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OCULAR EMULGEL: A NOVEL DRUG DELIVERY SYSTEM

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Abstract

The ocular drug delivery system is considered as crucial and challenging and difficult due to rapid removal of instilled drug due to low resident time in ocular tissues. Moreover, the conventional opthalmic formulations exhibit a short pre-corneal residence time and poor bioavailability. Newer research in ophthalmic drug delivery systems is directed towards incorporation of several drug delivery technologies, that includes to build up systems which is not only extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug. Emulgel is one of the novel strategy widely employed in various ocular problems. Emulgels are nothing but, the combination of emulsion and gel. It is emulsion, either of water in oil or oil in water type, which are gelled by mixing with gelling agent such as HPMC, carbopol etc. Emulgel has several constructive properties such as being thixotropic, emollient, easily spreadable, easily washable, greaseless, non-staining, water-soluble, greater shelf life, bio-friendly, clear and pleasant appearance.

Keywords: Emulgel, hydrophobic drugs, gelling agents, ocular drug delivery.

I. INTRODUCTION

Ophthalmic delivery offers several potential routes of administration and the selection of the promising route is mainly dependent on the target tissue. Topical, local ocular (ie, subconjunctival, intravitreal, retrobulbar, and intracameral), and systemic delivery are the most frequently used approaches of ocular drug delivery. Topical instillation of drug to the eye is the most desirable method of administration, considering that it is easy handled and cost effective. Topical drug instillation is handful when it comes in the management of disorders affecting the anterior segment of the eye (Neslihan U. 2020).

A gel is a jelly-like material with a three-dimensional crosslinked network of colloidal solid particles within which miraculous amounts of aqueous or hydro alcoholic liquid could be entrapped (Shen Y. et al. 2015). Development of ophthalmic drug delivery systems has always been an inspiring and challenging field for formulation scientists because of the drawbacks like anatomical, physiological, and biological barriers. These barriers reduce the efficacy of treatment used. Topical eye drops are the main dosage form used for the treatment of ocular tissues. Less than 5% of eye drops instilled cross the cornea to reach ocular tissues. Several factors affect their retention time such as blinking reflex, excessive tear turn over, lacrimal secretion drainage, non-productive absorption, impermeability of drugs to cornea, rapid dilution, elimination through nasolacrimal drainage, and other elimination mechanisms. Over the years, formulation scientists focus their efforts on developing dosage forms that prolong the retention time of drugs in the eye (Sreevidya V. 2019). Topical application of drugs to the eye is the well-established route of administration for the treatment of various eye diseases like dryness, conjunctivitis, keratitis, eye flu etc. New approaches have been investigated for delivery of drugs to the eye by making use of polymers that pays a key role in delivery of drugs to the pre and intra ocular tissues (Rukari T. et. al.2019). Such persistent attempts have resulted into achieving the increase in bioavailability and extending the duration of therapeutic action of ocular drug (Patil S. et. al. 2015). Emulgel is prepared both in oil- in- water and water- in- oil type emulsion mixed with gel. Oil- in- water type is used for lipophilic drugs and water- in- oil type is used for hydrophobic drugs' delivery. Several strategies were investigated and developed such as gels, ointments, minitablets, in situ formulations, drug releasing contact lenses, nanoparticles, liposomes, implants, and inserts (Sabry S. et al 2021, Gote V. et al.2019, Kelly L. Salwa K. 2021).

II. ANATOMY OF EYE

Anatomical view of human eye The eye is a slightly asymmetrical globe, about an inch in diameter. The front part of the eye (the part you see in the mirror) includes as shown in "Fig.1"

- The iris
- The cornea
- The pupil
- The sclera
- The conjunctiva

Just behind the iris and pupil lies the lens, which helps to focus light on the back of the eye. 80% of the eye is filled with a clear gel called as vitreous. Light passes through the pupil and the lens then it will reaches back of the eye. The inner part of the eye is protected by special light-sensing cells are together known as retina. The retina transforms light into electrical impulses. Behind the eye, the optic nerve conveys these impulses to the brain. The macula is a small extra-sensitive area which is present in retina that gives central vision. Which is located in the center of the retina and contains the fovea, a small depression or pit at the middle of the macula that gives the clear vision (Patil S.et. al. 2015, Ashir T.et. al. 2017).

The molecules up to 20,000 Da can cross the conjuctiva, while the molecules up to 5,000 Da can cross the cornea. The human conjuctiva shows 2-30 times more permeable for drugs than cornea and also loss of drug by this route is a major path for drug clearance. A thin fluid layer is covering the exposed part of the eye called as precorneal tear film. The film thickness is about 3–10 mm depending on the measurement method with the resident volume approximately 10 µl. The osmolality of the tear fluid is approx. 310– 350 m Osm/kg in normal eyes and is maintained by the monovalent and divalent inorganic ions present in fluid such as Na+, K+, Cl-, HCO3-, and proteins. The mean pH of normal tears is about 7.4. Diurnal patterns change the pH of tear, which is a general shift from acid to alkaline during the day. The buffer capacity of the tears fluid is determined by bicarbonate ions, proteins, and mucin (Sreevidya V.S. 2019). Tears exhibit a non-Newtonian rheological behavior with viscosity is about 3 m Pas. The mean surface tension of tear film value is approximately 44 m N/m (Patil S.et. al. 2015).

III. MECHANISM OF OCULAR DRUG ABSORPTION

Small drug molecules can efficiently cross the mucosal membrane whereas some drugs and peptides unable to cross the mucosal membrane. Simple solution have very low bioavailability when the drug is instilled into the eye firstly it penetrate through cornea and then through non corneal routes. The drugs which absorb poorly through cornea are diffused across cornea and sclera as given in “Fig.2” (Rukari T. et. al.2019).

IV.TYPES OF CONVENTIONAL DOSAGE FORMS

a) Solutions

Ophthalmic solutions are sterile, isotonic, which may be aqueous or oily preparation including emulsion & suspension of one or more active ingredients meant for instil into the eye, were the drug will absorbed or adsorbed into the eye to produce intended action. They may contain recipients which regulate osmotic pressure, pH, and viscosity of the preparations, some times which may or may not use preservative also.

b) Ointment

These are semisolid dosage forms which are meant for external use, generally it contains solid or semisolid hydrocarbon base of melting or softening point which resembles to human body temperature. After applying the ointment to the eye, it will converts into small drops, which remains for a long duration of time in conjunctival sac, thus increasing drug’s bioavailability. Eye ointments have few disadvantages such as blurring of vision and sometimes have irritating effects in eye, because of which they are mainly applied night-time, although they are safe and well tolerated.

c) Gels

Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. Instead of giving multiple doses in case of solutions the dosing interval can be reduced in case of gels. Cellulose acetate phthalate dispersion constituted a microreservoir system of high viscosity.

d) Emulgels

Emulgel is prepared both in oil- in- water and water- in- oil type emulsion mixed with gel. Oil- in- water type is used for lipophilic drugs and water- in- oil type is used for hydrophobic drugs’ delivery (Ashir T.et. al. 2017).

V. TYPES OF SUSTAINED DRUG DELIVERY SYSTEMS

In the novel drug delivery system various approaches like In situ gelling, use of mucoadhesive polymers, polymer coated Nanoparticles and Liposomal formulations are used. These delivery systems delay the elimination of active ingredient from eye and also improve corneal penetration of drug molecule.

a) Liposomes: Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter. They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption (Przemys B. et.al. 2014).

b) Niosomes: Niosomes are non-ionic surfactant vesicles that have potential applications in the delivery of hydrophobic or ampiphilic drugs. Niosomes are developed as they are chemically stable as compared to liposomes, non toxic and do not require special handling techniques (Przemys B. et.al. 2014).

c) Implants: For chronic ocular diseases like cytomegalovirus (CMV) retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs (Przemys B. et.al. 2014).

d) Dendrimers: Dendrimers are large and complex molecules with well-defined chemical structure. Dendrimers can successfully use for different routes of drug administration and have reported to have better water solubility, bioavailability and biocompatibility. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups (Przemys B. et.al. 2014).

e) Nano suspensions: Nano suspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of Nano suspensions, techniques like media milling and high-pressure homogenization have been used (Przemys B.et.al. 2014).

f) In situ gel

Forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel–sol) and pseudo plastic behavior to minimize interference with blinking. Such a system can be formulated as a liquid dosage form suitable

to be administered by instillation into the eye which, upon exposure to physiological conditions, changes to the gel phase, thus increasing the pre-corneal residence time of the delivery system (Roberta C.et.al 2021, Mandal G. et al. 2012).

VI. METHOD OF PREPARATION

Emulgel are prepared by **incorporating gel and emulsion**. The emulsion and gel are prepared separately and mixed together. For preparing emulsion, aqueous phase and oil phase are taken separately and mixed together. Then the gel is prepared by using gelling agent (Meshram S. et. al. 2015, Khullar R. et. al.2012).

VII. DIFFERENT INGREDIENTS OF EMULGEL FORMULATION

a) AQUEOUS MATERIAL: This forms aqueous phase of the emulsion. Generally, water is used.

b) Oils: The oil phase is important in the formulation of all type of emulsion like microemulsion, nanoemulsion. Usually, the oil, phase has the maximum solubilizing potential for the drug candidate. The choice of the oily phase is always a compromise between its tendency to solubilize the drug and its capability to facilitate the formation of the respective emulsion with desired characteristics. Few examples of Oils which are used in emulgel are like wheat germ oil, rose hip oil, isopropyl myristate, balsam oil, birch oil, castor oil and myrrh oil etc (Kumar et. al.2016).

c) Emulsifying Agents: Emulsifying Agents are used to stabilize emulsion and control emulsification process. The stability of emulsion can be enhansed by addition of suitable emulsifying agent, as they are thermodynamically unstable. Surfactants with greater than 8 HLB values such as the nonionic surfactant like spans and tweens are used in the formulation of oil in water (o/w) emulsions, whereas mineral types oil such as liquid paraffin have less than 8HLB value are used in the formulation of w/o water in oil emulsions (Kumar et. al.2016).

d) Permeation enhancer: These are the agents which helps in absorption of drug through the skin by temporarily thinning the impermeability of the skin. Ideally, these materials should be inert in nature and compatible with drugs and other excipients. Oleic acid, clove oil and menthol are used as penetration enhancers in emulgel (Kumar et. al.2016).

e) Gelling Agents: Agents which are added to form gel base known as thickening agents which can expand the consistency of preparation by swelling in the aqueous phase and forms gel like structure. Incorporation of gelling agent to a system makes it thixotropic. After incorporating emulsion into gel base can form emulgel. HPMC Carbopol. NaCMC Pemulen are used as gelling agents to prepare gelbase (Kumar et. al.2016).

VIII. PROCEDURE OF PREPARATION OF EMULGEL: IT IS CARRIED OUT IN THREE STEPS

Prepare gel: Using suitable gelling agent and allowe to hydrate. Add other ingredients to the aqueous dispersion with continuous stirring. Add required quantity of drug and mix properly. The dispersion can neutralized to required pH. and adjust final weight with distilled water. Lastly remove air bubbles by any means (Kumar et. al.2016).

Prepare Emulsion: Depending upon requirement O/W or W/O emulsion can formulated.

Incorporate emulsion into gel base: Finally incorporate emulsion in gel base to form emulgel.

IX. TERNARY PHASE DIAGRAM

Generally, emulsions are dispersed systems of different ratios of oil, surfactant(s) and aqueous phase. The different phases, their behavior and changes in volume fraction of different phases of the system can be checked by using pseudo ternary phase diagram. The different phases, their behavior and changes in volume fraction of different phases of the system can be checked by using pseudoternary phase diagram. A system consisting of water, oil, surfactant (or surfactants mixture) with various phases may be depicted on a phase tetrahedron whose apexes, respectively, present the pure components. The phase behavior can easily report on pseudoternary triangles. For making a productive formulation, study of phases obtained from several combinations of oil, surfactant/surfactant and co-surfactant mixture, water and their behavior is required (Kok K. Peh and Haroon k. Syed 2014).

Construction of ternary phase diagram

Pseudoternary phase diagrams comprises oil, Smix, and water can developed using the oil titration method, specific ratio of Smix (1:1,1:2,1:3,2:1, and 3:1), water take in test tubes and vortex for 5-10 min followed by add oil with a micropipette, the addition of oil continue till addition of one more drop produce turbidity. They are also visually observed for phase clarity and flowability. Note the volume of oil phase. The phase diagrams can construct using chemix software (Karishma Tole and Ganesh Deshmukh 2018).

X. EVALUATION OF EMULSION

Viscosity Cone and plate rotational viscometer with spindle can be used to measure viscosity Mandal G. et al. 2012).
pH:- pH can be measured by digital pH meter (Tahura.S.Sayeda, Dr. Iffath R. 2021).
Drug content:- Drug-loaded emulsion can be tested by extracting drug from the emulsion in an suitable solvent. Amount of drug can be estimated by UV visible spectroscopic method.
Centrifugation: - It is used to evaluate physical stability. Centrifuge the Emulsion at ambient temperature and observe visually for physical stability of emulsion.
Conductivity Electric conductivity of emulsion could be to estimate type of emulsion. It can be carried out by using suitable conductometer.
f) Dilution Test:- Dilution of emulsion could be carried out and visually checked for phase separation and clarity.
g) Zeta potential and Micelle Size Analysis: - Micelle size, size distribution and zeta potential of emulsion could be determined using particle size analyzer (Ashara K. et.al. 2016, Khullar R. et. al.2012).

XI. EVALUATION OF EMULGEL

a) Physical Examinations: - Physical examination like Color, homogeneity, consistency and texture. (Tahura.S.Sayeda, Dr. Iffath Rizwana 2021).
b) pH: - The pH of emulgel can be to measure by using digital pH meter. (Tahura.S.Sayeda, Dr. Iffath Rizwana 2021).

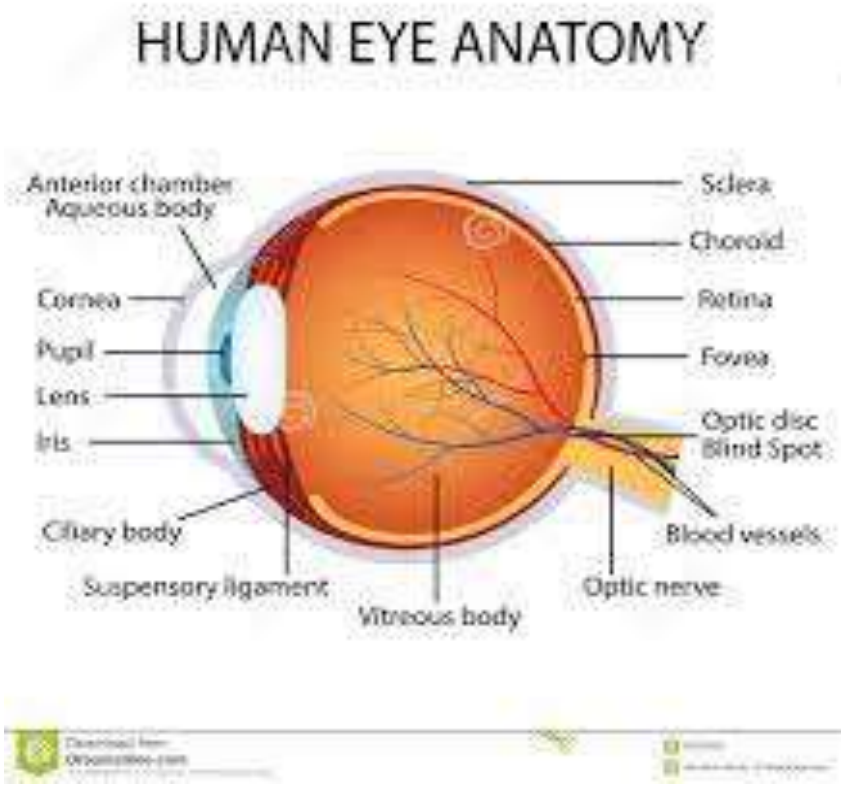
c) Syneresis measurement test: - On rest gel shrinks and little liquid is pressed out called syneresis. This could be measured by means of centrifuge tubes in specific apparatus.
Syneresis (%) = liquid separated from emulgel / Total weight of emulgel before centrifugation X 100.
d) Rheological study: - Mainly viscosity can be determined at 37℃ by the rheometer. (Mandal G. et al. 2012).
e) Drug content determination:- Drug content in emulgel could be estimated by the official method prescribed in pharmacopoeia for a drug. (Tahura.S.Sayeda, Dr. Iffath Rizwana 2021).
f) Tube test (extrudability test) Determines force necessary for removal of emulgel from tube and necessary to evaluate emulgel formulation for extrudability.
g) Diffusion study:- The in vitro release of emulgel can performed in simulated lachrymal fluid (SLF) and Franz diffusion cell also by modified method using magnetic stirrer and dialysis membrane (M. WT 3500Da) or By D-cell at 37oC using rat skin or dialysis-bag method. (Rao M. et.al, 2013).
h) Microbial assay of emulgel:- To assure the sterility of emulgel. The sterility test should be carried out. Ditch plate technique could be preferred for microbial assay and zone of inhibition should be calculated (Y.Shen et al. 2015, Patil S. et. al.2015).
i) In vivo eye irritation assessment:- It can be carried out by using rabbit (Y.Shen et. al. 2015, Mandal G. et al. 2012).
j) Isotonicity evaluation :- Isotonicity is important characteristic of the ophthalmic preparations. All ophthalmic preparations are subjected to isotonicity testing (Meshram S. et. al. 2015).

XII. VARIOUS MARKETED EMULGEL FORMULATION:

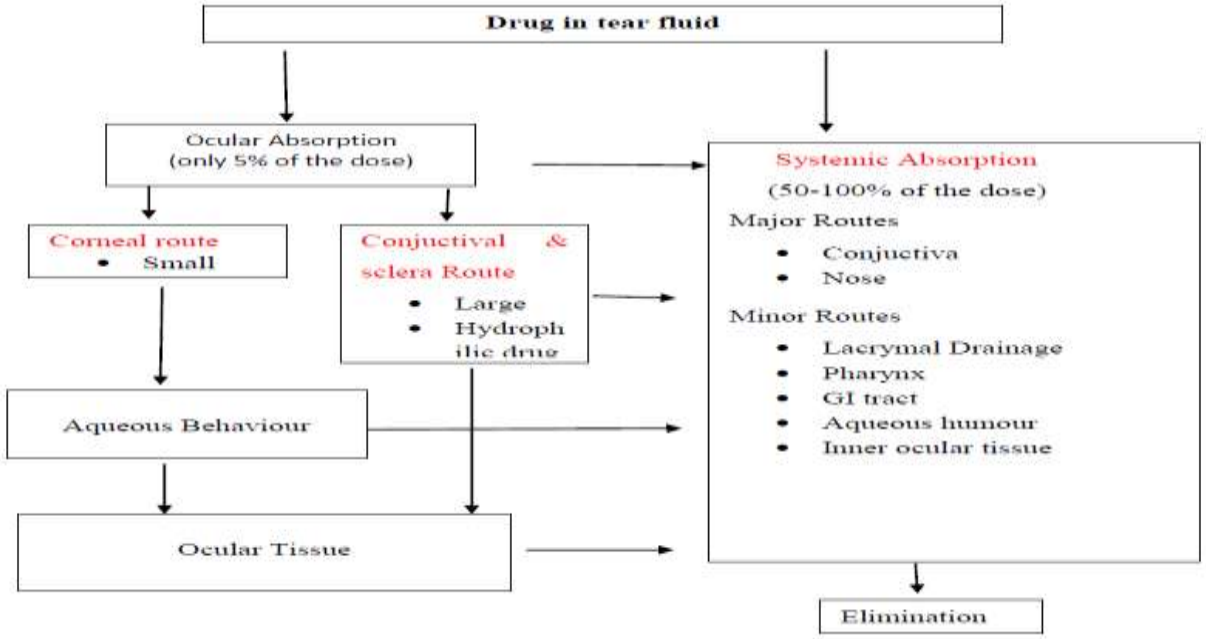
Emulgel are commercially available in markets; some preparations of which are listed as following in Table. Voltaren Emulgel is a topical analgesic gel that provides relief in shoulder pain, back pain and reduces swelling. Voltaren Emulgel is non-greasy, white pleasant-smelling gel which is available in a 100g tube having active ingredient diclofenac sodium one percent w/w (as diclofenac diethylamine). Another emulgel is Diclomax Emulgel which is used in treatment inflammation of the tendons, ligaments, muscles and joint and manufactured by Torrent Pharma. Miconaz H emulgel which is manufactured by medical union pharmaceuticals having active ingredient miconazole nitrate and hydrocortisone possess bactericidal, fungicidal, anti-inflammatory and antipruriginous properties (Kumar et al. 2016).

XIII. CONCLUSION:

The conventional dosage forms for ocular drug delivery is the challenging task for researchers now a day's. In order to overcome several disadvantages related to conventional dosage form a novel ocular emulgel drug delivery system has proved to be beneficial as compared to the conventional drug delivery. Likewise it is also challenging enough to establish successful ophthalmic drug delivery systems. However, the persistent attempts towards advancement in the understanding of principles and processes governing ocular drug absorption and disposition have led to the improvements in the efficacy of ophthalmic delivery systems. One such novel approach is development of ocular emulgels. Good stability and biocompatibility characteristics make the in emulgel dosage forms very reliable. Use of biodegradable and water soluble material for the emulgel can make them more acceptable and excellent drug delivery systems. Also can be administered in drop form and produce appreciably less inconvenience with vision. This type of dosage forms are used now a day in combat glaucoma, dry eye syndrome, Jorgen's syndrome, ARMD, trachoma etc.



"Figure 1"



"**Figure 2**"

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