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An Ocular Route of Administration for Drugs through Novel Approach of Self-microemulsifying Formulation – A Systematic Review

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Abstract

Drug administration through ocular route is associated to treat the ophthalmic diseases; glaucoma, conjunctivitis, retinal disorder, and diabetic eye problems. Various ophthalmic formulations as nanoparticles, nanoemulsion, microemulsion, nanosphere, microsphere, and nanosuspension have been developed. Such novel formulations have ability to prolonged the contact time of dosage form on ocular surface and reduce the drug elimination. Microemulsion is the thermodynamically stable and clear dispersion of oil and aqueous phase stabilized by surfactant and cosurfactant with target droplet size up to100 nm. Self-microemulsifying drug delivery system (SMEDDS) approach is generally adopted to enhance bioavailability of poorly water-soluble drugs. SMEDDS is the appropriate system for ocular drug delivery as it improves the ocular drug retention, high ocular absorption, and extended duration of action. The surfactant/cosurfactant combination used in SMEDDS has capacity to improve drug permeation across the cornea. The review gives the highlights to understand the feasibility of SMEDDS as dosage form for ocular administration to increases or improve the bioavailability. Review highlights the developmental steps of SMEDDS for the ocular drug administration as novel dosage forms to improve patient compliance.

Keywords: Long chain triglycerides, Medium chain triglycerides, Ocular drug delivery, Pseudoternary phase diagram, Self-microemulsifying drug delivery system

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Introduction

Drug administration through ocular route is associated to treat the ophthalmic diseases; glaucoma, conjunctivitis, retinal disorder, and diabetic eye problems. The ophthalmic preparations are sterile, that is, free from foreign particles.

They are to be instilled in eye cavities. The nasolacrimal drainage, interaction of drug with lacrimal fluid, absorption of drug into lacrimal tissue, dilution with tears has influence on ocular bioavailability of drugs.[1]

Anatomic and Physiological Features of Eye

The human eye has the spherical shape with a diameter of 23 mm. The eye is an isolated, highly complex, and specialized organ for photoreceptor.

The eyeball is structurally divided into three layers.

1. The outer most layers which consist of the clear, transparent cornea, and white opaque sclera
2. In the middle layer, anterior part is iris, posterior is the choroid and ciliary body lies as intermediate part
3. Retina is the inner layer, it is an extension of the central nervous system.

The aqueous humor and vitreous humor have important role in the eye. The refractive element of the eye is Cornea. Cornea is composed of optically transparent tissues. The diameter of cornea is diameter that is about 11.7 mm with anterior surface radius that is about 7.8 mm with corneal thickness of 0.5–0.7 mm. The cornea is composed of epithelium bowman's membrane, stroma, descement's, and endothelium. The ciliary body adjusts the shape of cornea and lens. It focuses the light on retina. The receptors of retina convert nerve signal and allow them to pass to the brain. The blinking action compresses and releases the lacrimal sac. The created suction allows pull excess moisture from eyes surface. The drug gets entry inside the eye through cornea. The reason for entry of drug is associated with the structures of the cornea. Cornea consists of epithelium – stroma – endothelium, such a sandwitch structure is equivalent to a fat-water-fat composition. Hence, penetration/diffusion of non-polar compound across cornea depends on oil/water partition coefficient value.[2]

The permeability of lipophilic drugs is higher across corneal epithelium. Stroma has water-soluble (hydrophilic) nature as it forms 90% of corneal tissue. The endothelium is responsible for moisturizing the cornea. This lipophilic and hydrophilic structure is an effective barrier for the permeability of hydrophilic and lipophilic drugs. Hence, bioavailability improvement is major step need to be taken for development of novel dosage form. There are the various formulations/dosage forms that have been developed for the delivery of drug to the ophthalmic delivery. The ocular delivery improves the precorneal residence time of the drug. New formulation such as nanoparticles, nanoemulsion, microemulsion,

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nanosphere, microsphere, and nanosuspension has been developed for ophthalmic use. Such novel formulations increases the contact time/residence time on a ocular surface and reduces the elimination. The self-microemulsifying drug delivery system (SMEDDS) is a newer approach for drug targeting through ocular route.[3]

The SMEDDS is a isotropic mixture oil, surfactant, and co-surfactant. SMEDDS has ability to form oil-in-water microemulsion on mild/gentle agitation when diluted with aqueous phase. SMEDDS is generally used for enhancement of bioavailability of poorly water-soluble drugs,[4] for example, ibuprofen, indomethacin, and furosemide. SMEDDS forms transparent microemulsion with the globule size range which is <100 nm on dilution. The SMEDDS is either solid or liquid SMEDDS. The SMEDDS is more suitable drug delivery system for ocular administration. The spontaneous formation of emulsion is facilitated by tear secretion at the ocular surface. The formed SMEDDS presents the drug in dissolved form and smaller droplet size can provide larger interfacial surface area for prolonged drug absorption. The presence of lipid in the formulation helps to improve the bioavailability, for example, cyclosporine, ritonavir, and ibuprofen by affecting the drug absorption.[5]

For selecting the self-emulsifying solvents, it is important to access following parameters

a. Droplet size of globules
b. The drug solubility in various compounds
c. Identification of self-microemulsifying zone using phase diagram.[6]

Advantages of SMEDDS

1. It is a novel/newer approach to improve solubility, dissolution rate, bioavailability of poorly water-soluble drugs, for example, ketoprofen, paclitaxel, and acyclovir[7,8]
2. Reduce the dose of the drug, for example, halofantrine[9,10]
3. Ease of industrial scale up[11]
4. SMEDDS provides protection to drug against degradation from hostile environment of gut, for example, progesterone[12]
5. Reduces the intra- and intersubject variability, for example, cyclosporine[13]
6. More consistent and temporal profile of drug absorption[14]
7. SMEDDS is easy to store as it belongs to the thermodynamics stable system[15]
8. Improve the precorneal residence time of the drug, for example, chitosan[14]
9. It has capability to sustain the release of drug, for example, ophthalmic lenses and celecoxib[15,16]
10. Prolonged/increases the contact time of drug on the ocular surface, for example, polycaprolactone and chitosan[17]
11. The certain surfactant/cosurfactant combination used in SMEDDS can enhancing effect of drug permeation across the cornea, for example, Span 20, Span 80, Tween 20, Tween 80, Propylene glycol, and PEG 400[4]
12. The dispersion of ME in an aqueous phase, it can be thermodynamically stable and will not breakdown overtime
13. The nanosized emulsion which can help to improve the patients' satisfaction and compliances.

Disadvantages of SMEDDS

1. Lipid-based formulation is lack of good predicative *in vitro* model for assessment of formulation that is a major challenge for lipid-based formulation. Digestion before release of drug is main concept, so traditional dissolution methods fail to justify
2. Formulation containing various component it become more challenging to validate.[18]

Composition of SMEDDS

For the development of SMEDDS formulations, selection of oil, surfactant, and cosurfactant is a major concern.

Oil Phase

Selection of oil and its proportion in formulation determines the amount of drugs that can be solubilized. The oil phase in the system has the capacity to solubilize the hydrophilic/lipophilic drugs to improve bioavailability. The oil phase represents long chain triglycerides (LCT) and medium chain triglycerides (MCT), both will be useful with different degree of saturation for the design of SMEDDS.[19]

LCT

Lipid contains the fatty acids chain of 14–20 carbons which are categorized as LCT. Fixed oil, that is, vegetable oils contain a mixture of glyceride of unsaturated long chain fatty acids. They are safe and commonly available in daily diet. LCT possess high capacity for lipophilic drugs. It is attributed to large hydrophobic portion of triglycerides.

MCTs

MCTs contain the fatty acid chain of 6–12 carbons. MCT is resistant to oxidation, high solvent capacity in comparison to LCT; it is attributed to high concentration of ester group. MCTs are formed by the distillation of coconut oil are known as glyceryl tricaprylate. Solubilizing capacity of oil for lipophilic moiety increases correlation of chain length of oils. Hence, the selection of oil is dependent between correlation of solubilizing potential of oils and its ability to form microemulsion.[20]

Surfactant

An amphiphilic molecules possess a polar group (hydrophilic) and non-polar group (lipophilic) in their structure. The non-ionic surfactants are widely recommended with relatively high HLB values. It is preferred over ionic surfactant. Ionic surfactant is toxic. Surfactants have less self-emulsification capacity. In general, the concentration of surfactant is range between 30% and 60% w/w to form a stable SMEDDS. The selection of surfactants is dependent on rapidity, efficiency, solubilizing capacity for drugs, nature of emulsion to be formed, and cloud point of surfactants. The surfactants which have high HLB immediately forms microemulsion and spread rapidly on the aqueous media. The dispersion is generally dependent on the intermolecular forces. Polyoxyethylene surfactants are widely used in formulation.[21]

Cosurfactant

For the formation of optimum SMEDDS, the cosurfactant is used to reduce the concentration of surfactants. The SMEDDS can

Table 1: Literature data for ocular drug delivery through SMEDDS formulations

Drug	*Oil*	*Surfactant*	*Cosurfactant*	*Outcomes*
Prednisolone	Linoleic acid	Cremophore RH 40	Propylene glycol	Improved the bioavailability, it has capabilities to form o/w microemulsion with uniform globular size.[30]
Fluconazole	IPM	Tween 80 and Span 80	PEG 400	Prolonged fluconazole release, higher bioavailability, and lower drug elimination rates in different eye tissues and aqueous humor. Improvement of fluconazole ocular bioavailability.[31]
Moxifloxacin	Isopropyl myristate	Span 20, span 80	Acetate buffer	Optimized ME having good stability, ability to increases the bioavailability through its longer precorneal residence time, and its ability to sustain the drug release.[32]
Dexamethasone	Isopropyl myristate	Tween 80	Propylene glycol	The average globule size is less than 200 nm. The developed microemulsion revealed stability for 3 months. The *in vivo* studies evidenced marked improved therapeutic effect of the incorporated steroids.[33]
Ofloxacin	Oleic acid	Tween 80	Ethanol 0.5 N NaOH as aqueous phase	The formulations were sterile and MIC values were the same for both M1OFX and M2OFX. The residence time of preocular was improved by microemulsion in comparison to solution.[34]
Moxifloxacin	Ethyl oleate	Tween 80	Sodium alginate	Moxifloxacin microemulsion gel exhibited better wettability, higher drug levels, and prolonged residence in the cornea. Moxifloxacin microemulsion gel represents an alternative for preventing corneal infections.[35]
Diclofenac	Isopropyl myristate	Tween 80	Glycerine	The droplet size for all formulations of ME was found in the range of 220–480 nm. The formulations showed the effect of sustained release up to 24 h.[36]
Brinzolamide	Triacetin	Tween 80	Transcutol	Brinzolamide poorly soluble drug helps in lowering the elevated intraocular pressure associated with ocular hypertension or open-angle glaucoma. The *In vitro* study using dialysis bag method and *ex vivo* transcorneal permeation test using franz diffusion cell (excised bovine eye) was performed. The refractive index is found to be 1.35–1.36 and pH less than 6 for the developed *in situ* gel nanoemulsion. The optimized *in situ* gel nanoemulsion showed improved transcorneal permeation over suspension form.[42]
Diclofenac sodium	Oleic Acid	Tween 20, Kolliphore RH 40,	PEG 200 PEG 400	Developed formulation showed an optimum particle size and shape confirmed by TEM and particle size analysis. The developed nanoemulsion gel formulation resulted easy permeation across the cornea.[43]
Celecoxib	Oleic Acid, Transcutol	Tween 80 Span 20	Propylene Glycol	Rabbit corneal permeability study was performed for the prepared nanoemulsion formulation of celecoxib. The results showed improved permeation across the corneal area. The study confirms that any change in content and composition of nanoemulsions could change permeability parameter.[44]
Dorzolamide hydrochloride	Isopropyl myristate, Miglyol 812, Triacetin	Tween 80, Cremophor EL	Propylene Glycol, Transcutol P, Miranol C2M	The research work is aimed to nanoemulsion-based eye drops for dorzolamide hydrochloride and formulation showed enhanced bioavailability.[45]
Indomethacin	Castor Oil	Tween 80	Cremophor EL	Indomethacin nanoemulsion was prepared as o/w type of nanoemulsion using high-pressure homogenization.[46]
Acyclovir	Triacetin	Poloxamer 407 Poloxamer 188	Transcutol P	Acyclovir thermosensitive *in situ* gel nanoemulsion prepared resulted in acceptable physicochemical properties and prolongs drug release as sustained release. Formulation resulted in high permeation of acyclovir through the excised bovine cornea.[47]
Prednisolone	Cator Oil	Tween 20	-	Prepared nanoemulsion is transparent. Optimized batch showed average globule size of 110 nm with PDI less than 0.11. The *in vitro* drug release study suggests sustain release behavior up to 12 h.[48]
Moxifloxacin	Ethyl Oleate	Tween 80	Solufor P	The nanoemulsion prepared was evaluated by ex-vivo permeation, antimicrobial activity and ocular irritation study. The optimized nanoemulsion is compared with conventional commercial eye drop formulation (control). The drug release kinetics follow Higuchi Diffusion controlled mechanism.[49]

follow the dynamic process. Cosurfactant and surfactant together provide sufficient flexibility for a film to form microemulsion over a wide range of composition. The proportion of surfactant and cosurfactant and its type used plays a major role in the formulation of SMEDDS. Hence, proper selection of surfactant and cosurfactant is prerequisite step for the development of SMEDDS. Ethanol, PEG, propylene glycol, and transcutol P are widely used of cosurfactants.[22,23]

Formulation Design

The formulation of SMEDDS that can involve the following steps are as follows.

1. Screening of excipients
2. Construction of pseudoternary phase diagram
3. Preparation of SMEDDS (Liquid SMEDDS)
4. Conversion of liquid SMEDDS to solid SMEDDS
5. Characterization of SMEDDS.

Screening of Excipients

Solubility studies

The solubility of drug in various oil, surfactant, and co-surfactant need to be tested.[37,38] These studies can be performed by shake flask method. The objective of solubility studies is generally performed for the selection of oil, surfactant, and cosurfactants. The oil, surfactant, and cosurfactants which possess maximum solubilization capacity will be used further for development of SMEDDS. Similarly, optimum drug loading with minimum total volume of oil, surfactant, and cosurfactants is the objective for the estimation of solubility of drug in various oil, surfactant, and cosurfactants.[24,39,40]

Construction of Pseudoternary Phase Diagram

The pseudoternary phase diagram represents changes in phase behavior of system according to the changes in composition. This diagram is used to study the phase behavior in three components as such as oil, water, and surfactant: cosurfactant mixtures. The ternary phase diagram contains the three corners that corresponding to the 100% of particular component. The ternary phase diagram can know as pseudoternary phase diagram as one of the corners corresponding to the mixture of two components such as surfactant and cosurfactant.[25]

Preparation of SMEDDS (Liquid SMEDDS)

The preparation of SMEDDS it involves the addition of drug to the mixture of oil, surfactant, and cosurfactant by homogenizing. In some cases, drug is dissolved in any one of the excipient and remaining excipients are added to the previously prepared drug solution. To allow the drug solubilization, the solution may be heated on water bath to obtain clear solution, if necessary. Then, the solution is properly mixed and tested for signs of turbidity/precipitation at the ambient temperature. The formulation should be store at room temperature until it use in subsequent studies.

Techniques for Conversion of Liquid SMEDDS to Solid SMEDDS

For the conversion of liquid SMEDDS to solid SMEDDS, various techniques were adopted as spray drying, adsorption to solid carriers,[26,41] melt granulation,[41] dry emulsion, etc.

Characterization of SMEDDS[27-29]

The developed SMEDDS formulations need to be evaluated/characterized by visual evaluation (for gradation of formed emulsion as Grade A, B, C, or D), droplet size analysis, zeta potential measurement, viscosity measurement, time for emulsification, cloud point determination, percentage transmittance, thermodynamic stability studies, stability assessment, *in vitro* drug release, and estimation of gelation temperature of gel nanoemulsion.[47]

Following Table 1 gives literature insights for the development of self-microemulsifying drug delivery for ocular administration.

Conclusion

SMEDDSs are effective novel approach for augmentation of ocular route bioavailability of poorly water-soluble/water-soluble drugs. Faster and enhanced drug release can be attained with small droplet which can be promote bioavailability. It enhances residential time on the cornea and improves the drugs bioavailability. The present review highlighted the developmental steps of SMEDDS (solubility studies, construction of pseudoternary phase diagram, and various evaluation tests) involved in obtaining a robust and stable dosage form. It is simple process with few steps which can be carried out at ambient temperature and does not require a large input of energy. SMEEDS is found to be appropriate delivery systems for ocular drug administration as it improves the ocular drug retention, high ocular absorption, and extended duration of action. The surfactant/cosurfactant combination used in SMEDDS can enhance effect of drug permeation across the cornea.

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Conflicts Of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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