A REVIEW: TOPICALLY ADMINISTERED OCULAR MINI-TABLETS

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ABSTRACT

The human eye is a unique and intricate structure which has made drug delivery to the eye a formidable undertaking. Anterior-segment eye diseases are ubiquitous, especially among elderly patients, and conventional eye drops, although a first-choice dosage form, are not always an efficient treatment option. The development of novel drug delivery systems for improved treatment is therefore imperative.
INTRODUCTION

Eyesight is a significant sense that most individuals may take for granted. It plays a vital role in our daily lives and enables us to function optimally. Thus, its presence must not be overlooked, and full effort in ensuring preservation of this essential feature must be exerted by science. Conditions such as cataracts, glaucoma and diabetic retinopathy are some examples of commonly occurring diseases that may be chronic in nature and require continuous treatment. The mere fact that the diseases are chronic exacerbates the despondency of patients and fosters a poor outcome. According to Pascolini and Marriot (2010), \(^1\) approximately 285 million people globally have a problem with eyesight, of whom about 14\% are completely blind. This is certainly a burden, and the majority of cases can be attributed to ageing or to preventable diseases.

On inspection, the human eye is divided into the anterior and posterior segments. Although anatomically separated; these areas function together and must be looked at in conjunction with respect to drug delivery. The anterior section consists of the cornea, iris, lens, ciliary body and aqueous humor. Liquid eye drop preparations are the most widely used dosage form for topical ocular drug administration. However, topical ocular drug bioavailability to the anterior eye using eye drops is approximately 5\%. \(^2\) This low level of drug bioavailability results in reduced therapeutic effects, as a minimal amount of drug reaches the actual target site. This is attributed to several hindrances to drug entry to the anterior chamber of the eye, which include nasolacrimal drainage, epithelial barriers of the cornea, clearance from the blood vessels in the conjunctiva, and reflex closure of the eye once the preparation is instilled. \(^3,6\) With respect to drug delivery in the eye there are three important factors to consider: contact time, target area and patient acceptability. \(^7\) Firstly, the duration can vary from a few minutes for eye drops up to months and years in the case of implant systems. Secondly, depending on whether the target is the anterior or posterior segment of the eye, different drug delivery systems are used. Topical systems are generally used for the anterior segment and implants or injections for the posterior segment. \(^8\) Finally, in terms of patient acceptability, the system has to be easy to use, comfortable and convenient for the patient. This will assist in ensuring that the likelihood of patient cooperation is increased, as the use of complicated techniques will be avoided.

Over the years, various approaches have been attempted to optimize the bioavailability of ocular topically administered drugs. Some of these approaches include viscous vehicles and hydrogels, \(^8\) facilitated transport via prodrugs, \(^9\) nanoparticles, \(^10,13\) contact lens delivery systems \(^14\) and penetration enhancers. \(^15\) These systems have been developed for and used to increase corneal contact time and allow for improved corneal drug penetration. The ultimate goal of improving drug delivery systems is to ensure compliance so that the disease can be effectively treated. Ocular diseases are common and often lead to blindness if left untreated. One such disease is glaucoma, which is characterized by an increase in pressure leading to damage to the optic nerve. In the USA, this disease is the second commonest cause of permanent blindness, and it is definitely a major concern worldwide. \(^16,18\) Thus, it cannot be taken lightly, and scientific attention should be given to it due to its prevalence and obviously devastating consequences.

Apart from improved bioavailability, an improved dosage form for topically administered ocular drugs is required to ensure patient compliance and that the drug reaches the target site. As mentioned above, eye drops may be difficult to instil and are easily flushed out, thus resulting in poor bioavailability. \(^19\) Thus, innovative thinking has transitioned towards the idea of novel drug delivery systems for ocular use. Solid vehicles have been investigated as possible delivery systems to overcome the challenges associated with the use of conventional eye drops. \(^20,21\) Previous reviews have delved into the structure, anatomy and physiology of
the eye and examined advances in devices developed for ophthalmic drug delivery. However, no significant focus has been placed on ocular mini-tablet drug delivery systems. The purpose of this article, therefore, is to discuss the barriers to ocular drug delivery and limitations of conventional systems and to summarize previously developed devices for topical administration to the eye and the advantages and limitations associated with these systems. The goal of the review is to discuss mini-tablets developed for ocular delivery in a chronological manner, from early developments to present formulations. In addition, other novel solid dosage forms are briefly mentioned. Recommendations for future considerations in the area of topical ocular delivery are also elaborated on.

**Basic anatomical and physiological characteristics of the eye**
In order to gain an understanding of drug delivery to the eye, the first step is to inspect the basic structure of the eye. This is of interest because the effects of the delivery system depend on where the actual target site is. The eye is a spherical structure that is made up of the sclera, choroid and retina. The outer sclera protects the inner layers; the choroid consists of blood vessels and is located inside the sclera. The retina is situated at the rear end of the eye and functions to detect light. The cornea is a protective barrier to the interior of the eye, has a small surface area and consists of five layers, namely epithelium, Bowman’s layer, stroma, Descemet’s membrane and endothelium. Two fluid media exist in the eye. The ciliary body, located in the anterior segment, secretes the aqueous humor. It functions to balance the pressure and as a means of nutrient and metabolite exchange for this portion of the eye. The vitreous humor, found in the posterior section, gives the eye shape and support. These facts provide a basis for understanding the operation of this organ, the anterior segment of which will be focused on in this review.

**Barriers to ocular drug delivery**
The eye remains impervious to foreign substances because of its anatomical and physiological defense mechanisms. It is protected from exogenous substances and able to prevent their entry because of the barriers described here under.

**Lacrimation, drainage and blood vessels**
When a drug is administered topically to the eye, reflex closure of the eyelid occurs due to a foreign-body sensation. This may result in the liquid preparation being forced out or even prevent entry into the anterior eye altogether. Furthermore, the lacrimal fluid flushes out instilled substances from the surface of the eye, and fluid is then drained by the nasolacrimal duct. Systemic drug absorption may also take place through vessels of the conjunctiva.

**Corneal–aqueous barrier**
The cornea serves as a protective layer of the eye and comprises several layers (Figure 1). The epithelium is the initial layer (0.1 mm). The multicellular epithelium consists of 56 layers of cells, and these layers pose a barrier to drug penetration. The tight junctions prevent movement of drugs from the lacrimal fluid into the eye, while the stromal layer, because of its hydrated nature, hinders the movement of lipophilic drugs. These defense mechanisms of the eye protect it against foreign bodies, and consequently they affect drug absorption. Therefore, evidently the cornea reduces drug absorption to the anterior eye and is the ratelimiting layer. The residence time of the drug on the eye surface and the permeability of the cornea to the drug are two important factors that influence drug absorption. Because the corneal layer is lipophilic, the corneal route remains the main mechanism of drug entrance to the aqueous humor, despite the challenges encountered. The lacrimal and corneal barriers, as explained, are the two most apparent challenges for drug delivery to the aqueous chamber. These mechanisms are inherent and cannot be changed, so ways around them should be given thought to.
Fate of ocular drugs after administration: distribution and elimination

When drugs are applied topically to the eye, they permeate the cornea, then enter the aqueous humor, and then move to the ocular tissues (iris/ciliary body, lens, vitreous humor and retina). Although conventional eye drops are a common and convenient drug delivery system, they fail to deliver effective drug levels to the posterior segment of the eye (lens, vitreous humor and retina). This is due to the fact that the use of eye drops results in a higher drug concentration in the anterior segment (cornea, conjunctiva, sclera, aqueous humor, iris/ciliary body). In terms of elimination, drugs are removed from both the anterior and posterior segments. From the anterior segment, drugs are removed in two main ways: aqueous humor turnover and anterior blood flow of the uvea. In the case of the vitreous humor, elimination occurs via the anterior chamber or posteriorly across the blood–retina barrier. The disposition and pharmacological action of certain drugs, depending on their properties, can be influenced by melanin binding, which can occur in the ocular tissue.

Routes of administration

Topical and subconjunctival routes are mainly used for targeting the anterior segment of the eye. Intravitreal injections, perioculcular routes (retrobulbar, peribulbar, subtenon and subconjunctival routes) and implants are used for the posterior segment. Topical routes remain the most convenient, as injections and implants are often invasive, are associated with discomfort and pose the risk of retinal detachment and cataracts. Each route of administration is associated with limitations. as depicted in Figure 2.
Anterior segment drug delivery
Although eye drops are the most common system used for drug delivery to the anterior segment, they are disadvantaged due to limited ocular-surface contact time. This has been improved by the use of viscous vehicles such as gels. Lipophilic drugs permeate to the anterior chamber by residing on the epithelial layer followed by movement into the stroma. Peak concentrations of drug in the anterior chamber are normally attained after approximately 30 min. Thereafter, the drug moves to the iris and ciliary body, where drug–melanin binding may occur, resulting in gradual drug release and improved drug effect.

Sub-conjunctival administration
Sub-conjunctival administration is another method of topical drug delivery. Injections administered via this route result in drug permeation across the sclera. Advantages of this route include the following: (1) the sclera is more permeable compared with the cornea; (2) large molecules (e.g. proteins) are able to pass through; and (3) the lipophilicity of the drug does not affect scleral penetration. However, although these injections increase drug levels in the target area, they cannot deliver entirely effective therapeutic amounts in the case of certain drugs. Conditions in the anterior segment of the eye require an effective, ‘easy’ topical drug delivery system that ensures effective therapeutic drug levels and patient compliance. The following specific points are of significance when considering the use of such formulations: (1) A very small volume of lacrimal fluid (7–9 μl) is found on the eye surface, while a dropper bottle dispenses more than this volume of liquid, the majority of which is flushed out upon instillation, which results in a loss of the drug contained; (2) instillation of the liquid, owing to foreign-body sensation, may trigger a flow of tears that causes more of the liquid to be lost; (3) the liquid may contain substances for preservation of the solution, which may not be well tolerated, triggering blinking and further loss of drug. Furthermore, although these dosage forms are convenient and widely available, they offer...
poor bioavailability due to dilution in the lacrimal fluid once the eye drop solution is administered and subsequent removal by the nasolacrimal drainage system. Thus, continual instillation of eye drops is required in order to achieve therapeutic effects. This can result in poor patient compliance and in turn hinder the overall treatment process. The use of conventional liquid eye drops presents the following challenges: (1) Most eye drops remain on the ocular surface for a small period of time, and only a limited amount of drug is actually absorbed; (2) nasolacrimal drainage and eyelid reflex closure result in loss of liquid preparation from the eye surface once instilled. This results in low bioavailability of ophthalmic drugs when they are administered using topical droppable dosage forms. In addition, patients often have difficulty instilling conventional eye drops for the following reasons:

(1) They have to be administered many times during the course of the day, and this can lead to non-compliance; (2) certain patients, such as the elderly or those with conditions that impair hand movement (e.g. arthritis), have difficulty instilling the eye drops because a certain level of pressure has to be applied to the bottle to expel the eye drop, so that these patients are disadvantaged due to lack of control of the dropper and bad timing; (3) if not correctly held, the plastic tip of the eye drop bottle may come into contact with the eye surface itself, leading to contamination of the bottle after several uses or to injury of the cornea; (4) patients often present to health practitioners with a reduced intraocular pressure in conditions such as glaucoma, as they instil the drops prior to the appointment, whereas in those who are not willing to adhere to therapy, glaucoma progresses.

**The effects of topical drugs and drug delivery systems on ocular tissue**

An important consideration with regard to both drugs and delivery systems is safety and toxicity to the eye surface. Ideally, these, as well as additional formula components, should be non-noxious to the eye tissue. Unfortunately, this cannot always be achieved; thus, careful consideration must be given in the initial stages of preformulation. According to a study conducted by Fraunfelder (2006), some commonly prescribed drugs were found to induce corneal toxicity in certain patients. Selected examples include glaucoma drugs, non-steroidal anti-inflammatory drugs, preservatives in liquid preparations, and aminoglycosides. Furthermore, with advances made in delivery systems, permeation enhancers have been included in eye preparations. Permeation enhancers are substances that allow for better movement of drug through the cornea via increase of corneal cell membrane permeability or opening of tight junctions between cells. Some of these include bile salts (sodium deoxycholate), calcium chelators (EDTA), preservatives (benzalkonium chloride) and surfactants (Tween 80). However, a few of these enhancers have a tendency to produce negative effects on the cornea. For example, use of benzalkonium chloride is known to result in changes in the corneal morphology, while saponin causes irritation and increases rabbit blinking rate. Thus, the ocular permeation of drugs is improved at the cost of an unfortunate increase in corneal irritation and damage. The risk–benefit ratio certainly has to be considered. Thorough investigations need to be undertaken in order to ascertain the acceptability of drugs, polymers and other excipients prior to application.

**Approaches employed to augment ocular drug bioavailability**

Over the years, various approaches have been investigated to enhance the bioavailability of topically administered ocular drugs. This goes beyond the use of ‘traditional’ suspensions/solutions to advanced ‘versatile’ delivery systems. These systems include but are not limited to the following selected examples:
(1) Controlled-release ocular drug delivery systems. These can be either erodible or non-erodible inserts. Erodible inserts dissolve once in contact with the ocular surface; examples include implants and ocuserts. However, they may cause discomfort for patients, and they require insertion or removal, resulting in poor patient adherence.55

(2) Viscous vehicles and in-situ-forming hydrogels. Viscous vehicles have been mentioned as a means of increasing corneal contact time with the formulation. However, their use is associated with a few disadvantages. For example, gels and ointments can blur vision and cause reflex blinking. Therefore, phase-transition gels have been investigated. They are initially in a liquid form upon instillation and convert to a gel once in the eye. The phase change can be triggered by temperature, pH or electrolytes.57 Polymers that display these properties include caribomers, celluloses, poloxamers and xylglucans.58

(3) Liposomes. They are vesicular or colloidal systems that are easy to synthesize. They have the disadvantage of instability and rapid clearance from the eye surface.56

(4) Nanoparticulate drug delivery systems. Nanoparticles are defined as particles in the size range of 10–1000 nm. Upon administration to the eye, the particles reside at the delivery site, and the drug is released from the particles through diffusion, chemical reaction, polymer degradation or ion exchange. Smaller particles are better tolerated by patients and offer prolonged-action ophthalmic drug delivery systems. However, it was observed that nanoparticles consisting of poly(alkyl cyanoacrylate) damaged the corneal epithelium by disrupting the cell membrane.13

Rationale for the development of mini-tablets as drug delivery systems

Mini-tablets are defined as tablets with a reduced diameter (2–3 mm) in comparison with conventional tablets.59 They have several advantages as oral drug delivery systems. These include the following: (1) several mini-tablets can be used in combination to make up a single capsule or tablet; (2) they can act separately from the rhythm of food transport,60 and (3) they can be coated repeatedly, with a reduced amount of coating substance required owing to the consistent area.61 Mini-tablets have various applications, of which use as oral delivery systems is the most common. In a study, it was concluded that paracetamol could be tabletted in greater amounts if mini-tablets were produced.59 Likewise, Lopes et al.62 developed and investigated biphasic delivery systems, with a positive outcome. Recently, Tissen et al.63 produced mechanically robust 1-mm quinine hydrochloride mini-tablets for the first time, by direct compression (Figure 4). When the advantages were taken into account, mini-tablets’ initial use as oral delivery systems led to application of mini-tablets for ocular drug delivery.

Mini-tablets for topical ocular drug delivery

The shortcomings of and improvements that have been made to eye drop formulations were outlined previously. Apart from contact time and bioavailability, patient compliance is an important factor to consider. The use of eye drops is convenient and ensures little discomfort for the patient. It remains the most common method of topical ocular delivery. However, patients often have difficulty instilling eye drops because they cannot aim the bottle, and ultimately this leads to poor patient compliance.64 It is for this reason that a solid formulation would be more appropriate. The following advantages of solid ophthalmic drug delivery systems are apparent: accurate doses, reduction in systemic absorption, improved patient compliance owing to absence of continual instillation, longer residence times in cul de sac, less likelihood of being affected by the naso lacrimal drainage system, reliable drug release, and lower incidences of visual and systemic side effects. With the aim of improving contact time and bioavailability of ocular preparations, mini-tablets for ocular drug delivery have been formulated. In terms of ophthalmic application, in recent years, mini-tablets have gained momentum, with early ophthalmic inserts prepared by mini-tabletting as freeze-dried, sponge-like mini-tablets.
Some advantages that these systems offer include:
(1) easier patient administration due to absence of necessity of manipulating an eye drop bottle; (2) greater convenience for elderly patients, as they do not have to apply pressure to a bottle to expel the eye drop; (3) no risk of flushing out due to lacrimation and drainage once administered, as they are in solid form; (4) increased corneal contact time owing to the use of bioadhesive polymers; (5) outer layers that swell when hydrated, with the drug being released gradually as the liquid penetrates into the tablet; (6) cost-effectiveness and ease of production; and (7) no irritation as a result of use.

Commonly employed polymers in ocular mini-tablets
The initial approach for improving contact time in the field of ocular delivery was the selection of polymers that improved adhesion to the eye. The choice of polymer to function as drug carrier in mini-tablets is an important factor to consider because it contributes to the manner in which the delivery system operates and to how the drug is released. The increased viscosity of polymers reduces drainage from the eye surface. Polymers employed should display certain properties for easier manufacturing and to avoid any harmful reactions or potential damage to the ‘sensitive’ eye. Specifically, they should be (1) biocompatible, (2) biodegradable, (3) non-toxic, and (4) inexpensive and readily available. Common polymers used in mini-tablets include acrylates, celluloses, chitosan and drum-dried waxy maize starch. Their advantages for ocular use are discussed below.

Acrylates
Poly(acrylic acid) and carboxomers are mucoadhesive polymers employed in various ophthalmic formulations. The use of polyacrylates or carboxomers has been proposed in the treatment of dry eye syndrome. The mucoadhesive properties these polymers display on the eye surface are due to hydrogen bonding. The polymer interacts with mucin on the eye surface to form a hydrogel. Cross-linked poly(acrylic acid) (Carbopol) is favourably and widely employed as a vehicle in the ocular field. In contrast to other polymers, Carbopol displays excellent mucoadhesive effects on the eye surface. Ocular minitablets made of Carbopol 974P have been formulated and demonstrated good corneal adhesion.

Cellulose derivatives
Cellulose polymers have been used artificial tear solutions and as viscosity-enhancing ophthalmic vehicles. These polymers display coil formation as temperatures increase and helix formation when temperatures are dropped. Methylcellulose solutions form gels at higher temperatures (40–50°C), while hydroxypropyl methyl cellulose displays this behavior at 75 and 90°C. Similarly, solutions of ethyl(hydroxyethyl) cellulose are also influenced by temperature, but their viscosity decreases with temperature. Apart from use in artificial tear formulations, these polymers have been employed in various ocular mini-tablets. Table 1 depicts the structure of methyl cellulose.
Chitosan

Chitosan is a naturally obtained cationic polymer that has been widely studied in ocular drug delivery due to its favourable properties.\textsuperscript{81,82} It is a biocompatible, non-toxic mucoadhesive polymer that has shown good ocular tolerance. Its mucoadhesive properties are due to its positively charged amine groups, which interact with the negative sialic acid mucus layer, thus prolonging contact time with the eye surface.\textsuperscript{83} A disadvantage of this polymer is its water-insolubility. However, by decreasing the molecular weight through depolymerization, improved solubility can be achieved.\textsuperscript{84} In addition, the antibacterial properties of chitosan are important for its ocular use. Chitosan displays activity against a variety of organisms (yeasts, moulds, bacteria), depending on the type of chitosan used. For example, chitosan’s antibacterial properties are advantageous in conditions such as keratoconjunctivitis sicca. Chitosan mini-tablets have been found to have good antimicrobial properties and bioadhesive strength, as well as being effective sustained-release drug delivery systems in the eye.\textsuperscript{85}

Table 1 shows the typical chemical structure of chitosan

**Mini-tablets developed for topical ocular drug delivery**

**Timolol-containing mini-tablets**

Developed timolol maleate-loaded minitablets by compression; they varied the acrylic coating to control the drug release. The use of acrylic polymers to coat the mini-tablets resulted in the attainment of zero order kinetics. Mini-tablets were prepared using glyceryl palmito stearate and hydroxypropyl cellulose. They were tabletted using a single-punch press of diameter 3.5 mm. Mini-tablets contained either 0.34 or 0.68 mg of the active ingredient. Tablets were coated with acrylic polymers to 5\% (w/w). Uncoated mini-tablets showed diffusive or anomalous release. Samples coated with an 80 : 20 Eudragit RS : Eudragit RL mixture, which had a reduced permeability, showed zero-order kinetics, in which the release rate decreased with increasing amount of coating. Coating tablets with a small amount of the more permeable polymer mixture, consisting of 60 : 40 RS : RL, resulted in anomalous, non-Fickian release kinetics. Tablets containing hydroxypropyl cellulose displayed fast drug release due to swelling in the dissolution medium. Mini-tablets were sterilized by gamma radiation, and it was shown that drug content was unaffected by this process. The time taken to release 30\% of timolol maleate content was in the range of 1–47 h for both types of tablet.\textsuperscript{27} Shortcomings of this study were that the tests were limited to in-vitro tests (i.e. there were no in-vivo tests).
Figure 6 (a) Ocular mini-tablet (6 mg weight, diameter 2 mm) prepared with 90.5% (w/w) drum-dried waxy maize starch, 5% (w/w) Carbopol 974P, 1% (w/w) sodium stearyl fumarate and 3.5% (w/w) ciprofloxacin hydrochloride. (b) Macroscopic examination of the gelling mini-tablet in the eye, 4 h after application.
Carbopol/DDWMS mini-tablets
A polymeric combination containing Carbopol 974P and DDWMS was developed by Ceulemans et al.\textsuperscript{70} (Figure 5). A dispersion of Carbopol 974P, sodium stearyl fumarate and DDWMS was formulated and compared with a mini-tablet. Sodium fluorescein was used as a fluorescent marker for in-vivo evaluation in the rabbit model. The mini-tablet became fully hydrated after 2 h and transformed into a concentrated gel. In comparison with the dispersion, the mini-tablet increased fluorescence in the anterior chamber. The mini-tablet was seen to be advantageous as a delivery system for infections of the anterior segment of the eye or glaucoma.\textsuperscript{70}

Ciprofloxacin-loaded granules compressed into mini-tablets
Weyenberg et al.\textsuperscript{73} prepared ciprofloxacin-loaded DDWMS/Carbopol 974P granules for compression purposes in order to obtain ocular mini-tablets. To produce the mini-tablets in higher quantities, it was necessary to improve the flow properties of the powders. This was achieved through the dry granulation process by means of a roller compactor. The physical properties of the bioadhesive granules were optimized by adjusting the speed and force of the roller. Minimal flow time and friability were yielded by milling with maximum force and at the lowest speed. Improved compactibility correlated with smaller particle size, as a higher surface area was available for bonding when a finer particle size was employed.\textsuperscript{59} The tablet strength was significantly higher when less roller compaction force was employed for the preparation of the granules. Based on the tablet strength, friability and dissolution, a low compaction force and a high roller speed were shown to be preferable. The mini-tablets did not cause mucosal irritation in volunteers. In-vivo studies of this delivery system are necessary for further insight.

Evaluation of physical properties and irritation potential of Carbopol/DDWMS mini-tablets
The effect of the force of compression on the physical properties, drug release and in-vivo behaviour of mini-tablets was gauged by Weyenberg et al.\textsuperscript{71} (Figure 6). Bioerodible mini-tablets consisting of Carbopol 974P (5% w/w), DDWMS (92% w/w), sodium stearyl fumarate (1% w/w) and sodium fluorescein (2% w/w) were produced at different compression forces. Increasing the compression force caused an increase in the crushing strength of the mini-tablets together with decreased friability, water uptake and porosity. These results implied that the mini-tablets were robust structures, absorbed fluid more slowly and had fewer voids/spaces within their matrixes. The administration of mini-tablets prepared at greater forces resulted in longer residence of sodium fluorescein in the tear film. The irritation potential of mini-tablets was determined by Weyenberg et al.\textsuperscript{72} by means of a slug mucosal irritation test. The pharmacokinetics of ciprofloxacin in lacrimal fluid were determined in human volunteers after topical administration of a mini-tablet and a liquid eye drop preparation. Results of the mucosal irritation test demonstrated that the mini-tablet was non-irritating and well tolerated.

Amioca/Carbopol mini-tablets
Weyenberg et al.\textsuperscript{77} evaluated new powder mixtures in tablets to obtain an improved fornix residence time compared with the Carbopol/DDWMS tablets containing 5% (w/w) Carbopol 974P. Mini-tablets of diameter 2 mm with sodium fluorescein as model active ingredient were manufactured by direct compression and sterilized by gamma irradiation. Carbopol concentrations in the co-spray-dried powder mixtures and gamma irradiation had no significant influence on the crushing strength and friability of the mini-tablets evaluated but did affect their in-vitro behaviour. The slowest release was obtained with tablets containing 25% (w/w) Carbopol 974P. Co-spray-dried Amioca, a food grade waxy corn starch consisting
primarily of amylopectin, and 15% (w/w) Carbopol 974P displayed a slower release compared with the physical mixtures of DDWMS or Amioca starch with Carbopol 974P. The mini-tablet was tolerated by humans and did not cause irritation. The gelling behavior of the minitablets was an advantage, as it resulted in an extended residence time (8 h). For the minitablets prepared with the physical mixture, fluorescein was found in the tear film only up to 6 h, while with co-spray-dried mini-tablets, the concentration in the tear film remained >50 ng/ml between 4 and 11 h after insertion. The in-vivo release of the ocular minitablets was prolonged by employing the co-spray-dried mixture of Amioca® starch and Carbopol 974P instead of the physical mixture.

**Ocular gentamicin mini-tablets**

Gasthuys et al. evaluated the behavior of ocular minitablets versus eye drops in ponies. The mini-tablets were 2 mm in diameter and prepared by compression using DDWMS, Carbopol® 974P, sodium stearyl fumarate and 5% gentamicin sulfate. Two mini-tablets were inserted into

![Digital image depicting in-situ gelling after insertion of two ocular mini-tablets (arrow) onto the ventral bulbar conjunctiva of the right eye in a sedated pony.](image)

the bulbar conjunctiva of the ponies’ right eye, and liquid drops were administered in the left eye of ponies (Figure 7). The tablets swelled 5 s after insertion. An increase in drug concentration occurred after administration, with subsequent reduction in all cases. The average drug concentration declined to 10.8 Ig/ml after 60 min, while a minimal concentration (<3 Ig/ml) was obtained after 2 h. The minitablets were well tolerated, and their administration resulted in high gentamicin sulfate levels in the lacrimal fluid over an 8-h period.
Mucoadhesive microdiscs formulated in a rapidly dissolving tablet
Choy et al. synthesized microparticles <10 μm in diameter by an emulsification method using the polymers poly(lactic-co-glycolic acid) and poly(ethylene glycol). A microdisc shape was used because its flattened surface can increase the contact area with the mucus surface of the front of the eye. Microparticles were formulated as a suspension and in a tablet form (Figure 8). The aim was to investigate the effect of the formulation on the ability of the microparticles to be retained on the eye surface. Mannitol tablets with mucoadhesive microdiscs had better retention times than the other formulations. Fluorescence images showed that the microdiscs remained in the fornix of the eye for approximately 1 h. As microdiscs formulated in a dry tablet form had a prolonged residence time, this could be a potential ophthalmic drug delivery system.

Figure 8 Scanning electron micrographs of microparticles prepared for ocular adhesion studies using poly(lactic-co-glycolic acid) (PLG) and poly(ethylene glycol) (PEG): (a) PLG microspheres; (b) PLG microdiscs; (c) PLG/PEG microspheres; (d) PLG/PEG microdiscs. Scale bars 10 μm
Pregelatinized starch and Carbopol mini-tablets
Bozdag et al. developed ocular bio-adhesive mini-tablets containing gentamicin and vancomycin as model drugs. Pregelatinized starch and Carbopol were used as polymers, and they were either physical or co-spray-dried mixtures. Granules were formed using the slugging method, followed by mini-tablet compression (2 mm diameter) and gamma irradiation sterilization at a dose of 25 kGy. Irradiation sterilization did not have an effect on the properties of the formulations, and electron paramagnetic resonance showed the presence of radicals up to one month after sterilization, with no alteration of drug properties. The mini-tablets absorbed water to form a gel, which slowed the drug release. Drug release for preparations containing physical powder mixtures of Pregelatinized starch and Carbopol 974P (96 : 4) was faster than for the co-spray-dried formulations (95 : 5 and 85 : 15). Drug was detected in tear film up to 6 h after administration, which is advantageous for a sustained release effect. The slug mucosal irritation test indicated that the mini-tablet produced minimal irritant effects; in-vivo evaluation is necessitated for confirmation of results.

Ocular mini-tablets for the treatment of microbial keratitis
Bioadhesive, gatifloxacin-loaded ocular mini-tablets using sodium alginate, calcium gluconate and chitosan were prepared by Gilhotr et al. The resulting mini-tablets had a drug content of 4 mg and a surface area of 50 mm. The ocular mini-tablets were sterilized by gamma radiation after packaging. The drug release of mini-tablets was improved by higher ratios of calcium gluconate. Minitablets containing 80% (w/w) sodium alginate and 16% (w/w) chitosan without calcium gluconate exhibited sustained drug release for the longest period of time, which was 24 h. The ocular tolerance studies indicated that the Formulation was well tolerated in rabbits and could be safely administered to humans. The alginate/chitosan minitablet was found to have good antimicrobial activity. Formulations With higher chitosan content had improved bioadhesive strength and force of adhesion. It was concluded that this was a good vehicle for the treatment of bacterial keratitis and conjunctivitis.

Ciprofloxacin-loaded mini-tablets
Mortazavi and co-workers prepared and evaluated mini tablets using ciprofloxacin as the model drug with the aim of obtaining sustained and controlled release of the drug. Sustained-release polymers such as hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, and hydroxyethyl cellulose were used, together with Carbopol 974P. Direct compression was used to obtain mini-tablets of 3 mm diameter. Carbopol improved adhesive properties in all the formulations and contributed to the integrity and compactness of the mini-tablets. Results indicated that the choice and concentration of cellulose derivatives used affected the rate of drug released. In-vitro studies showed that a formulation containing 72% (w/w) ethyl cellulose, 4% (w/w) Carbopol 974P, 1% (w/w) NaSF, 20% (w/w) mannitol and 3% (w/w) ciprofloxacin demonstrated the most sustained drug release over a period of 5 h. In-vivo studies were not carried out.

Developments and future outlook
It is evident from research that the eye poses a hurdle to drug delivery owing to its complexity. Mini-tablets were evaluated, with favourable results. However, despite the positive findings, some limitations are present. For instance, it was reported that in some cases the mini-tablets displayed a tendency to move around in or fall out of the eye. This Could hinder the drug release process and cause discomfort for the subject. Thus, advanced systems are constantly being sought and tested for improved topical ocular drug delivery. Innovations are necessary to assist in overcoming the limitations of current systems and offer hope for treatment of debilitating ocular diseases. Commercialization of products has been
minimal. For example, only one non-invasive inserts (Ocusert), developed by Alza Corporation, and was commercialized, in 1974. However, it was not widely used because of difficulty in inserting and ejecting the device from the eye, as well as irritation during insertion.\textsuperscript{104} this led to commercial failure, which resulted in the withdrawal of the product from the market.\textsuperscript{7} In 1982, Lacrisert was approved for dry eye treatment. As pointed out by Kumaran \textit{et al.},\textsuperscript{21}such setbacks may be attributed to factors such as reluctance of manufacturers and health care providers and receivers to move away from traditional systems, high cost, and flaws in the delivery system itself at the application level. Extensive progress in the field of ophthalmology and pharmaceutical drug delivery has been made, but evidently the simplest and earliest-developed delivery systems, Namely eye drops, still dominate the market. For example, Voltaren contain the active ingredient diclofenac sodium and are indicated for inflammatory conditions. The solution contains hydroxypropyl-\(\gamma\)-cyclodextrin, an excipient of interest, which assists with corneal permeation of the drug.\textsuperscript{110} additionally, gels and suspensions are also commonly prescribed for conditions such as dry eye, glaucoma and infections.

A forward-thinking approach to achieve improved drug delivery to the anterior eye through the use of fast-dissolving mini-tablets is proposed. Fast-disintegrating systems (also called ‘fast-melt’ or ‘fast-dissolving’) have been investigated as novel replacements for conventional solid tablets. These systems are solid dosage forms that disintegrate rapidly, usually in the time frame of minutes or seconds. Most commonly used orally, these systems quickly dissolve once exposed to salivary fluid, and this minimizes the need for external water or fluid medium.\textsuperscript{111,112} Solid, fast-disintegrating systems offer the following Advantages: (1) lack of discomfort, owing to small size and light structure; (2) less force/pressure required for preparation of fast-disintegrating tablets and thus minimal Chances of damage and degradation\textsuperscript{113}; (3) easier handling during transport and storage\textsuperscript{114}; (4) aesthetically pleasing, elegant cake-like appearance; (5) convenient administration and accurate dosing compared with liquid formulations\textsuperscript{115}; and (6) rapid hydration owing to their porous structure, thus reducing foreign-body sensation in the eye. Preservatives are not required, as in the case of conventional liquid formulations. Thus, to help improve the administration, compliance and bioavailability of topically administered drugs the concept of fast disintegrating systems can be implemented for ocular drug delivery systems

**CONCLUSIONS**

Topical drug delivery systems remain standard and acceptable for treatment of conditions of the anterior eye. However, patients often find frequent instillation of medication challenging, resulting poor compliance. Numerous systems have been developed, and others are still being investigated, as seen from this review. Solid ophthalmic dosage forms display interesting and significant in-vivo behaviour. Mini-tablets are promising ocular drug delivery systems, with mucoadhesive properties, for the treatment of conditions that would otherwise require continual eye drop instillation. An increasing number of people are being faced with ocular conditions that affect sight and can lead to irreversible vision loss. Therefore, the development of newer ocular drug delivery systems – and more importantly, their success – is of paramount importance and will surely benefit patients who suffer from ocular diseases.

Novel systems resulting in improved ocular drug delivery are required to overcome the barriers to treatment posed by the eye and, ultimately, to improve patient safety and compliance. Development of solid ocular drug delivery systems may lead to further advancements in the future. At a manufacturing level, these systems are feasible and viable to produce with simple procedures employing cheap and readily available components. Their superior properties would allow for the development of a suitable delivery system, which could be used as a platform for delivery of drugs to various other sites.

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