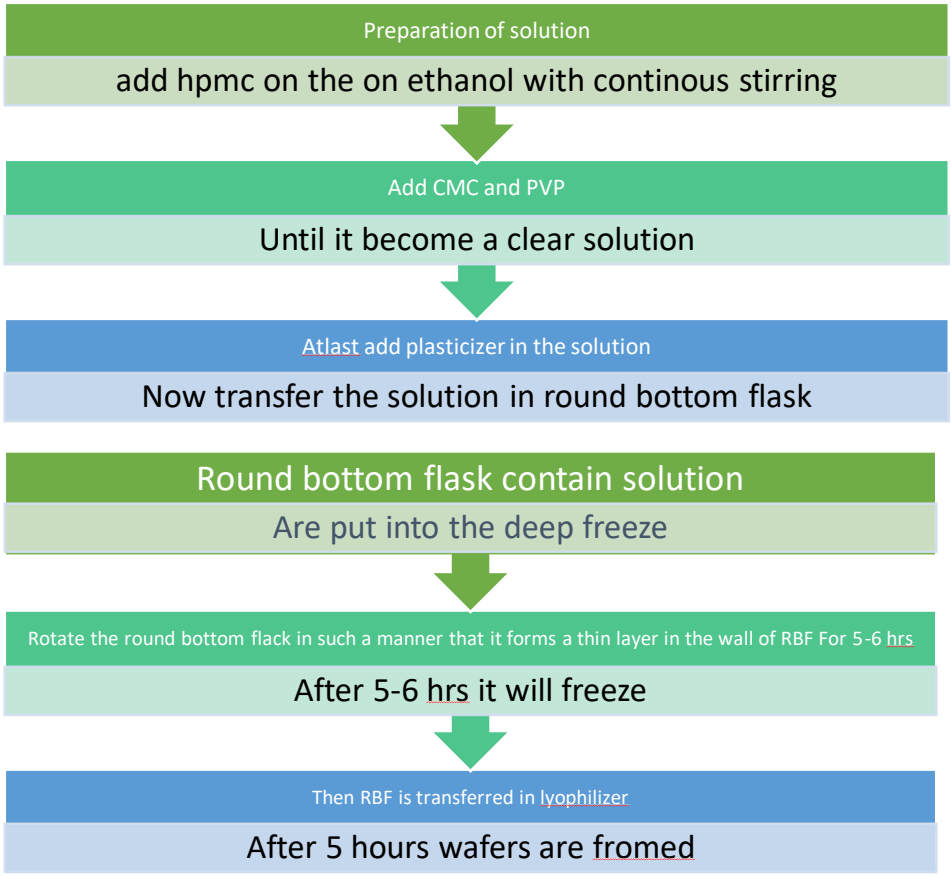
MATERIAL	USE
HPMC K 100	Polymer for sustained release
CMC	Thickening agent
PVP	Surfactant
Ethanol	solvent
Propylene glycol	Plasticizer

METHOD PREPARATION OF WAFER

- PREPARATION OF SOLUTION:
  - Added of the HPMC Polymer to the ethanol on the magnetic stirrer for the continuous stirringso that no lumps of HPMC formed.
  - After the addition of HPMC add carboxymethyl cellulose for the thickening agent of the wafers
  - Along with the carboxymethyl cellulose poly vinyl pyroovidone as a surfactant are added with the continuous stirring of the solution.
  - Stir the solution until it become a clear solution
  - At the end after the addition of the excipients Propylene glycol are added as the plasticizer to maintain the plasticity of the wafer and also add mannitol as a cryoprotectant.
  - After the preparation of the solution transfer the solution in a round bottom fla

➢ LYOPHILIZATION PROCESS:

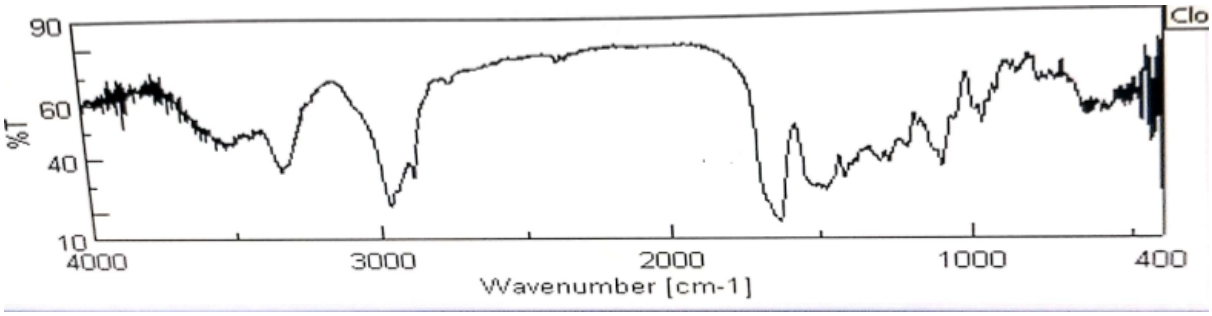
- PRETREATMENT -
- This above solution is then undergoes for the pretreatment then lyophilisation that is deep freezing of the solution.
- Deep freezer Space are fully dipped from the IPA (Isopropyl alcohol)
- Placed the round bottom flask inside the deep freezer and rotate the round bottom flask on such a manner that it forms a thin film inside the wall of the RBF.
- It takes 5-6 hours and will crystallized inside the wall
- Afterwards the round bottom flask was placed to the lyophilizer (freeze drier)
- Later on completion of lyophilisation process dried product wafer are formed.



- **PREFORMULATION:**

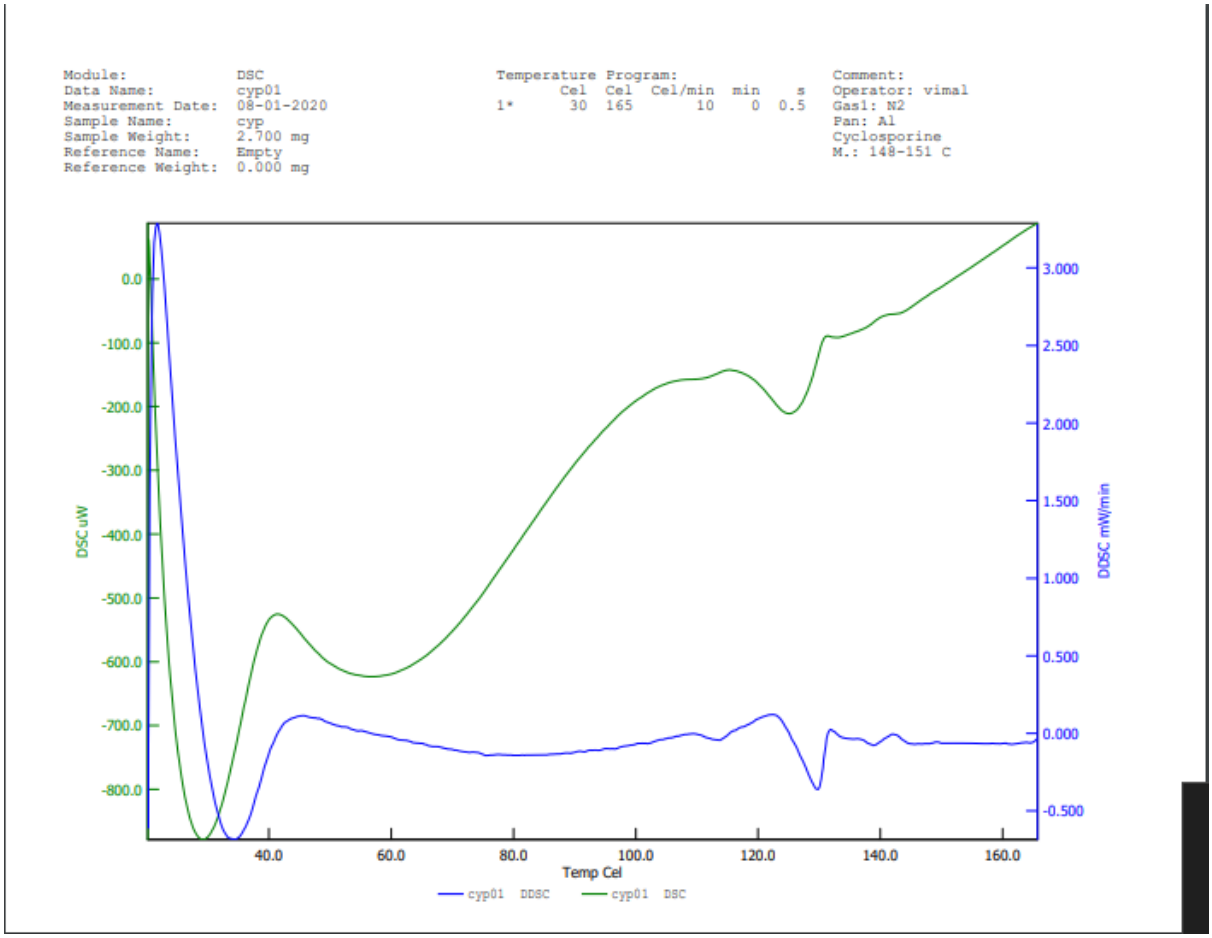
1. CHARACTERIZATION OF DRUG:

- **FT-IR of cyclosporine**



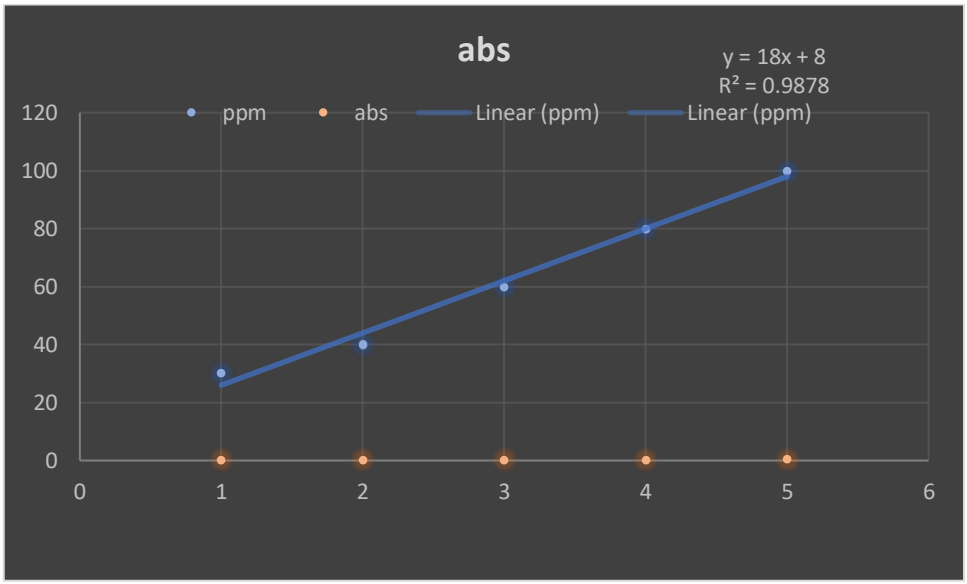
Frequency	Functional group	Types of strechinh
3300-3500	Amine group	N-H strech
1670-1780	Carbonyl group	C=O strech
2850-2960	Methyl	C-H strech

2. DSC of cyclosporine



- Calorimetric estimations were completed by utilizing a DSC. Roughly 5 mg of tests were set on the DSC pan (5 mg) made of aluminum pan and fixed. DSC follows were recorded somewhere in the range of 30 and 165°C**.**
- DSC Thermograph of the cyclosporine exhibited at endothermic peak at 139.51ºc

3. Uv of cyclosporine



STANDARD CURVE OF CYCLOPORINE

REGRESSION ANALYSIS

REGRESSION PARAMETER	VALUE
Correlation factor	0.9878
Slope	18
Intercept	8

FORMULATION OF SIMULATED TEAR FLUID

Composition (mg/mL)	**Simulated Tears**
• Sodium bicarbonate	- 192.4
• Potassium chloride	- 111
• Calcium chloride (1)(as CaCl2·2H2O)	- 2.29
• Sodium chloride	- 672.8
• Albumin	- 669
• Glucose	- 2.5
• Properties	
• pH	- 7.4

STANDARD CURVE OF CYCLOSPORINE IN SIMULATED TEAR FLUID

Preparation of stock solution

10 mg of cyclosporine was accurately weighed and transferred in 10 ml in volumetric flask. It was dissolved in the silmulated tear fluid with (pH 7.4) and the volume of solution made up to the mark with the simulated tear fluid (pH 7.4) to get 100 µg/ ml solution.

Preparation of standard curve in Simulated Tear Fluid:

From the stock solution 1, 2, 3,4, 5 ml sample were now shifted to the 10ml volumetric flask and then diluted with the distilled water. . The wavelength maxima of cyclosporine in the solution was found to be 210nm. Absorbance of each solution was measured at 210 nm.

FORMULATION AND DEVELOPMENT

Selection of excipients

excipients	USE
HPMC k100	Polymer for sustained release
CMC	Thickening agent
PVP	Suspending agent
Ethanol	solvent
Propylene glycol	Plasticizer

BATCHES:

Trials 1	QUATINTY
HPMC 5CPS	1g
ETHANOL	12ml
PROPYLENE GLYCOL	20% of polymer

RESULT & DISCUSSION: In this trial solution were kept in the biofreezer for 24 hours and -20º C temperature. But the issues involves in this batch as it could not freeze when it kept into the biofreezer rather than deep freeze as a resultit will not form crystal layer on the surface of the round bottom flask it was remain in liquid state. So it will not processed further for the lyophilisation.

Trial 2	
Hpmc k100	**0.5g**
Cmc	**2.0g**
Pvp	**0.5g**
Ethanol	**7.0ml**
Propylene glycol	**30% of polymer**

RESULT &DISCUSSION: in this batch HPMC K100 grade was used as it has the property of sustained released of drug. solution of this batch was kept for 1hour at -20 ºc as a result after the pre freeze solution it forms a crystal

inside the wall of the round bottom flask. After the lyophilisation process it forms a thin layer which in turns forms a powder on scrapping the product.

Trial 3	
Hpmc k100	1.0
Cmc	3.0
Pvp	2.0
ethanol	8.5

RESULT& DISCUSSION: This batch consist of CMC is used as a thickening agent and PVP as a surfactant for the formulation of wafers. After it forms clear solution Pre-freezed for 4-5 hours and at the -80 temp. And further processed for the lyophilisation this result in the formation of wafer inside the surface of the RBF.

Fig6: lyophilisation process of solution

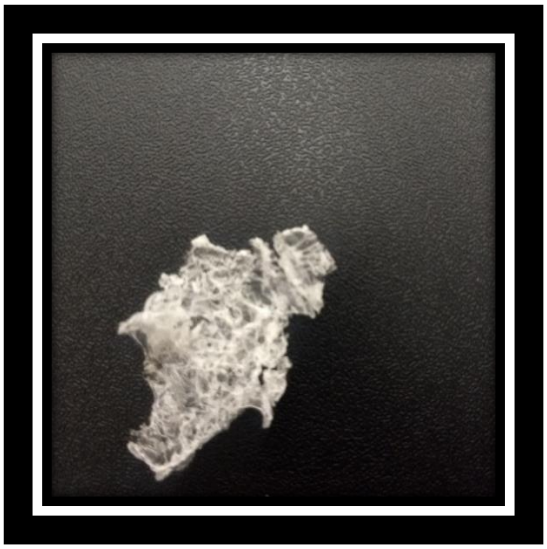


Fig 7: formulated wafers after lyophilization

Conclusion:

From the information I have drawn that wafers for the dry eye syndrome found to be more convienient from the aspect of patient and also from the manufacturer as Drug delivery through wafers for dry eye syndrome are the convenient drug delivery. Drug delivery from the wafer releases the drug in a sustained and in a controlled manner. Wafers increases the bioavailability upto 5-10% compare to the other opthalmic drug delivery wafers are present for the longer duration at precorneal site which to provide therapeutic effects for longer duration and also it gives the better therapeutic effects as it completely dissolves at theprecorneal site and vanishes.Some of the study likeevaluation parameters : Organoleptic evaluation , Mechanical properties Thickness, Dry test, Tensile Strength Percent, Elongation Tear Resistance, Folding endurance, Swelling properties Assay/Content uniformity, Disintegration time ,In-vitro Dissolution test Stability testingetc are the parameter that supposed to be study for this project but due COVID-19 pandemic it was not executed further

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