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Review Article

DISCOSOMES: A FUTURISTIC UPHEAVAL IN VESICULAR DRUG DELIVERY

AMITHA MARY JOSE[1], V. U. LAKSHMI[1], GAYATHRI S.[1], SREEJA C. NAIR[1*]

[1]Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Aims Health Sciences Campus, Kochi 682041, Kerala, India
Email: sreejacnair@aims.amrita.edu

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ABSTRACT

The formulation system employed to convey pharmaceutical drugs compound in the body to attain the desired therapeutic effect at a predetermined rate depending on pharmacological aspects, drug profile, and physiological conditions can be referred to as a novel drug delivery system (NDDS). Due to the intricately sensitive anatomy and physiology of the eye pharmacologist find the ocular delivery system to be more involuted than other routes. Pre-corneal, static and dynamic is the 3 types of ophthalmic barriers, which along with the inflow and outflow of lacrimal fluids, nasolacrimal drainage, are some of the germane factors that affect bioavailability. Unlike conventional dosage forms, where the distribution of drugs in non-targeted body fluids and tissues transcends the quantity of required drug in targeted tissues and causes repercussions, these modified drug delivery systems surpass the ocular barriers and adverse reactions, emphasizing on less invasive, prolonged action. It also promotes sustained release formulation that subjugates the drug loss or degradation to treat many ocular diseases effectively. The current review recapitulates the fundamentals of discosomes, a type of vesicular drug delivery system that acts as a vehicle for the drug delivery of both hydrophilic and lipophilic drugs. Discosomes are giant, disc-shaped structures modified from niosomes by arresting the vesicles at the discosome phase. Due to their idiosyncratic size, it provides all due benefits compared to other ocular drug delivery systems. From the review, it can be culminated that discosomes are a potential subject of opposition and opportunities in the arena of safe and effective ocular drug delivery.

Keywords: Discosomes, Novel drug delivery, Disc-shaped, Giant niosomes, Non-ionic surfactant, Ophthalmic, Cul-de-sac

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INTRODUCTION

Vesicular drug delivery system is of great latitude in immunology, modelling of biologic membranes, diagnostic techniques, genetic engineering, transport of active pharmaceutical moiety, etc. It is a combination of new dosage forms and advanced techniques that have proved to be far more efficient than conventional dosage forms. This commendatory outlook overthrows the issues of drugs having poor bio-availability and rapid elimination from the body. Trans-dermal delivery is a commonly used route for the delivery of pharmaceutical compounds through dermal diffusion. The solid-lipid particulate system, emulsion-based system, solid lipid tablet, and vesicular system are the 4 kinds of lipid-based drug delivery system [1]. The targeted drug delivery system was embellished by Paul Ehrlich in 1909. The biological origin of vesicles in the delivery of drugs dates back to 1965 by Bingham and was thus named "Bingham bodies" [2]. The incorporation of a drug into vesicular structures in a system extends the bio-availability of the drug in systemic circulation and boosts its efficacy. It also alleviates toxicological effects that have been a source of hindrance in every novel drug discovery [3]. Vesicles are formed from a wide range of extremely organized amphiphilic building blocks. These building blocks confront water to incarnate as a vesicular system. Vesicular systems are defined as ordered assemblies of one or many concentric lipid bilayers. The primary objective of a vesicular drug delivery system is to deliver the therapeutic drug entity selectively to the desired site of action (receptor or organ) and restrict the drug concentration in remnant tissues. Hence the drug distribution is restricted, by en-capsuling it into a carrier system, either by structural alteration OF the drug molecule or modulation of the drug input into the biological environment [4]. It maintains the concentration of the drug at an optimum therapeutic level at the targeted site and precludes the requirement for repeated dosing. Discosomes improve the therapeutic index, stability, solubility, and rapid dissolution of the drug [5]. The different types of carriers are particulate or colloidal carriers, polymeric carriers, macro-molecular carriers, and cellular carriers. They are utilized to overcome the limited permeation of drugs into body tissues [6]. The carriers or chemical derivation may help to constrain the activity of a drug spatially in a diseased organ or tissues adjacent to it [7]. The formulator must also give due contemplation to the tolerance and stability of the final drug product, along with bio-availability. The ideal final formulation should be a combination of all these mentioned attributes [8].

Research has been conducted on recent drug forms to facilitate a controlled release of drugs to eyeball tissues as it would remarkably reduce the cost of therapy due to increased bio-availability [9, 10]. The demand for a multi-compartmental system emerged with liposomes encapsulated with drugs containing a bi-layer that showed high stability and retention [11]. The main carriers of drug compounds include immunoglobulins, certain serum proteins, erythrocytes, synthetic polymers, micro-spheres, transferosomes, liposomes, niosomes, discosomes, pharmacosomes, emulsosomes, transferosomes, ethosomes, virosomes, bilosomes, aquasomes, sphingosomes etc. Niosomes are bio-compatible and bio-degradable carriers that prolong the time of corneal contact and drug which successively hikes the bio-availability of the drug. Discosomes are a modified form of niosomes or "giant niosomes" containing solulan 24 or poly-oxy-ethylene cholesteryl ether, capable of confining aqueous soluble solutes. They are a type of vesicular drug delivery, expedient to deliver the drug to a prolonged and efficient magnitude in the systemic circulation at the ocular site, ascertain better fitting into the conjunctival sac, and do not penetrate the general circulation due to their size and disc shape [12]. They are large, soluble, structural surface-active agents which serve as drug reservoirs that catalyze the breakdown of vesicles and imparts them into a mixed micellar system. In this review paper, we propose to focus on various aspects of discosomes such as advantages, disadvantages, mechanism of action, method of preparation, characterization, evaluation, applications, and the future perspectives of discosomes. We have utilized sources like Google Scholar, Pubmed, Medscape, Medline Plus, ResearchGate, Cochrane Library, Embase, Scopus, and Science Direct. The range of years used as the filter was from 2010 to 2021 to evaluate and describe the progress of vesicular drug delivery in the past one decade.

Need for discosomes

Discosomes perform via ligand-mediated drug-targeting and are osmotically active dosage forms [13]. It imparts better drug targeting within the ocular globe by prolonging the circulation of drug molecules entrapped in vesicles [14]. It lengthens the retention time of the drug and its distribution at the ocular site, thereby

limiting fluctuations in the metabolism of the drug [15]. This escalates the ocular bioavailability of the drug that subsequently minimizes the need for frequent administration of expensive drugs, thereby reducing the cost of therapy. It also results in the perpetual action of the ophthalmic drug by averting the loss of the drug into non-selected tissues [16]. This maximizes the therapeutic benefits of the ocular drug and hence, increases patient comfort due to the convenience of administration. Exemplary active drugs available in this type of system are Ganciclovir, Timolol, Cyclopentolate [17].

Advantages of discosomes

Discosomes have a multitude of advantages due to their size, shape, physio-chemical and structural peculiarities. Because of their colossal size (12-16 µm), the drainage of discosomes into the systemic pool is restricted, thereby abating the risk of drug toxicity and renders excellent bio-compatibility [18]. The disc shape provides an accurate fit for discosomes into the cul-de-sac of the eye, and lodges onto the eye surface, which is an added eminence of discosomes over niosomes [19, 20]. Discosomal form also enhances the efficacy of the en-captured drug molecules [21]. It provides a superior mucoadhesive property to the drug by the presence of non-covalent bonds and protracts the contact time with the corneal tissue, before being flushed by tear dynamics [22]. It can be said that the adverse effects of pulsed dosing are overcome by discosomes. As discosomes embody non-ionic surfactants, they can enmesh both hydrophilic (di-hydro streptomycin sulfate) and lipophilic (tri-aminoloneacetonide) drugs in the aqueous layer or lipid bilayers. This arrests the metabolism of the drug by enzymes at the tear-corneal epithelial surface and confines the outflow of the drug through the nasolacrimal duct, thus refining the pharmacokinetics and pharmacodynamics of administered ocular drug [23]. The addition of surfactants aides the formation of the micellar structure by solubilization or breakdown of vesicles into the giant disc-like structure hence provides closer contact time with the cornea and augments bio-availability [24]. The release contour of active drug entity from a discosomal formulation is moderately gradual at the site of application due to the swelling of other carrier layers and hence it gives a steady, sustained therapeutic effect. Smaller particles of niosomes are remarkably less stable due to increased surface tension and require a higher input of energy. This is overcome by discosomes which provide a larger surface area of increased entrapment proficiency [25, 26]. Another principal benefit is that the presence of non-ionic surfactants, which are biodegradable and non-immunogenic, cause only minimal irritation to the eye. Discosomes provide the drug with enhanced corneal permeability compared to other ocular drug delivery systems [27]. Water-insoluble drugs can also be applied in a liquid dosage form using discosomes [28]. Discosomes also have negligible opacity that imposes no hindrance to vision and systemic side-effects. It also ensures better patient compliance and medication adherence due to the ease of administration as it reduces the frequency of administration. Discosomes can achieve zero-order release kinetics readily. The active ingredient can be incorporated into the vesicular system by itself. Discosomes can be stored at ambient temperature and hence have increased shelf-life compared to aqueous solutions (table 1). Discosomes also possess improved malleability [29]. It is also thermo-responsive to liberate the drug in a conserved manner before being eliminated by the consecutive process of blinking and nasolacrimal discharge [30]. However, no special conditions are required for the handling of surfactants [31]. It helps to minimize the total expenditure for treatment and acts as a reservoir for drugs that overcome the problems of conventional dosage forms [32]. Predominantly, it also protects encapsulated drugs from the external environment. Ex: Discosomes act as a photo-protective for ocular drugs like Naltrexone that change when exposed to sunlight [33].

Disadvantages of discosomes

The main disadvantage of discosomes is that a prerequisite of high temperature during the preparation of discosomes may influence the chemical stability of some thermo-labile therapeutic agents [34]. It is also a matter of concern that if discosomes are used for a perpetuating period, prospective opacity in the eye has been observed in some individuals. Discosomes also have limited drug loading capacities, which is a cardinal disadvantage. The movement of this drug delivery device in pre-corneal space may cause some perturbation to the patient when placed and removed periodically from under the eyelid [35]. Self-insertion of discosomes and the inadvertent loss of discosome from one eye may pose a difficulty. The preparation and preservation of discosome requisite specialized equipment have increased production cost and is time-consuming. There are possibilities of inefficient drug loading, and leakage in the preparation, preservation, and transportation of discosomes. There may also be a fusion of encapsulated drug molecules or vesicles during the process of manufacture. These are some of the aspects that require further review and rectification.

Structure of discosomes

The discosomal structure consists of a bilayer formed by non-ionic surfactants and the assimilation of cholesterol which functions as an excipient, so depicted in fig. 1 [36]. The self-assembly of non-ionic surfactants in aqueous media is the prompting factor that leads to the evolution of this bi-layer. Discosomes can entrap drug molecules with a broad range of solubility due to the presence of amphiphilic moieties in the structure [37]. To form the enclosed bi-layer structure, a source of mechanical energy such as thermal energy or physical agitation is essential. The surfactant molecules tend to organize themselves in a system where the hydrophilic heads of non-ionic surfactants that are polar are oriented outwards, whereas the hydrophobic tails, which are non-polar face each other to form a bi-layer [38]. The center of the discosome consists of an aqueous core in which the hydrophilic drugs are assimilated. The sandwiched area between the hydrophobic (lipophilic) non-polar tails envelopes hydrophobic drugs [39]. Various repulsive forces are accountable for maintaining the integrity of the discosomal structure [40]. The high interfacial tension between the aqueous medium and lipophilic tails of the amphiphile is the associating factor of this system [41, 42]. Recently it was validated that the intercalation of cholesterol in bi-layers reduces the volume for entrapment during formulation in niosomes, which has a structural resemblance to that of discosomes.

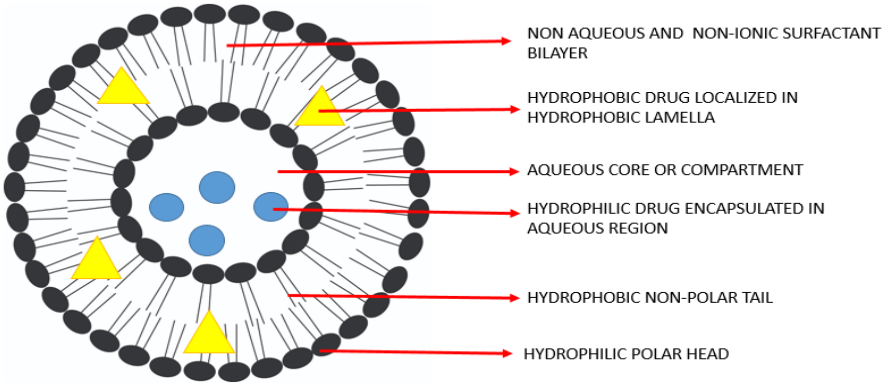

Fig. 1: Structure of discosome [40]

Differences between niosomes

Table 1: Major differences in characteristics between niosomes and discosomes

Niosomes	Discosomes	References
• Reduced corneal permeability	• Enhanced corneal permeability	[43]
• Short shelf life	• Prolonged shelf life	
• Decreased production cost	• Increased production cost	[44]
• Preparation and preservation do not require specialized equipment	• Preparation and preservation may require specialized equipment	
• The manufacture is less time consuming	• The process is comparatively more time consuming	[45]
• They show increased toxicity	• They show reduced toxicity	[46]

Mechanism of action of discosomes

Discosomes can be referred to as non-ionic surface-active agents, which are niosomes solubilized with non-ionic surfactant solutions, predominantly from the class of poly-oxyethylene-cetyl ether, as depicted in fig. 2 [47]. They have a size of 12-16 µm with a progressive potential for the exclusive drug administration of water-soluble drugs into the ocular cavity with negligible reduction in the systemic absorption of drug compounds [48]. They have bi-layers that can Ingrid both hydrophilic and lipophilic drugs in the aqueous core and within the bi-layer shell of the particle, respectively. Non-ionic surfactants own both polar and non-polar segments and manifest a high interfacial activity. It carries no particular charge and comprises a hydrocarbon chain which is the main integral of a discosomal structure. However, the tail may be branched, linear or aromatic. The choice of surfactant to be used may depend upon many salient factors like Hydrophilic-lipophilic balance (HLB) preferably between 16-17, Critical Packing Parameter (CPP), Critical Micelle Concentration (CMC) values [49]. These non-ionic surfactants also accelerate the rate and extent of drug absorption by the envelopment of the therapeutic drug molecule, facilitates the easy penetration through the ocular barrier, and nullifies the irritant effect of the drug. Additionally, it can also ameliorate the rigidity of bi-layer, along with cholesterol molecules that serve this complementary function. The addition of a surfactant may mitigate the formation of the micellar structure by the dose-dependent breakdown of vesicles into a giant disc-like structure which further contributes to better contact time with the cornea and amplifies bio-availability. Mucoadhesive polymers like chitosan and carbapol-coated discoidal niosomes improve bio-availability and pre-corneal retention too.

Upon administration into the ocular cavity, the particles reside at the site of delivery and then diffuse into the membrane through the ligand-gated mechanism. The residence time of the drug is concomitant to the corresponding spreading coefficient of the vehicle and the competency of polymer to drag aqueous fluid as the vehicle spreads over the surface with each blink. Discosomes cause thermodynamic activity gradient of drug which acts as the perforating stimulant for lipophilic drugs transverse across the cell membrane.

Some studies involving penetration enhancers to multiply the bio-availability of the ocular drug by either promoting the permeability of corneal epithelial membrane due to removal of the mucus layer, loosening up the junctional complexes, or both. Examples of some penetration enhancers are actin filament inhibitors, chelators, etc.

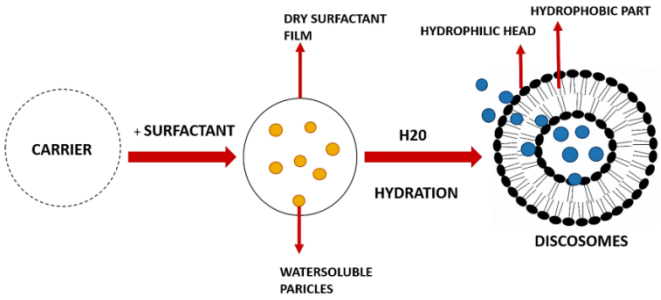

Fig. 2: Schematic representation of the mechanism of action of discosomes [50]

Method of preparation of discosomes

Bhardwaj P *et al.* (2020) demonstrated the preparation of discosomes. The niosomes were prepared from the hexadecyl diglycerol ether (C16), cholesterol, and diacetyl phosphate by mechanical agitation and sonication which was followed by incubation with soluble poly-oxy-ethylene cholesteryl ether and Solulan C24, at 74 ℃. The vesicles that were developed within the discosome phase, were found to be large (volume distribution mean diameter which is about 12-60 mm) and showed a gradual increase in its dimension instantly after sonication [51]. Discosomes were shown entrapping water-soluble solutes. Discosomes of 5(6)-carboxy-fluorescein were developed and started in retaining 50% of entrapped CF over a 24 h period at room temperature [52, 53]. Discosomes are voluminous discoidal structures that subsist under definite conditions of this phase of non-ionic surfactant vesicle formation.

Characterization of discosomes

Discosomes are compact disc-shaped modified forms of niosomes and provide better ocular localization. Their size conventionally varies from 12 to 16 *µm*. This drug delivery system comprises of non-ionic surfactants, Solulan C24 which is a derivative of Lanolin. Their huge size is an added advantage in the case of ophthalmic preparations which helps in impeding its drainage into the systemic pool and the disc-shaped structure also ascertains the superior and closer fitting of a discosome into the conjunctival sac [54]. Discosomes are osmotically active, stable, biodegradable, bio-compatible and cost-effective. They entrap solutes and are carriers of both hydrophobic and hydrophilic drugs. They are non-ionic surfactants based on discosomes of Timolol maleate. Prepared discosomes have been found to entrap a large quantity of Timolol and improving the ocular bioavailability when compared with the Timolol maleate solution. The possible reason for the scarce availability of discosomes is associated with the need for a relatively high temperature during discosome preparation that may interfere with the chemical stability of some thermolabile therapeutic agents [55]. The prepared system is distinguished on the basis of shape, size, and drug release profile *in vitro*. They began to emancipate contents succeeding biphasic profile exceptionally in the case where the drug was loaded using a pH gradient technique.

Evaluation of discosomes

Discosomes are evaluated mainly for: The thickness of the film, uniformity of drug content, uniformity of weight, drug encapsulation, entrapment efficiency, vesicle diameter, and *in vitro* release.

The thickness of the film is estimated by a dial caliper at different points of the discosome, followed by the calculation of its mean value. However, the uniformity of drug content is determined by the use of a cast film, cut at discrete places and tested for active drug moiety as per monograph. Uniformity of weight is analyzed using three patches, weighed randomly and any patch crossing the acknowledged threshold difference in weight is disqualified [56]. To obtain high drug encapsulation efficiency, respective principal components consisting of the shape of the selected surfactant, lipid level, content of cholesterol, and drug content must be optimized [57]. Discosomes are also evaluated for the spreading coefficient, ability to combat the oxidation of drugs like naltrexone, morphological properties as well as rheological properties, wetting properties, photo-protective properties, etc [39].

Entrapment efficiency evaluation involves the split out of residual drug that is not entrapped by dialysis, centrifugation, or even by gel filtration, and the amount of drug remaining entrapped is determined using complete vesicle disruption [58, 59]. The vesicular diameter of discosomes can be measured due to their spherical shape, which is an added perk. The breadth can be assessed using photon correlation microscopy, light microscopy, and freeze-fracture electron microscopy [60]. The method of *in vitro* release study encompasses the use of dialysis tubing wherein a dialysis sac is scrubbed and immersed in distilled water. The vesicle suspension made up of tubing is pipetted into a bag and sealed. The bag restraining the vesicles is set in 200 *ml* of buffer solution in a 250 *ml* beaker combined with continuous shaking at 25 ℃. The buffer is inspected for drug content by a suitable assay method at various time intervals [61].

Applications of discosomes

Discosomes are used in the effective targeting of ophthalmic drugs and to preserve the therapeutic moiety in ocular blood circulation. It helps to improve the stability and physical properties of an ophthalmic drug. Discosomes are comprised of cholesterol and hence they withhold a more stable membrane than polyhedral ones. It plays an important role in improving the medication adherence of a patient as it condenses the need for frequent administration. Discosomes do not interfere with oxygen permeability in the eye and also significantly reduce the visual and systemic adverse effects that may materialize during the administration of a drug when compared to other ocular drug delivery systems. It is also practical to intend to ocular diseases in hypersensitive patients, as the exclusion of complex preservatives makes discosomes relatively safe from causing anaphylactic reactions. Discosomes are used in some pharmacokinetic studies to analyze the reproducibility of drug release kinetics (zero-order drug delivery) [62]. Timolol maleate is a drug used to alleviate ophthalmic pressure to treat diseases like ocular hypertension and glaucoma. This drug in discosomal form captures a substantial quantity of active drug components and hence elevates its bio-availability. Discosomes are used to treat diabetic keratopathy. Diabetic keratopathy refers to the abnormalities in the cornea caused by high blood sugar, characterized by kerato-conjunctivitis, delayed healing of a corneal wound, and diminished corneal nerve sensation. Naltrexone hydrochloride is an opioid antagonist in discosomal form that is used in the treatment of opioid dependence and alcoholism. It also normalizes the secretion of lacrimal fluids in diabetic patients, expedites the revitalization of the wound in the cornea, and rejuvenates the sensitivity of ocular nerves. Some drugs are used in discosomal forms to scrutinize their extent of irritation potential [63]. Discosomes may also be used in the treatment of inherited retinal diseases (IRD) that consequently results in the degeneration of retinal cells in the eye due to the mutation of retinal layers. It is used to treat conjunctivitis, which can be defined as the inflammatory condition of the conjunctiva. The conjunctiva is a translucent mucous membrane that is situated in the sclera, where the drug is directly released on placing the discosome. The causes of conjunctivitis may be bacterial, fungal, viral, parasitic, certain allergens, toxicities, or irritants depending on the contagiously of the disease. Keratitis, the inflammation of the cornea produced by pathogenic microbes that causes redness in the sclera, pain, blurred vision, and excessive lacrimal discharge, can be relieved instantaneously by the administration of discosomes. The use of discosomes as ocular anesthetics in eye surgeries is under scrutinized studies [64].

Future perspective on discosomes

Treatment of chronic ocular diseases has always remained a challenge for health care practitioners and patients alike. Over the past two decades, ocular drug delivery research has rocketed about the evolution of attentive, patient-compliant and cost-effective formulations, devices and systems that can permeate the barriers of the ocular system and as well as maintain exclusive tissue drug concentration. The selection of a pertinent conventional dosage is a formidable task due to the various anatomical and physiological barriers of the eye and also because of poor ocular bio-availability [65]. The need of the hour is to create a substantial as well as non-toxic system that can be used for treatment in chronic patients. Pharmaceutical challenges for the eye are more composite when compared to that of the skin, and hence there is a need to pinpoint more on the non-invasive sustained drug release for eye diseases in both posterior and anterior segments. Drug delivery devices are attaining interest, especially in the prolonged management of recurring diseases. This outlook provides insight into the development of diffusion-based drug delivery devices [66]. An ideal system is the one in which we must be competent to administer a persistent drug concentration at the targeted site for a prolonged period, though modulating the corporal exposure. The outcome obtained from such methodically structured systems makes them simple and comfortable to use. Patient compliance and medication adherence are some of the paramount factors requiring fundamental concern when it comes to the formulation and clinical use of vesicular drug delivery systems in the eye. A plethora of relevant strategies in the ocular delivery system is appended and integrated for the rectification and improvement of possible drawbacks from each technology. This system mainly involves liposomes, discosomes, niosomes etc [50]. Both anterior and posterior segment drug delivery break-through has progressed predominantly by the modulation of conventional topical solutions along with enhancers of viscosity as well as permeation [67].

The drug delivery using discosomes can be very useful in the case of diseases like diabetic retinopathy, age-related muscular degeneration etc. where drug delivery to the target site has become an uphill assignment. Discosomes are more site-specific and show considerable patient acceptance in clinical studies. When timolol maleate was entrapped in niosomes and discosomes, the *in vivo* bioavailability of discosomes was seen to be better than that of the niosomes. Hence the use of discosomes can circumvent systemic side effects with recurrent administration of an abundant concentration of drugs. The use of drug delivery system like discosomes enhance drug permeation and provide optimal drug delivery. The current momentum in new drug delivery invention holds a promise for much progressed ocular therapies in the future to cure diseases that are vision-threatening [30].

Further studies and research are essential for the exploration and authentication of aspects like absorption, permeability rate, susceptibility to oxidative degeneration, possible adverse effects and their management, the major site of action, bioavailability enhancement etc. of discosomes. Several scientific and technological advancement needs furtherance in this field and zones like biomedical science may impart new methodologies for the progress of ophthalmic drug delivery systems. There has been a prominent advancement in the clinical scope of discosomes during these two decades. Treatment of ocular diseases in an effective manner is a major challenge for scientists working in the empirical area of ocular drug delivery because of the nature of the ocular diseases, the unique structure of the eye, and barriers, particularly as the posterior ocular segments make the system easily unapproachable. Many attempts have been made to enhance ocular bio-availability and corneal residence time by the manipulation of the product formulation using various factors like viscosity and the use of mucoadhesive polymers. Therefore, it can be stated that this type of

novel vesicular drug delivery system opens new windows of challenges and broad opportunities.

CONCLUSION

Vesicular drug delivery systems like discosomes are an effective means of ocular drug delivery system that play an opposite role in improved ocular absorption along with minimal or reduced side effects. Discosomes act as major carriers for ophthalmic drug preparations and due to their enlarged size, they are of pronounced advantage in regulating the entry into the systemic circulation. This particular characteristic of discosomes differentiate it from all other vesicular drug delivery system and make them more preferable for ophthalmic drugs. A sustainable satisfactory activity profile could be produced by the prepared system on administration into the ocular cavity. The discosomal delivery of drugs is deemed to be an encouraging and favorable prospective for controlled ocular administration of aqueous soluble drugs. Utilization and figuring of various critical matters in the field of pharmaceutics by the vesicular drug delivery systems like discosomes tend to be very beneficial as drug delivery system in the current field and they also tend to have a conspicuous place in the area of pharmaceutical dosage forms in addition to the conventional drug delivery system.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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