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Review Article

OCULAR DRUG DELIVERY: ASSORTED OBSTRUCTIONS AND CONTEMPORARY PROGRESSES

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ABSTRACT

Carriage of medicaments assigned in the forms of conventional dosage is restricted to the eye; moreover, favorable drug concentrations in the destination tissues are not kept up for an extended time spread given that the eyes are escorted via an inimitable anatomy, physiology and biochemistry. The clear-cut aim of designing a therapeutic system is to attain a desirable concentration of a drug at the active site for the relevant duration. A successful design of a drug-delivery system, therefore, desires an integrated knowledge of the drug molecule and the restrictions offered by the ocular route of administration. In last decade, with the emergence of miscellaneous powerful and multifaceted medicinal substitutes, the assortment of traditional ophthalmic preparations has progressively developed; drawing out considerably apart from ordinary solutions, suspensions and ointments, presently comprises a diversity of drug administration formats. Present communication echoes miscellaneous barriers and successive blossoms in the field of ocular therapeutics.

Keywords: Ocular drug delivery, Ophthalmic, Ocular, Ocular obstruction.

INTRODUCTION

Ocular drug delivery is one of the most appealing and arduous endeavors facing by the pharmaceutical scientist. The primitive ophthalmic solutions, suspensions and ointment dosage forms are unquestionably no longer satisfactory to combat some current virulent diseases. An analysis write-up proclaims that almost 90% of ready for use ophthalmic formulations in the US, and an equivalent percentage is still supposedly valid for the present international trade. The proportionate percentages were 62.4% in favor of solutions, 17.4% for ointments and 8.7% for suspensions. In spite of the constraints of swift elimination from the precorneal cavity of eye, ocular formulations in the form of solutions are still granted highest precedence by formulators because they are comparatively uncomplicated to prepare, refine and disinfect [1].

On the ground of anatomy and physiology eye is a complex and incomparable structure guarded by a number of defensive attitude machineries. The framework, biochemistry, and physiology of the eye set down this organ tremendously impervious to strange entities [2]. Assorted adaptations guarding the eye from noxious entities and agents such as lacrimation, reflex blinking, rapid tear turnover, drainage, and pre-corneal loss concludes in remarkably inadequate absorption of topically executed ophthalmic drugs. As a

consequence intermittent installation of significantly concentrated solutions or suspension of drug is needed [3]; substantial volume of the instilled dose is desired (up to 50 µl vs. 7-8 µl of the tear film) [4]; annoyance in the eye due to drug penetration; drug solubility and stability in the eye fluids, trouble in passing the blood-corneal barrier [5]. The pre-corneal half-life is supposed to be 2-3 minutes following installation of a surplus volume of fluid. Usually less than 5% of the topically assigned drug penetrates the cornea and attains the posterior segment of the eye [6]. A bigger divide of the introduced dose is absorbed systematically through the nasolacrimal duct. This may give rise to systemic adverse effects such as tachycardia, hypertension and bronchial asthma [7]. Fate of the drug on topical ocular application can be explained by fig. 1.

In the domain of formulation buildup of ophthalmic dosage form, preeminent constrained is inadequate corneal residence time of the drug molecule, turning out in indigent pharmacotherapeutics. In order to sort out this annoyance, a number of efforts were brought off in the former eras by formulating miscellaneous ophthalmic drug-delivery systems in disparate forms such as oil derived preparations, high viscosity eye drops, ophthalmic inserts, emulsions, particulate carriers, liposomes, soft contact lenses, hydrogels, collagen shields, dendrimers and trans-corneal iontophoresis, etc. Whole of the attempts made throughout the former times were enforced with an objective to overthrow the prompt elimination of active agent from the precorneal cavity of the eye and to uplift the corneal residence time of the drug molecules. Over the last decade, assorted newborn systems

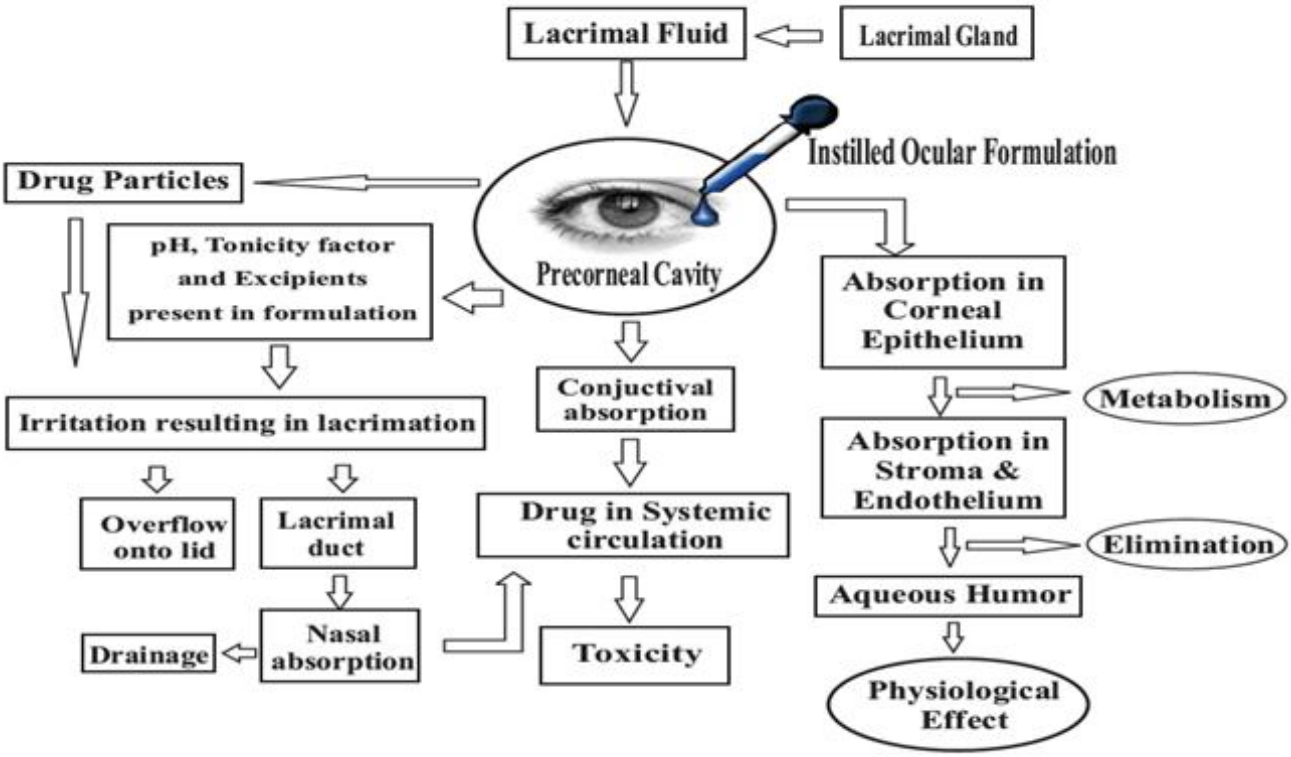

Fig.1. Fate of the drug administered on topical ocular application

An absolutely censorious question to the formulator is to vanquish the sheltering boundaries of the eye without conferring imperishable tissue devastation, evolvement of newer, additionally approachable diagnostic arrangements and innovative therapeutic agents continue to serve ocular delivery systems with high remedial efficacy [8].

such as liposomes, microparticles as well as nanoparticles, intended for the ophthalmic administration of active drug moieties has been developed, and such formulations claim prolonged action accompanied by convenient application of formulation in eye drop form. The objective of pharmacotherapeutics is to treat a disease in a steady and

anticipated fashion. A hypothesis is made that a correlation exists between the concentration of a drug at its intended site of action and the subsequent pharmacological effect [9]. The clear cut aim of designing a therapeutic system is to attain a desirable concentration of a drug at the active site for the relevant duration [10]. Ocular disposition and elimination of a therapeutic agent is relying on its physic chemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug-delivery system, therefore, desires an integrated knowledge of the drug molecule and the restrictions offered by the ocular route of administration [11].

Various snags associated with ophthalmic drug-delivery systems

In spite of the fact that topical administration accesses many advantages to treat disorders of anterior structures within the eye, it suffers from a serious disadvantage of poor bioavailability owing to a number of biological influences, which exist to safeguard the eye and as a repercussion limits the entry of ocular drugs [9]. The limitations in topical delivery to the eye are conversed below.

Insubstantial space of the Lower Conjunctival Sac (cul-de-sac)

Lower conjunctival sac (cul-de-sac) is the adopted location for the instilment of eye drop formulations. For the instillation of eye drop formulation, dragging downward the lower eyelid skin of the lower conjunctival sac molds a funnel-shaped reservoir providing capacity to take in highest volume of 25 mL, provided that this volume is supplemented rapidly [12]. On setting free eye lid to revert its primary location, the volume of the conjunctival sac shortens by 70% - 80% i.e. less than 10 mL. The space of the conjunctival sac is in addition insubstantial for untaught, incompliant, or impaired patients. Conjunctival pathologies such as the cicatricial, hypersensitive or inflammatory protocol will additionally restrict the volume of the conjunctival sac.

Tear discharge

In the stable state, on the ocular surface the volume of the tear film is about 7 ± 2 µL[4]. The degree of discharge of the tears has been stated 1.2 mL/min. In an unexcited human eye, tear reversal count in a minute is closely 16% of the whole tear film volume. Whenever an annoying stimulus excites cornea and conjunctiva, reflexive lacrimation takes place consequenting in the increase of the tear film volume to about 16 ml, with a range of 5 to 66 mL [13]. Any circumstance, involving formulation parameters founded for the solvability and stability of instilled preparation may set going tearing from eye and will follow up in immediate wash out of instilled eye drop. Usually eye drops are instilled in sizeable volumes (50 mL) to the lower conjunctival sac and in this range, the unprovoked tear turnover was apparently appraised to play at most an insignificant function in the waste of instilled drug dose [14].

Involuntary nictitating phenomenon

Involuntary nictitation of the eye is pompous protection machinery, which is normally rapid, adequate to come before unfamiliar subject matters accessing the eye and is additionally needed for the recurrent reformation of the trilamellar tear film. Winking of the eye also turns on a pumping tool for the drainage of tears through the lacrimal drainage apparatus. The wink speed in humans is 15 to 20 per min (almost unity wink every 5–7 s). In one investigation, the author inferred that low wink speed can consequence in over appraisal of the transcorneal infiltration when statistics procured from animal experiments is projected to humans [15].

Pre-ocular retention

One consideration that impacts ocular bioavailability following topical delivery is the retention of the therapeutic dose in the pre-ocular area. The volume of liquid that the conjunctival sac can take in is ~20-30 µL [16] and the volume of the tear film is 7 ± 2 µL [4]. Owing to physical restrictions of eye drop volume when produced from a standard dropper, however, most bottles transfer 30-50 µL instead of the ideal drop size of 10-20 µL [16]; the delivery of this larger volume roots reflex blinking, which boosts the drainage rate to the nasolacrimal canal, spilling on the cheeks and splashing the surplus of the solution to the eyelashes [17, 18], this consequence in both wasted amounts of medication and possible negative side effects due to high systemic absorption.

Corneal absorption

Cornea of the human eye is the principal path for the intraocular absorption [19]. Specific attributes of the cornea like small surface area and its corresponding impermeableness transcribe this eye region as an effective barrier to drug absorption. In comparison, the area of the conjunctiva in humans is nearly 17 times bigger than the

cornea and along with 2 and 30 bends additionally permeable for drugs than the corneal region [20, 21]. Accordingly, when the drug is topically administered to the pre-ocular area, conjunctival drug absorption phenomenon results in a substantial loss of drug and notably alters the proportions of drug absorbed via corneal absorption [22].

On noticing the construction of the cornea, it unveils that three layered framework of this zone of the eye is accountable for its miserable permeability. Outer epithelium is a lipophilic layer; stroma which is the thickest part of the cornea is hydrophilic; and the inner endothelium is a single-layered structure of the flattened epithelium like cells. Occupancy of together hydrophilic and lipophilic arrangements in the cornea, turns like a barricade to the absorption of both hydrophilic and lipophilic drugs.

Nasal cavity as an additional major route intended for the riddance of topically assigned drugs from the precorneal area. Attribute of this region like its bigger covering zone and strong permeability of the nasal mucosal membrane is liable to absorption into systemic circulation by means of the nasal mucosal lining, which is uninterrupted with the conjunctival sac [23].

Drug binding into tear proteins

Tears of human beings accommodate approximately 0.7% of the total-body protein. For that reason, whenever a drug comes in contact with tear fluid it could bind to the tear proteins like albumin, α-globulin, γ-globulin and lysozyme, resulting in a cutback of unattached drug concentrations attainable for pharmacological proceeding at the target site [24]. The biological action of several ophthalmic drugs is manipulated by drug-protein interaction in tissues and fluids of the eye. In both general as well as clinical circumstances exalted denseness of protein in lacrimal fluid united with a comparatively quick renewal of this fluid result in relocation of the drug solution apart from the eye, undergoes to a substantial deprivation in drug action for drugs that bind to protein [25].

Melanin binding

Ocular melanin is found in the retina and can influence the ocular bioavailability of the topically assigned drug. It possesses relevant pharmacological repercussions and necessitates prudent thoughtfulness in ocular drug delivery. Melanin binds to drugs by electrostatic and Van der Waals forces or by simple charge transfers [26]. On the ground of published literature, it may be concluded that all basic and lipophilic drugs bind to melanin [27]. Melanin binding in the iris–ciliary body influences drug concentrations in anterior ocular tissues as well as drug response [28]. Thereby, melanin binding may significantly lower pharmacological activity [29]. Drugs like ephedrine and timolol can bind to the melanin with an intense binding efficiency, and at most a pint-sized divide of the bound drug is steadily liberated. As a rule melanin-bound drug is not normally attainable for receptor binding demanding the administration of bigger dosages [30].

Drug metabolism

Miscellaneous enzymes in the eye can metabolize the active drug, consequenting in declined ocular bioavailability. Drugs that are bio-transformed via oxidation or reductions are not so much liable to metabolism than those altered by hydrolysis on account of the ampleness of ocular hydrolases. The corneal epithelium and the iris ciliary body are the most metabolically active.

Multifarious formulations emergence in the direction of better ocular bioavailability

Empirically established ophthalmic dosage forms such as solutions, suspensions and ointments are indisputably the most prevalently soiled as well as admitted formats. They are reasonably uncomplicated to formulate, purify and disinfect. However, all those formulations comprise diversified restraints as conversed abovementioned. In contemporary years, widespread exploration has been committed to lengthening the retention time of medicaments on the eye facade also to the amelioration of trans-corneal penetration of conventional and of new curative entities. In favor of these objective diverse advents like viscosity enhancement, use of mucoadhesive, particulate drug delivery, vesicular drug delivery, pro-drugs, and other controlled systems, like ocuserts, are being navigated. Such promising newer arrivals are talked about below.

Mucoadhesive polymers

The affluent evolvement of newer mucoadhesive dosage forms designed for ocular delivery, still fronts enumerable obstacles. The mucoadhesive dosage form divulged greater bioavailability of the drugs as equated to conventional dosage forms [31, 32]. This emergence is grounded on the orchestration of non-covalent bonds between polymers to

conjunctival mucin. Accordingly, securing liaison of the drug with the precorneal tissues up to the time of mucin renewal roots riddance of the polymer [33]. For a polymer in order to be an affluent bio-adhesive matter, it must hold a molecular weight of minimal 100,000 Da. Undue cross-linking in the polymer cutbacks the chain length attainable in favor of interfacial penetration. On the other hand, exorbitant configuration of inter-chain formation, hydrogen bonding and physical entrapment in polymer itself may turn out to confirmation hindering polymer diffusion through the mucus layer [34, 35].

Polymers having mucoadhesive properties are chiefly hydrocolloids in nature, including numerous functional groups that are hydrophilic in nature such as hydroxyl, carboxyl, sulphate, and amide. These functional groups are capable in interaction with mucus substrates by the happening of electrostatic interactions, hydrophobic interactions, hydrogen bonding and van der Waals intermolecular interactions. Hydrogen bonding predominantly plays a significant role in mucoadhesion for numerous polymers; accordingly, the company of water assumes obligatory for a majority of mucoadhesive phenomena [33].

Penetration enhancers

This advent comprises of expanding transitorily the permeability attributes of the cornea with relevant materials, recognized as penetration enhancers or absorption promoters. Obviously, the peerless peculiarities and considerable sensitiveness of the corneal/conjunctival tissues enforce admonition in the choice of enhancers, in respect of their capability to influence the integrity of epithelial surfaces. Absorption promoters such as actin filament inhibitors; surfactants, bile salts, etc. have been soiled to boost the bioavailability of topically executed proteins and peptides [36]. However, the attainment was lessened owing to the local toxicity linked with enhancers [37].

Articles communicated portrays that the preservative substances put to use in the majority of ophthalmic preparations function as penetration enhancers, 0.01% benzalkonium chloride has been manifested by Swanson. An upsurge in the penetration of fluorescein in the usual eye has been reported company of chlorohexidine gluconate and benzalkonium chloride. The degree and proportion of corneal penetration of sodium cromoglycate was changed while an ion coupled with dodecylbenzylmethylethyl ammonium chloride [38].

In situ forming gels or Hydrocolloids

This approach is stationed on phase transformation logics, and such systems are liquid dosage forms, which rearrange to gel or solid phase whenever introduced in the cul-de-sac. Hydrogel comprises of high molecular weight, hydrophilic, cross- linked polymers or co-polymers that form a three-dimensional matrix in water [39]. These gels spectacle integrated considerably longer residence times accompanied by increased drug bioavailability in the cul-de-sac [40]. This conceptualization of drug delivery to eye is immensely used considering that it boosts the viscosity and diminished the drainage of medication from the cornea. Accordingly, the bioavailability of drug automatically intensified. The in-situ gelling technique can be controlled by temperature, pH or ion activation [41]. Polymers whose viciousness rises whenever its temperature is elevated to 37 °C have been actively engaged in situ forming gels like Lutrol FC-127, Poloxamer-407 [42]. This kind of dosage forms is used at the present time in miscellaneous types of eye ailment like glaucoma, dry eye syndrome, eye infection [43].

Ocular inserts

Ocular inserts are aseptic, thin, multilayered, drug loaded, solid or semisolid dosage forms placed into the cul-de-sac or conjunctival sac, whose dimension as well as build are specifically planned intended for ophthalmic application and can conquer the hindrance stated with traditional ophthalmic systems. The ocular inserts assert an efficient drug concentration within the intended tissues [44]. Ocular inserts tender an appealing optional advent to the formidable arduousness of circumscribed pre-corneal drug residence time [45]; another promising benefit of insert therapy is the potentiality of endorsing non-corneal drug penetration, consequently enlarging the effectiveness of a number of hydrophilic drugs that are awfully absorbed via cornea.

The inserts are classified according to their solubility as insoluble, soluble, or bio-erodible inserts. The release of drug from the insert depends upon the diffusion, osmosis, and bio-erosion of the drug [46, 47].

Liposomes

On the foundation of the number of concentrically alternating sheets of phospholipids and aqueous phases, liposomes are

multilamellar or unilamellar vesicles. Liposomes can be formulated by a number of approaches like sonication of dispersion of phospholipids, reverse phase evaporation, solvent injection and detergent removal or calcium induced fusion [48]. For a wide variety of drug molecules, proteins, nucleotides and plasmid liposomes can be utilized as a suitable carrier, this characteristic confers them a pronounced prospective meant for their implementation in ophthalmic drug delivery [49]. Additional aspiring edge of liposomes is their aptness to come in close liaison with the corneal and conjunctival surfaces, thereby, enlarging the prospect of ocular drug absorption. This skill is particularly worthwhile for drugs that are awfully absorbed i.e. drugs with low partition coefficient, poor solubility or those with medium to high molecular weight and enzymes [50, 51]. Liposomes acquiring positively surface charges were proclaimed to display an extended precorneal retention as juxtaposed with neutral and negatively charged liposomes, on account of electrostatic interaction with the negatively charged corneal epithelium. It is brought up that these liposomes bind closely on the eye surface to increase the residence time and thus enhance drug absorption [52].

Niosomes

Structurally niosomes are analogous to liposomes. They are the non-ionic surfactant vesicles and are bilayer organizations, which can ensnare both hydrophilic and lipophilic drugs either in an aqueous layer or in vesicular membrane, constructed of lipids [53]. One critical inconvenience related with liposomes as an ocular drug delivery carrier is the susceptibility of phospholipids to oxidative degradation in air. This requires that purified phospholipids and liposomes have to be stored and handled under an inert atmosphere [54]. Niosomes are promising drug carriers as they hold finer stability as matched to liposomes, can entrap both lipophilic and hydrophilic drugs, lowest level toxicity on account of their non-ionic nature, no specific safeguards in manipulation of surfactants, pliability in their organizational characterization, biodegradability, biocompatibility, non-immunogenicity and absence of various drawbacks related with liposomes, such as high cost and the fluctuating purity troubles of phospholipids [55, 56].

Collagen Shields Collagen is the constitutional protein present in bones, tendons, ligaments and skin, and encompasses greater than one fourth of the complete protein in mammals. Collagen is considered as one of the most applicable biomaterials. The outstanding biocompatibility and security owing to its biological attributes such as biodegradability in addition to weak antigenicity made collagen the rudimentary assets in medical implementations. Friedburg *et al.* developed collagen shields to promote wound healing and conceivably more meaningfully to deliver a variety of medicaments to the cornea and other ocular tissues [57]. Drugs can be integrated within the collagen matrix in the course of manufacture absorbed into the shields in the eye. As the shield dissolves the drug and releases gradually in the tear film and into the aqueous humor [58]. Collagen shield frequently causes a few distress and blurred vision and are not fitted for every patient. For enhancement of this trouble, Kaufman invented a new conceptualization of drug delivery by blend of collagen shield particles, and contact lenses baptized collasomes. Collasomes could be introduced underneath the eyelid and diminish the blurred vision trouble [59].

Ocular iontophoresis

Iontophoresis is a modern non-invasive approach specifically designed for ocular drug delivery [60]. Theoretically, iontophoresis is limited to drugs of a small size, an ionic nature and with low molecular weight. The practice of iontophoresis implies assigning an electric current to an ionizable material to step-up its transportability across a surface, a theory that dates back to the 18th century. The initial transscleral iontophoretic effort for vitreal drug delivery was proclaimed in 1943 [61]. Subsequent, David Maurice performed a vital function in upgrading the utilization of iontophoresis to intensify ocular drug delivery [62, 63]. If the drug molecules hold a positive charge, they are driven through the tissues at the anode; whether negatively charged, at the cathode. Ocular iontophoresis overtures a drug-delivery system that is rapid, pain free and secure; furthermore, in the majority of cases, it consequences in the delivery of a high concentration of the medicament to a particular site. Implementation of iontophoresis approach in case of antibiotic's delivery to ocular route may heighten their bactericidal activity and may diminish the acuteness of disorder; correspondingly, solicitation of anti-inflammatory

agents might stave off or curtail vision intimidating side effects [64].

Nanoparticles

Nanoparticles are solid, submicron, colloidal particles ranging in dimension from 10 to 1000 nm, in that drug molecules may be present in dissolved, entrapped, adsorbed or covalently attached form [65]. Based on formulation approaches nanoparticles can be acquired with distinct properties and release attributes for the capsulized drug [66, 67]. These colloidal particles can be assigned in the liquid form just like eye drops and diminishes uneasiness provoked by application of semisolid ointments. They are patient friendly owing to less frequent application, extended duration of retention in the extra ocular portion deprived of blurring vision.

Nanoparticles have been established to be the most promising of all the formulations developed over the past a couple of years of marked navigate in ocular therapeutics, payable to their sustained release and prolonged therapeutic concern. Polymeric nanoparticles are additionally capable in the targeting of ailments in the posterior segment of the eye [68]. Nanoparticles made of biodegradable polymer that combines the capabilities of stimulus response and molecular recognition hold a pronounced aptitude in ocular drug delivery. Biodegradable polymers formulated as colloidal systems hold significant promise for ophthalmic drug delivery. Supplementally, surface altered nanoparticulate carriers may utilize to acclimatize a sort of actives [69, 70].

The serious concerns with regard to the formulation of nanoparticles comprehend stability, particle size homogeneity, control of drug release rate, and sizeable production of uncontaminated preparations [71]. Nanocarries possessing polyethylene glycol or surface-segregated chitosan have been established to be correspondingly stable as well as proficient at overcoming mucosal barriers [72].

Prodrugs

Chemical moderation such as prodrug aiming diverse nutrient transporters (amino acids, peptide and vitamin) has emerged a pronounced deal of interest to ameliorate ocular drug delivery. Prodrugs intensify corneal drug permeableness via adjustment of the hydrophilicity or lipophilicity of the drug. The approach comprises the transformation of the chemical framework within the drug molecule, consequently modeling it selective, site specific and a secure ocular drug delivery mode. Drugs with intensified perviousness by means of prodrug formulations are epinehrine, phenylephrine, timolol, pilocarpine [73].

Dendrimers

Dendrimers are complicated although thoroughly defined multibranched chemical compounds, with a high degree of order, and the feasibility of comprising chosen chemical units in predestined positions of their tree−like construction [74]. Dendrimers, a nanoparticle based drug delivery system, hold a lot of implementations in pharmaceuticals such as improving the solubility of miserably soluble drugs, improving the delivery of DNA and oligonucleotides, targeting drug at specific receptor site, and possess the ability to mimic as carrier for the evolvement of drug-delivery systems [75].

A perfect ocular drug-delivery practice should be nonirritating, aseptic, isosmotic, biocompatible, biodegradable, and does not run out from the eye [76]. The utilitization of aqueous PAMAM dendrimers has been revealed to be of importance in the ocular route. In fact, PAMAM dendrimers displayed physicochemical attributes (pH, osmolality, viscosity) that are congruous with ocular formulations. The outcomes advocate that, in inclusion to dimension and molecular weight. The charge and molecular geometry of bioadhesive dendrimers additionally impact ocular residence time. The unchallenged benefit of these polymers is the lengthening in corneal residence time along with augmented bioavailability of drugs embodied in eye drops. The pharmacodynamic consideration's accented finer bioavailability for drugs when DG1.5 and DG4.0 (OH) dendrimers accompanied by carboxylate and hydroxyl surface groups, correspondingly, are combined with the eye drops. This form of logical approach to characterizing the impact of the physicochemical properties of polymeric macromolecules on residence time will assist the plan of novel polymeric biomaterials with prolonged-release profiles for the ocular route [77].

CONCLUSION

On reveling heterogeneous progressions in the field of ocular pharmacotherapeutics throughout last two or three decades, it comes forth that miscellaneous formulations of diverse formats hold their individual benefits and detriments due to assorted anatomical, physiological and biochemical barriers

of the eye. Some latest inventions have been commercialized as a consequence of the investigation into ophthalmic drug delivery. The accomplishment of these fresh marketed products yet is still realistically not impeccable. Most auspicious developments such as nanoparticles and dendrimers on further investigation may become boon for the medication of several anterior and posterior segment eye ailments.

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