Review Article
Ophthalmic Dosage Forms

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Abstract

Topical dosage forms represent about 90% of the formulations available in market. Since many years ago till now, ophthalmic dosage forms elucidate major challenges in clinical and pharmaceutical fields, thought a lot of progress and advanced technology have been achieved to improve the currently available ophthalmic drug delivery systems. Generally, the ocular diseases are complicated and difficult to treat. Besides, the ophthalmic dosage forms should be sterile, isotonic, safe and non-allergic for the patients. This review article briefly introduces different types of ophthalmic dosage forms and the advantages and limitations of each.

Key words: Ophthalmic, dosage forms, drug delivery system.
Conflict of Interests: None.

الاشكال الصيدلانيه المخصصه للعيون

دعاء جعفر جابر ابراهيم التميمي, افاق مهدي عمو الجنابي, ميس عماد العاني, جعفر جابر ابراهيم التميمي

ألخلاصه

تشكل الاشكال الصيدلانه الموضعيه حوالي 90 بالمائه من التركيبات الموجوده في السوق ومنذ عه سنوات ولحد الان فان المستحضرات الصيدلانيه المخصصه للعيون تشكل تحدي كبيرفى المجالات السريريه والصيدلانيه بالرغم من التقدم التكنولوجي الكبير اللذي حصل لتحسين الاشكال الصيدلانيه المخصصه للعيون وبصوره عامه فان امراض العيون معقده وصعبه العلاج هذا بالاضافه الى ان مستحضرات العيون تحتاج الى التعقيم ويجب ان تكون امينه ولا تسبب الحساسيه للمريض لذلك فان هذه المراجعه تقدم شرح مختصر للاشكال الصيدلانيه المخصصه للعيون بالاضافه الى الفوائد والعوامل التي تحدد استعمال هذه المستحضرات

1. Introduction

Ophthalmic drug delivery systems might be preferable relative to other delivery systems in spite of its potential risks and complications (1, 2). Moreover, in comparison to oral drug delivery systems, ocular drug delivery may provide equivalent or better bioavailability in the eye (3). Many approaches were tested for the improvement of the rate and/or the extent of bioavailability

of the ophthalmic drugs, the controlled release of the dosage from, and consequently improving the therapeutic effect and reducing the side effect of the drug (4).

The main objectives for the development of ophthalmic drug delivery systems are to achieve the required and appropriate drug concentration in the site of absorption and sustaining the drug levels for necessary time intervals which in turn contributes to reducing application frequency. Many approaches were investigated to increase the rate and/or the extent of absorption of ophthalmic formulations. One of the these approaches involved modifications of the conventional ophthalmic drug products by introducing polymers to the formula which lead to lengthening the contact time of the active ingredient(s) in the corneal surface and consequently elevation in the rate and/or the extent of bioavailability of the active ingredient(s). The other approach is by introducing excipients to ophthalmic formula which lead to enhancement in the penetration of the active ingredient(s) into the eyeball. These excipients included and (not limited to) cyclodextrins, chelating agents and surfactants. These excipients form inclusion complexes with the active ingredient(s). This approach leads to elevation in solubility, permeability, and consequently in the rate and/or extent in drug absorption and the bioavailability of poorly soluble drugs. The primary advantages of applying the above-mentioned approaches in addition to improving bioavailability of active ingredient(s), involving the possibility of increasing resistance to eye defense mechanisms (such as tearing), targeted therapy, ensuring patient's comfort and reducing the loss of drug to other tissues (4, 5). The disposition of ophthalmic dosage forms including the absorption, distribution and elimination of ophthalmic drug delivery systems is summarized in Diagram 1 (6).

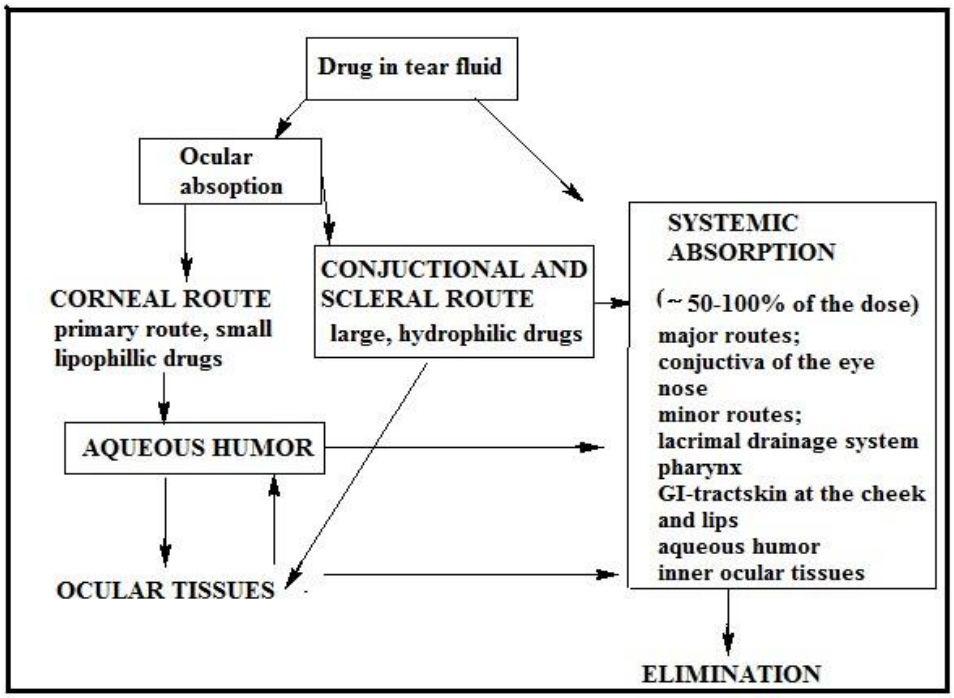

Diagram 1: disposition (absorption, distribution and elimination) of ophthalmic drug delivery systems (6).

The current manuscript was aimed to present a brief review concerning the ophthalmic dosage forms including the ocular physiology and anatomy, in addition to some of the available ophthalmic products.

2. Physiology and anatomy and of the eye

The eyeball is composed of many layers with specifics structures and it is divided to two segments. The first one is the anterior segment which include cornea, conjunctiva, aqueous humor, iris, ciliary body and lens. The second one is the posterior segment which involve retina, choroid, sclera and vitreous humor (3, 7, 8). The ocular structure and barriers are depicted in figure 1 (7).

The eye is surrounded by three different layers including the layer, the medium and the inner layers. The outer layer is composed of the cornea and the sclera which are fibrous tissue and have a protective function for the eyeball. The anterior and posterior segments of the eye are anatomically separated by the sclera and the cornea (figure 1).

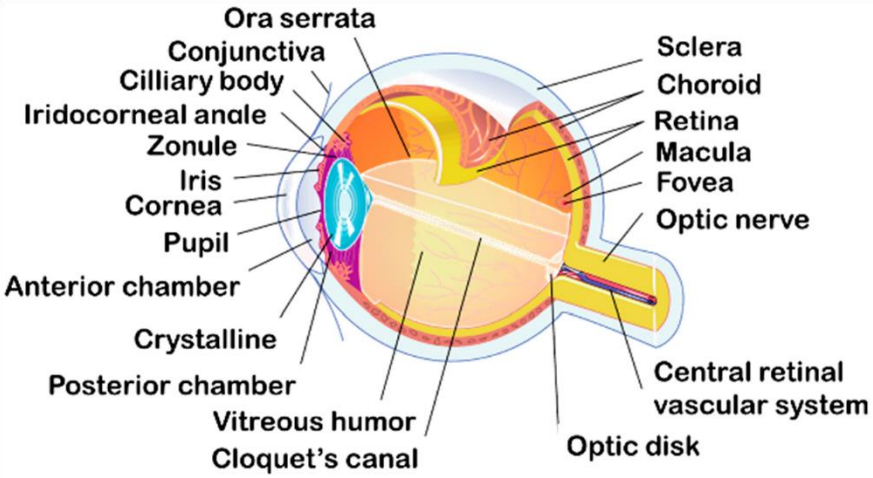

Figure 1: Schematic illustration of ocular structures and barriers (7)

The middle layer is a vascular envelope which is also called uvea. This layer formed by the iris, the choroid and the ciliary body. The iris is a contractile, circular membrane opened at its center by the pupil. It is the color part of the eye located to the posterior region of the cornea. At the posterior part of the middle layer (uvea) is the choroid which is a highly vascularized membrane. The uvea supplies nutriments and oxygen to the iris and retinal photoreceptors. The ciliary body is located between the sclera and the retina and secrets the aqueous humor with the ciliary processes and contains smooth muscles that control the shape of the lens. The retina is the innermost tissue of the eye. The retina is the neuronal tissue responsible of the vision and composed of two types of tissues (figure 1).

The inside of the eye is composed of three major compounds including the crystalline, the aqueous and the vitreous humors. The crystalline is a biconvex, transparent lens located behind the iris and the pupil. It is avascular, elastic organ connected to the optical layer by the ciliary

body. The crystalline separates the aqueous humor from the vitreous humor. The crystalline function is to allow the accommodation by concentrating the light on the retina with its contraction. The aqueous humor is a clear optical fluid with low viscosity located in the anterior and the posterior chambers of the eye (9). The anterior and the posterior chambers contain 0.250 and 0.060 ml of aqueous humor, respectively (10). The aqueous humor also maintains the intraocular pressure of the eye and the convex form of the lens. The vitreous body which is also called vitreous humor is located between the crystalline and the retina and composed of 99% of water. The vitreous body helps in maintaining the structure of the eyeball and plays the role of a lens in the delivery of the light ray (figure 1).

The ocular annexes represent the external anatomic parts of the eye, it is necessary for the proper functioning of the ocular apparatus as the muscles, the eyelids and the lacrimal apparatus. The eyelids are the first protection for the eye. They are movable folds of skin that covers the ocular surface, hydrate the cornea and clean the surface of the eye from debris. The superior eyelid regulates the light reaching the eye by using extraocular muscles (figure 1).

The meibomian glands are located inside of the eyelid. The meibomian glands are small, oily and sebaceous annexes secreting lipids and proteins to cover and protect the surface of the eye and reduce the evaporation of water contained in the tears. The lacrimal apparatus is responsible of the tear secretion, which allows the evacuation of the debris from the ocular surface and the hydration of the eye. Human tears have a mean osmolarity of 310 mOsm/kg and a tonicity equivalent to that of 0.9% sodium chloride solution (8). The tears film represents the first line of the entire ocular barrier. It washes the surface of the eye from the debris and protects the eye from the desiccation (figure 1).

The blood ocular barriers are composed of the blood/aqueous and the blood/retinal barriers.

They are physical barriers between the blood and the eye that has a main function in the penetration, the elimination of ophthalmic route's drugs and the maintenance of the homeostatic control (11). The blood retinal barrier is a posterior segment barrier forming an inner barrier in the endothelial membrane of the retinal vessel and an outer barrier in the retinal pigment epithelium (11, 12). The blood retinal barrier prevents diffusion of the drugs in the posterior part of the eye and is responsible for the homeostasis of the neuroretina. The blood retinal composed of nonleaky tight junctions, these junctions have a high degree of control of solute and fluid permeability. The retinal pigment epithelium controls exchange of nutriments with colloidal vessels. Retinal capillary endothelial cells and retinal pigment epithelial cells are connected to one other with tight junctions (13). The permeability of the blood/aqueous barrier is controlled by the osmotic pressure due to the sodium, chlorine and bicarbonate transport and by the physical-chemical characteristics of the drugs. Passages from the aqueous humor to the blood of lipophilic molecules are passive, and active for hydrophilic molecules. These barriers restricted the entry of drugs from systemic circulation to the posterior eye segment and conversely. Ocular inflammation, intraocular surgery, trauma and vascular disease can alter the ocular barrier.

Breakdown of blood/ocular barrier may occur due to acute inflammation caused by intraocular surgery, induced ocular hypotony, and the use of inflammatory mediators. These cases can be

solved by self-limited action of the inductive drug, administration of anti-inflammatory or anti-hypotensive drug (figure 1).

For many years, the investigators explored and developed different routes and dosage forms for ophthalmic administrations as shown in figure 2 (13). These drug delivery systems can penetrate the eye through the anterior or the posterior segments of the eye.

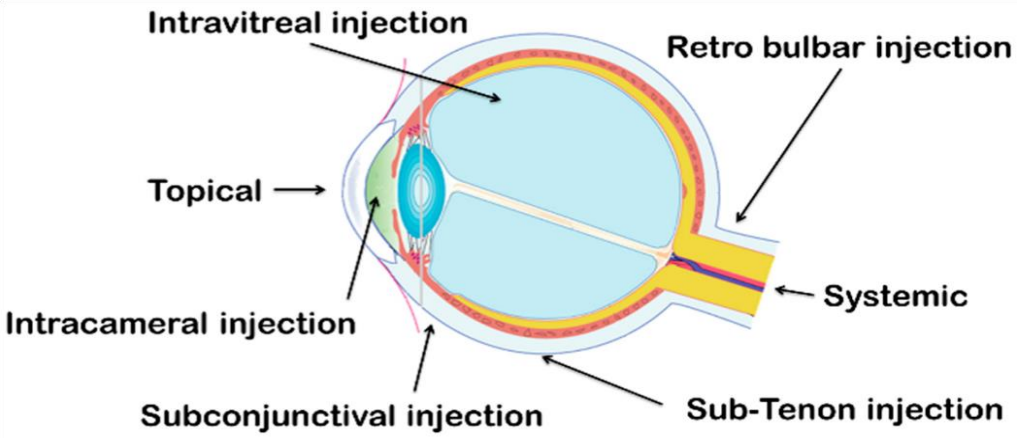

Figure 2: Routes of ophthalmic administration (13).

3. Ophthalmic dosage forms

3.1. Liquid ophthalmic dosage forms (14-27)

Several investigations and technological researches were conducted for the modifications of liquid ophthalmic drug delivery systems. Besides, many approaches were proposed in order to extend the time interval of contact of liquid dosage forms with eye tissues to increase the active ingredient(s) absorption and consequently bioavailability to eye tissues. These modifications involve (and not limited to) many approaches such as addition of substances which increase viscosity, drug penetration and using prodrugs or cyclodextrins.

Extending the contact time of drug(s) with cornea and consequently improving bioavailability may be obtained by increasing the preparation viscosity by the addition of substances such as hydrophilic polymers of high molecular weight. These polymers do not diffuse through biological membranes of the eye tissues and can form three-dimensional networks in the water. Examples of such polymers involve polyvinyl alcohol, poloxamers, hyaluronic acid, carbomers, and polysaccharides, which include cellulose derivatives, gellan gum, and xanthan gum (15, 19). It appeared from investigations that maximum increase of penetration through the cornea by a solution in the form of eye drops occur when the viscosity falls into the range of 15 to 150 millipascal second (mPa.s.). An extreme example of using substances increasing viscosity is the forming gels which would enable reducing the frequency of drug application to once daily. The main disadvantage of this formulation is blurring of vision which limit its acceptability by patients (15, 19). The hydrophilic polymers employed recently in many ophthalmic products as compounds that exhibit mucoadhesive properties rather than for increasing viscosity (15).

Mucoadhesive ophthalmic drug delivery system is characterized by higher bioavailability in comparison to conventional forms (16). Candidates polymers which were tested in the direction of mucoadhesion and elevation drug(s) bioavailability in ophthalmic liquid formulations involve (and not limited to) polyacrylic acid, hyaluronic acid, sodium carboxymethyl cellulose, and chitosan. Other candidates which extend the time interval of contact with eye surface are lectins (15, 16, 19). Examples of such ophthalmic liquid formulations are NyoGel produced by Novartis (timolol maleate) and Pilogel produced by Alcon Laboratories (pilocarpine hydrochloride) are containing cross-linked polyacrylic acids Carbomer and Carbopol, respectively, which exhibit mucoadhesive properties (25).

Further important developments on liquid ophthalmic drug delivery systems were achieved by adding penetration increasing materials. The main objective of adding penetration increasing materials for active ingredient(s) used in liquid ophthalmic preparations is to enhance their corneal absorption by modifying the continuity of corneal epithelium structure. The investigations demonstrated that substances including bile acid salts, chelating agents, surfactants, and preservatives (like benzalkonium chloride) could be used as penetration increasing materials. However, the usage of these materials was restricted due to their local toxicity on the eyes (14, 15).

Liquid ophthalmic drug delivery systems are mentioned below:

3.1.1. Eye drops:

Eye drops are presented in different sterile and isotonic forms including water and oil solutions, emulsions, or suspensions containing one or more active ingredients. The eye drops may contain preservatives if stored in multiuse packaging. The optimum pH for eye drops should be identical to tear fluid which is about 7.4. Besides, buffering the active ingredient(s) should take into consideration concerning the stability of the active ingredient(s) and the tolerance of eye tissue to the eye drops. The pH of the eye fluids range between 4–8, if the PH of eye formula is out of these ranges, the eyes dose not tolerate the formula and the patient may feel discomfort and irritation and lead to reducing the active ingredient(s) bioavailability due to tearing of the eye (18-21).

3.1.2. Ophthalmic solutions:

Ophthalmic solutions are aqueous sterile solutions used for cleansing and rinsing eyeballs, in addition to other purposes. The ophthalmic solutions may contain excipients which regulate the PH, osmotic pressure and viscosity of the formula. Besides, preservatives may be added to the preparation if the ophthalmic solution is stored in multiuse packaging (18).

3.1.3. Microemulsions:

Among the drugs which have been developed as microemulsions are difluprednate (22), cyclosporine (23), flurbiprofen axetil and the prodrug of flurbiprofen (24). Microemulsions are promising preparations since they possess the possibility for containing larger quantities of active ingredient(s), stable, inexpensive to produce and easy to sterilize. It appeared from clinical

investigations in healthy subjects that active ingredient(s) prepared as microemulsions eye drops lead to elevation in bioavailability and elongation in duration of action of drug(s).

3.2. Semisolid ophthalmic dosage forms

Semisolid ophthalmic drug delivery systems include the following dosage forms:

3.2.1. In-situ gels or sol-to-gel:

Active ingredient(s) used in research conducted on in-situ gels, for examples ciprofloxacin hydrochloride, timolol maleate, fluconazole, ganciclovir, and pilocarpine. In-situ gels are viscous liquids having the ability to undergo sol-to-gel transitions when exposed to external factors such as appropriate pH, temperature, and the presence of electrolytes. This property lead to reducing drug drainage from the eyeball surface and elevate the bioavailability of the active ingredient(s). The polymers used in developing in-situ gels include gellan gum, poloxamer, and cellulose acetate phthalate (14–16, 19).

3.2.2. Eye ointments:

Eye ointments are semisolid dosage forms for external use and usually composed of solid or semisolid hydrocarbon base of melting or softening point close to human body temperature. Eye ointments decomposes into small drops after applying to the eye, these drops remain in conjunctival sac for longer period, thus, the bioavailability of eye ointment is higher than eye drop. Generally, most eye ointments are safe and well tolerated by patients, however, they have some disadvantages such as irritation and blurred vision, therefore, eye ointment is recommended to by applied at bedtime (19).

3.3. Solid ophthalmic dosage forms

Solid ophthalmic drug delivery systems include the following dosage forms:

3.3.1. Contact lenses coated with drugs:

Interest in contact lenses is still growing and confirmed by increment in the number of researches presented in recent years. Examples of drugs whose pharmaceutical availability from contact lenses include timolol (28), ciprofloxacin (29), dexamethasone (30), and cyclosporine (31). This dosage form can absorb on its surface water soluble substances which are released after application over the eyeball for a longer period. The first and most widely used polymer in the production of lenses was the cross-linked poly(2-hydroxyethyl methacrylate) with small amount of ethylene glycol dimethylacrylate (26, 27). Recently, some investigations were conducted on employing silicon-based lenses (28–31).

3.3.2. Ocular inserts (32-38):

Ocular inserts are solid or semisolid dosage forms. An example of well-known insoluble insert is Ocusert produced by Alza Corporation containing pilocarpine as an active ingredient and built from copolymer of ethylene and vinyl acetate (16, 19, 38). There are many advantages of ocular inserts over the conventional ophthalmic drug delivery systems. Among these advantages are: accurate dosing, the possibility of slow release of the active ingredient(s) with constant speed and limiting systemic absorption, less susceptibility to defense mechanisms (like outflow through

nasolacrimal duct), stay in conjunctival sac for a longer period, and are more stable than traditional ophthalmic dosage forms. Besides, using ocular inserts enables reducing the frequency of drug application frequency and decreasing the occurrence of adverse effects and blurred vision (16, 32).

The primary defects and factors limiting the application of ocular inserts in therapy are the compliance since most patients are still unwillingness to leave the conventional ophthalmic dosage forms due to the feeling of ocular inserts as foreign body in the eye and sporadic failures in using and introducing inserts such as unnoticed excretion from the eye (15, 16, 32, 38).

Polymeric substances are most often employed in developing ocular inserts including methylcellulose (33) and its derivatives (hydroxypropyl methylcellulose (HPMC) (19, 32–34), ethylcellulose (33, 35, 36), polyvinylpyrrolidone (PVP K-90) (19, 32, 36), polyvinyl alcohol (19, 34), chitosan (32) and its derivatives (like carboxymethyl chitosan) (33), gelatin (35, 37), and various mixtures of the abovementioned polymers. Employed polymers indicate the division of inserts into soluble, insoluble, and biodegradable.

3.3.3. Soluble ophthalmic drug inserts (SODI):

This form of ophthalmic drug delivery system was originally developed for astronauts to apply it in the state of weightlessness. The SODI are soluble eye inserts in the form of small oval wafers produced from acrylamide, N vinylpyrrolidone, and ethyl acrylate. After application of SODI to conjunctival sac, they are moist ended by tear fluid and then they soften and adhere to eyeball surface. This dosage form ensures prolonged effect since the release of the active ingredient(s) from SODI is in pulsational and uncontrolled manner. Examples of drugs employed in SODI involve sulfapyridine, neomycin, tetracaine, kanamycin, atropine and pilocarpine (15, 39, 40).

3.3.4. Minidiscs/ocular therapeutic system (OTS):

This ophthalmic drug delivery system (OTS) is identical to contact lens with 4 to 5 mm diameter. The candidates drugs employed in OTS are sulfisoxazole and gentamicin sulfate. The OTS may be either hydrophilic or hydrophobic which enables extended time interval of the release of poorly water soluble and water soluble active ingredients. The OTS is a profiled, convex outside, concave from the side of contact with eye surface. The main copolymers used in OTS preparations are α-ω-bis(4-methacryloxy)-butyl poly(dimethylsiloxane) and poly(hydroxyethyl methacrylate) (15, 39, 41).

3.3.5. Artificial tear inserts:

Artificial tear inserts were developed from hydroxypropyl cellulose. It is available on the market under the name Lacrisert. It is employed for treating dry eye syndrome. It is a long, rod-shaped pellet, containing no preservatives. After introducing the artificial tear insert to conjunctival sac, the insert absorbs water from conjunctiva and cornea forming a hydrophilic layer which stabilizes the tear film and moistens the cornea (16).

3.3.6. Collagen shield:

Collagen shields were studied on animal and human models and may be used as carriers of anti-inflammatory drugs such as dexamethasone, antibiotics like gentamicin or antiviral drugs. Applying collagen shields leads to obtaining higher drug level in the cornea and the aqueous humor in comparison to contact lenses and eye drops (15, 41). Collagen shields were developed from porcine sclera since this collagen show similarities to the collagen found in human cornea. The Collagen shields should be stored in dry condition and hydrated before they are introduced to the eye. The main defects of collagen shield is that the standard dosage from applied by an ophthalmologist are not individually suited to the eyeball of the patient and may cause certain discomfort due to interfering with vision. Besides, collagen shields may be accidentally excreted from the eye just after introduction to the eyes (16). A dosage form was recently built from collagen called collasomes which are small pieces of collagen (1mm×2 mm× 0.1 mm) suspended in 1% methylcellulose vehicle. This dosage form (collasomes) has succeeded to overcome all the defects of collagen shields (16, 41).

3.3.7. New ophthalmic delivery system (NODS):

In comparison to traditional eye drops, NODS ensure delivery of the required drug dose to the eyeball and improve its bioavailability even for several times as in case of pilocarpine in which there was eightfold improvement in its bioavailability. Besides, NODS do not contain preservatives and can be sterilized by gamma rays. This ophthalmic drug delivery system was patented by Smith and Nephew Pharmaceuticals Ltd. It is composed of solidified paper handle and a flag from polyvinyl alcohol (containing the drug) attached to the handle with a soluble membrane. A film containing drug separates from the paper handle at the point of introduction to conjunctival sac, and then dissolves in the tear fluid, and consequently releasing the drug from the film (42–44).

3.3.8. Minitablets:

The candidate drugs which were formulated as minitablets ophthalmic delivery system involved gentamicin, acyclovir, piroxicam, timolol and ciprofloxacin (45-48). Minitablets are biodegradable, solid drug forms, that when introduced to conjunctival sac transit into gels. The formation of gel lead to extending the time interval of contact between the drug and the eyeball surface and consequently improve the bioavailability of the drug (49). There many advantages of minitablets dosage form involving: resistance to defense mechanisms by tearing or outflow through nasolacrimal duct, easier for introducing to conjunctival sac, longer contact time with the cornea due to the presence of mucoadhesive polymers, and the gradual release of the drug from the preparation at the application site caused by swelling the outer carrier layers (45, 46). The development of minitablet formulations are by applying direct or indirect compression methods. The indirect approach is achieved by tableting the granules obtained from the direct compression method. The advantage of indirect approach is the dry granulation stage which improve the flow properties of powders (which often contain bioadhesive polymers). The indirect

compression method enables larger production scale (relative to laboratory scale) of minitablet dosage forms (49).

4. Conclusions

In the last decades, pharmaceutical and clinical researchers in addition to the drug industries have made major advances in the field of ophthalmic drug delivery systems. Besides, ongoing developments and several outstanding achievements have been published. However, still vast majority of drugs intended for ophthalmic applications are formulated as eye drops. The researches are still looking for the ideal and perfect ophthalmic delivery system which have the desired properties such as ease of application, non-irritating, controlled release characteristics, reduction in the systemic effect(s), and extended retention time at the site of application. The primary problems and difficulties associated with the development of new ophthalmic drug delivery systems include the need for adequate knowledges in the physicochemical properties and invitro/invivo correlation. The current article presents brief review of some published data which ought to help the investigators for future studies to be achieved on conventional and new ophthalmic dosage forms.

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