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SPANLASTICS AS A PROMISING VEHICLE FOR NOVEL DRUG DELIVERY –A REVIEW

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ABSTRACT

The aim of Novel drug delivery is to accomplish a predetermined drug action rate while simultaneously maintaining a desired drug level in the body and limiting adverse effects. Vesicular drug delivery systems offer significant advantages by overcoming the obstacles associated with traditional dosage forms. Therefore, Novel systems like liposomes, nanoparticles, nano emulsions and nanosuspensions are being developed to improve drug delivery efficiently. As a development in drug delivery systems, a new system known as Spanlastics which has lesser side effects, was released in 2011. The Spanlastics are a new type of elastic vesicular Nano carrier that are based on surfactants and are composed of spans and edge activators. This Nano vesicular system is elastic and deformable, which entraps the drug in the core cavity as bilayer. These are composed of surfactants and encapsulated by aqueous media. Spanlastics are chemically stable and offers targeted delivery and regulated release and improve drug availability at the desired site. They have improved various short comings of the standard dosage form, including providing targeting and controlled release of natural medicinal components, as well as other benefits. They solve a variety of issues that are associated with the conventional dosage form by delivering the active pharmaceutical components in a targeted manner and regulating the rate at which they are released. Spanlastics have discovered a wide range of applications via different routes of administration. Their applications through various routes of administration in a variety of diseases for a variety of drugs have been discussed. The purpose of this review is to highlight the application of Spanlastics.

KEYWORDS: Spanlastics, controlled release, targeted delivery, applications.

INTRODUCTION

Novel drug delivery systems (NDDS) are becoming trendy in recent years because they offer great benefits in terms of reduced dosing frequency, increased bioavailability, protection is provided specifically against the harsh gastric environment, site specificity and minimized side effects.[1] It delivers the drug at a rate directed by the body's need during the period of treatment, and channel the active entity to the site of action. The biologic origin of these vesicles was first reported by Bingham in 1965 and it was named as Bingham bodies. Various new vesicular drug delivery systems have emerged, covering multiple administration routes to achieve targeted and controlled drug delivery.[2] These systems have also been utilized to enhance the therapeutic index, solubility, stability and rapid degradation of drug molecules.[3]

Spanlastics represent a novel approach to vesicular drug delivery system that effectively encloses the drug within a bilayer structure located in the core cavity. The term "Spanlastic" (derived from the combination of "Span" and "Elastic") was initially introduced in the year 2011. These elastic carriers have the capacity to undergo deformation. Compared to a drug solution, these deformable vesicular carrier systems exhibit improved permeability.[4] These are surfactant-based elastic deformable nanovesicles they are formed by the combination of non-ionic surfactant and an edge activator. They are non-immunogenic, biodegradable systems these are compatible with biological membrane which shows minimum toxicity due to presence of non-ionic surfactant.[5] The formation of nanovesicles depends on following factors that is hydrophilic-lipophilic balance (HLB), critical packing parameter (CPP), and phase transition temperature.[6] These nanovesicles maintain acceptable stability compared to other dosage forms like liposomes. They are non-irritant when compared to other dosage forms that contain cationic surfactants, and they also provide enhanced delivery due to their highly elastic deformable nature.[7] These carriers act as site-specific drug delivery systems where it delivers the drug to the target sites including ocular, oral, topical, nasal and transungual applications.[8]

Salient Characteristics of Spanlastics[9]

1. These are osmotically active and stable,
2. They can entrap the solutes.
3. They discharge medication in a controlled way by means of its bilayer which gives supported the arrival of encased medication.
4. They have malleable structural characteristics, allowing them to be modified to fullfill specific requirements.
5. They provide better availability of the medication at the targeted site just by protecting it from a biological environment.

Advantages[10]

1. Spanlastics allows hydrophilic or lipophilic medicines to pass through biological membranes, including the cornea.
2. They are biodegradable.
3. They do not trigger an immune response.
4. They are osmotically active and stable, as well as increase the stability of the entrapped drug.
5. They have increased bioavailability in contrast to conventional one.
6. They can be made to reach the site of action by oral, parenteral as well as topical route.
7. They play an important role in delaying the clearance of drug molecules from the systemic circulation during sustained drug delivery.
8. By encapsulating the drug inside a lipid bilayer membrane, they shield it from the biological environment.
9. Handling and storage of surfactants require no special condition.

STRUCTURE AND COMPOSITION OF SPANLASTICS[11]

Spanlastics systems are spheroid structures consisting of amphiphilic molecules acting as suitable matrices for bio encapsulation. It consists of concentric bilayers, these can be Unilamellar or Multilamellar. Depending on the size of vesicles, these can be (SUVs) Small unilamellar (10-100nm) or (LUVs) Large unilamellar (100-3000 nm). These consist of two integral parts, an Edge activator and a nonionic surfactant. Since these vesicles are primarily composed of Spans (Surfactants) hence, they have been named as Spanlastics.

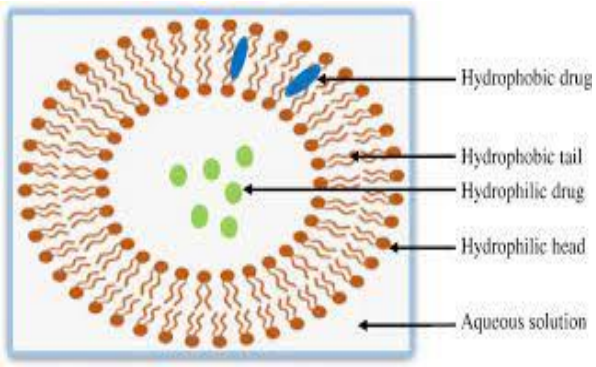

Fig. 1: Structure of Spanlastics.

Non-Ionic Surfactants[12]

Non-ionic surfactants are also known as Surface-active substances. They reduce the interfacial tension between two liquids. Non-ionic surfactant do not contain any charge. Sorbitan alkyl esters (Spans) is the essential class of non-ionic surfactants which results in the formation of concentric bilayers of spanlastics. The polyoxyethylene sorbitan component of the molecule, known as span, comes in various types, including Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate). The type of span has a major role in predicting the stability of the vesicular formulation. Vesicles based on Span 80 and Span 40 shows significant disruption, aggregation, and instability. In contrast, the incorporation of saturated alkyl chains in Span 60 improves its sustainability.

Edge Activators

These are unique class of surfactants with elevated hydrophilicity, as indicated by their high hydrophilic-lipophilic balance (HLB) value. These surfactants contain ingle chain. Edge activators help in softening the bilayer such as biocompatible surfactants to which an amphiphilic substance is added to increase the permeability and flexibility of the lipid bilayer which increases the deformability of the bilayer by lowering the interfacial tension between them. These have a tendency to produce larger spherical vesicles, which results in smaller particle sizes. Tween 80 is an edge activator helps in making the vesicles more elastic. Any vesicle having larger pore size than the biological membrane can easily transfer from the outside to the inside as a result of the tween-80's temporary increase in pore size. These hydrophilic surfactants, destabilizes the vesicular membranes which results in increased deformability.

Ethanol

It has beneficial effect on the properties of these nano-vesicular carriers. It facilitates in enhancing drug entrapment and partitioning within the vesicles. The thickness of the vesicular membrane is reduced, and the ability of the spanlastic to entrap drugs is improved. Additionally, by changing the system's net charge toward a negative zeta potential, it stabilizes the steric effect to some extent.

APPLICATION OF SPANLASTICS[13]

Novel drug delivery system has played a vital role in delivering drugs to target sites. These nano vesicles firstly emerged in the field of cosmetics and now gaining attention across various fields as a vesicle- based drug delivery system. Due to the fact that they are capable of entrapping hydrophilic (lipophilic) medicines in addition to hydrophobic (lipophobic) medications. Spanlastics can be an ideal system for delivery of the drug. A large range of pharmaceuticals, including doxorubicin, vaccines, insulin, siRNA, and many more, are already built into the nano-vesicle delivery system that has been constructed. These vesicles can also be used as a co-delivery system as two different kinds of drugs can be easily loaded to

achieve the desired therapeutic effects. When it comes to formulation, these vesicles possess biocompatibility, low toxicity, biodegradability, good stability, low cost and ease of storage. All of these characteristics are desirable. Because of their microscopic size, these nanovesicles have the potential to be used in the cancer therapy. This can be achieved through various modifications, and leading to increased permeability and retention period in tumour tissue. The applications of Spanlastics in site specific drug delivery are described below:

A. Ocular delivery
B. Nasal delivery
C. Oral delivery
D. Transdermal delivery
E. Topical delivery
F. Ototopical delivery
G. Ungual delivery

A. OCULAR DELIVERY[14]

In ocular treatments, drug administration is a challenging problem due to its unique anatomical and physiological barrier. The posterior segments of eye require site-specific drug delivery systems targets the vitreous cavity, choroid and retinal pigment epithelium. The limitations associated with ophthalmic drug delivery system are accounted to various pre-corneal and corneal barriers such as pre corneal drug loss due to lacrimation, reflex blinking, lower residence time of drug in cul-de-sac, complex structure of cornea acting as a barrier for penetration of drugs. This complex structure of cornea act as a selective barrier to drugs. This leads to lower concentration of the drugs to targeted ocular tissues, thus limiting ocular bioavailability. Ocular fungal infections may involve the cornea (keratitis), the interior of the eye (endophthalmitis), retina (retinitis) or the orbit and may occur following trauma (including surgery) or upon systemic disseminated infection. Fungal infections of the retina are among the most severe optical infections, with candidal chorioretinitis being the most common form, generally caused by *Candida albicans*. Following this, infections caused by *Aspergillus* species are the alternate most frequent, frequently affecting the choroid and retina. Nanotechnology has significantly improved ophthalmic drug delivery by overcoming the limitations of conventional systems. Spanlastics, a distinct type of vesicular carriers acts as site specific drug delivery systems for targeting drugs to the anterior segment of eye that constitutes corneal membrane and aqueous humour as well as to the posterior eye segments.

Imidazole antifungals[15]

Clotrimazole (CLT); being a hydrophobic antifungal drug. The nano vesicular carriers were formulated using Span60, sodium cholate (SC) or sodium deoxycholate (SDC) and Tween 80 as edge activators. The antifungal activity against Candida albicans were compared between niosomal formulation as well as the clotrimazole suspension. The optimized formulation was determined and comprised of sodium deoxycholate as edge activator and Span-60: edge activator ratio as 90:10. The drug loaded spanlastics formulation showed remarkable entrapment efficiency % as 87.92% along with a zeta potential of -33.7 mV. Clotrimazole loaded spanlastics showed sustained antifungal activity for a period of 12 hrs.

Bis- triazole antifungals[16]

Fluconazole for ocular delivery were successfully prepared and characterized. Fluconazole being hydrophilic with low molecular weight and having low protein binding was unable to reach in sufficient concentration to target ocular sites. To overcome this barrier, Span-60 based nano vesicles, a type of non- ionic surfactant was prepared. These nanovesicles exhibit flexibility and the ability to deform in the presence of edge activators. Drug loaded spanlastics were prepared by ether injection method. This preparation showed better permeability across cornea in contrast to available market formulation Zocon (0.3% w/v solution of fluconazole). The system demonstrated to be stable and safe regarding genotoxicity, cytotoxicity and ocular irritation (as per OECD guidelines). The vesicular preparation showed good drug entrapment % (-66%) indicating the capabilities of spanlastics as carriers for multiple classes of drugs to ocular regions.

Carbonic anhydrase inhibitor[17]

Formulation of mucoadhesive gellan gum/ HPMC solutions *in-situ* gels containing methazolamide nanovesicles. The tested systems were designed to combine high corneal permeability of Spanlastics as well as ease of application and prolonged eye retention of *in-situ* gels. Different preparations consisting of a mixture of span-60 and various edge activators (Brij-35, Brij-58, Tween-60 and Tween-80) were formulated and evaluated for corneal permeability, residence time, intra ocular pressure reduction. The examination of Spanlastics systems included assessment of entrapment efficiencies (EE%), particle sizes, and relative deformability. The prepared formulation showed more prolonged lowering in Intraocular pressure when compared to methazolamide control solution and were found to be safe and well tolerated. It was found that *in-situ* gel containing 10% Tween 60 (90:10) had better corneal permeability, highest residence time and considerable reduction in intra ocular pressure. Thus, spanlastics can be employed in delivering anti-glaucoma agents to eye.

B. NASAL DELIVERY[18]

The intranasal route has been extensively explored to deliver the drugs directly to the brain via trigeminal pathway and olfactory neuron, which will bypass the blood–brain barrier (BBB), blood–cerebrospinal fluid barrier and hepatic metabolism. Nasal application offers several advantages over conventional oral IV preparations such as, eliminates first pass metabolism, non-invasive technique, reduce the risk of drug degradation by gastric fluids and eliminates the need of frequent dosing. However, nasal delivery includes some setbacks such as, low permeability of nasal membrane

for large molecules, mucociliary clearance, tissue irritation and presence of proteolytic enzymes. These challenges can be overcome using spanlastic dispersions. Several studies have shown that spanlastics can deliver specific drugs to the brain through nose-to-brain delivery.

Antiemetic agent[19]

Research has been conducted to develop spanlastic mucoadhesive gels containing Granisetron hydrochloride in the form of nasal inserts as nasal drug delivery. This helps to improve bioavailability and brain specific delivery. HPMC and Carbopol 934 were incorporated in spanlastic in nasal gels. Gelatin and HPMC act as matrix former, glycine as a collapse protecting and mannitol as an insert filler and sweeting agent were used to formulate granisteron hydrochloride spanlastic loaded in lyophilized inserts. The prepared gel were analysed for pH testing, drug concentration, rheology, and in vitro drug release. Biological study including pharmacokinetics studies and brain-targeting efficiency dimensions was conducted on rats (LC–MS/MS). The results obtained were within physiological range, drug content (89.9–98.6%), (82.4–98.38%) for gel and insert, respectively and rapid release rate of GH. Biological studies showed that C_{max} and $AUC_{0-6\ h}$ in brain and plasma after intranasal administration of gel and insert were higher compared to IV administration of drug solution. On the basis of the current study, it could be concluded that granisetron spanlastic loaded in a nasal gels and inserts are a promising to improve bioavailability and provide increased drug levels in the brain.

Antimigraine agent[20]

Zolmitriptan spanlastics were formulated by means of ethanol injection method. Its being a potent second generation triptan used in the treatment of migraine attacks. It undergoes low bioavailability (40%) after oral administration due to the hepatic first-pass metabolism. Spanlastics are flexible vesicular drug delivery systems that utilize surfactants as their primary components. These vesicles are effectively involved in transporting hydrophilic drugs which are capable of crossing blood-brain barrier. This study aims to design and optimize intranasal spanlastic formulations as an alternative approach that directly targets brain delivery, enhancing its bioavailability and avoiding the first-pass effect. The optimized formulation showed a particle size of 117.5 nm and entrapment efficiency of 45.65%, with a low percentage of error between the observed and predicted values. 70% of drug was delivered through the nasal membrane within 30 min, and it completely delivered within 2 hours. The optimized formulation exhibited enhanced drug permeation across the nasal membrane, confirming the effectiveness of the intranasal route for brain targeting.

Antiepileptic agent[21]

The preparation of piperine-loaded spanlastics helps to improve piperine solubility, bioavailability, and permeation through nasal mucosa for intranasal delivery. Despite of its diverse therapeutic effects, its poor water solubility (0.04 mg/mL), poor permeability, low bioavailability and extensive first-pass metabolism delayed its transport across the blood–brain barrier and hence limits its use in emergency epileptic seizures. Thereby, alternative routes are preferred to treat emergency conditions. The intranasal route has been widely studied for delivering drugs directly to the brain through the trigeminal pathway and olfactory neuron, allowing it to bypass the blood–brain barrier (BBB), hepatic metabolism, and blood–cerebrospinal fluid barrier. Several studies have shown that spanlastics can delivery drugs to brain through intranasal route. This formulation was aimed to develop piperine-loaded spanlastics by thin-film hydration method using phospholipon 90G, span 60, and sodium cholate. For the optimization of the developed formulation, a Box–Behnken design was employed. In order to enhance piperine intranasal – brain delivery for the treatment of epilepsy, this study aims to combine the benefits of spanlastics delivery, nanotechnology's ability and the leverage provided by the nose-to-brain delivery.

C. ORAL DELIVERY[22]

The oral route is the most preferred method of drug administration due to its advantages, including patient compliance and ease of administration. Although oral medications have issues with bioavailability for a variety of reasons, including low solubility, frequent dosing, drug interactions, unpredictable absorption, first-pass metabolism, and systemic side effects. To improve drug bioavailability several strategies have been incorporated. One such approach is the development of a novel surfactant based vesicular system. This requires the encapsulation of the drug in the spanlastics system to overcome the barriers associated with oral drug delivery. Spanlastics are amphiphilic nature which traps the drug in core cavity and results in bilayer formation. They are chemically stable, and demonstrate elasticity and deformability characteristics due to the presence of an edge activator. In addition, they have advantage of being biodegradable, non-immunogenic, target-specific, and enhances the bioavailability and stability of entrapped drugs.

Anticancer agent[23]

Research was carried out with the aim of achieving sustained delivery of Simvastatin, an antihyperlipidemic agent that has been investigated as a possible anti-cancer agent. One challenge for drug-based malignant tumor therapy is delivering sufficient amounts to the cancer cells while reducing adverse effects after systemic injection. The researchers turned to the field of nanotechnology in order to overcome this difficulty, taking advantage of the formulation's Nano-size to passively target the tumour cells. Thus, simvastatin

spanlastic with minimized particle size and maximized zeta potential were developed to enhance the antineoplastic activity of the drug. Spanlastics were prepared using ethanol injection method. A significant improvement in the cytotoxicity of the optimized formulation against three different cancerous cell lines was observed. The measured responses of the optimized formulation were 128.50 nm for the vesicle size, 0.329 for the polydispersity index (PDI), and 29.11 mV for the zeta potential. The measured responses align closely with the predicted results, confirming the validity of the numerical optimization approach used in this study. The study revealed that simvastatin loaded spanlastic can be a good approach to provide sustained drug delivery for the treatment of cancer.

Calcium channel blocker[24]

Bioavailability of lacidipine, a calcium channel antagonist, is lower than 10% due to extensive first pass metabolism and lipophilic nature of drug which poses a challenge in antihypertensive therapy. In this study, spanlastic oral dissolving films of lacidipine were prepared to improve its bioavailability. A 2^3 factorial design model was used in the spanlastics development processes to determine the effect of the formulation components over the response parameters. The spanlastics were prepared by a modified ethanol injection method using Span 60 and Tween 80. These were then made into orally dissolving films with hydroxy propyl methyl cellulose E5, polyvinyl alcohol and polyethylene glycol 400 using the solvent casting method. The optical microscopy and high resolution-transmission electron microscopy images of the developed formulation depict presence of nano sized vesicles which have good entrapping efficiency. Evaluation studies demonstrated that the casted films possessed good mechanical properties and have flexibility. This novel drug delivery system effectively enhances the availability of lacidipine for makes lacidipine antihypertensive therapy.

D. TRANSDERMAL DELIVERY[25]

With the advent of modern medicine, there are numerous ways through which drugs can be delivered. However, in chronic conditions, such as hypertension, transdermal drug delivery systems are more effective, as they improve the patient's overall quality of life. Unlike oral dosage forms, transdermal drug delivery is better because there is no hepatic first-pass metabolism and there is controlled drug release into the body. Due to these factors, transdermal systems can be used to deliver drugs for systemic effects while at the same time, maintaining adequate plasma concentrations for the desired therapeutic effect, thereby reducing the frequency of dosing and increasing adherence to medication.

Antipsychotic agent[26]

Haloperidol (Hal) is one of the most prevalent used antipsychotics. Its oral consumption is often limited due to its low bioavailability because of a first pass hepatic metabolism. This study focused on preparing Haloperidol spanlastic with penetration enhancer for improved transdermal delivery of Haloperidol with controlled release. Spanlastics were successfully prepared using ethanol injection method showing reasonable values of percentage entrapment efficiency, particle size, polydispersity index and zeta potential. Preliminary analysis of the ex vivo permeation parameters F1L were selected, which consisted of Span 60 and Tween 80 in a weight ratio of 4:1 coupled with 1% w/v Labrasol V R as Select Formula. This was transformed into hydrogel by adding 2.5% w/v HPMC K4M. The hydrogel exhibited good *in vitro* characteristics. The Select Formula radio labelling showed the highest yield when 100ml of the diluted formula was mixed with 50ml of saline containing 200MBq of 99mTc, 13.6mg of reducing agent (NaBH4) and the pH adjusted to 10 with saline completed to 300ml for 10 minutes as reaction time. The aim of this work was to formulate haloperidol spanlastic for transdermal delivery. This was expected to provide enhanced permeation and sustained release of the drug.

Immunosuppresant[27]

Tacrolimus is an immunosuppressant, which is administrated orally, to prevent the rejection of liver and kidney transplants. The drug belongs to class II BCS system. The poor solubility of the drug contributes to some extent to lower its bioavailability. The drug has large molecular weight (822.95 g/mol) and high lipophilicity (partition coefficient, log P = 3.96 0.83) these properties limit its transport through skin tissue. To improve the permeability Tacrolimus loaded spanlastic were formulated. These were effectively formulated with two different concentrations of permeation enhancers by ethanol injection techniques. The prepared drug loaded vesicle were characterized in terms of particle size, zeta potential, entrapment efficiency (EE%), *in vitro* release, and *ex vivo* permeation through hairless rat skin. In this study, Tacrolimus was loaded into spanlastic as an alternative delivery system to improve its skin permeation.

E. TOPICAL DELIVERY[28]

Topical drug delivery is advantageous for various diseases because irritation and the first pass effect of the liver is ignored, while unnecessary adverse reactions are reduced when the lesion is directly accessed. The skin protects the body from a large percentage of external threats and is considered one of the most critical lines of defense. Nevertheless, the strong barrier ability provided by the skin stands as a massive hurdle to the efficacy of topical medications. The fundamental requirement of a bioactive component seeking to utilize its therapeutic effect is to facilitate the stratum corneum barrier to let the active bio composition bypass towards the needed site. Individualized disease detection, dosing planning, and selection of delivery system for the bioactive component along with the state of the skin barrier determine the effectiveness of topical medications.

Anti-inflammatory agent[29]

Rheumatoid arthritis is an autoimmune disorder which propagates chronic inflammation of the joint's synovial membranes. The most common pharmacological intervention available to treat Rheumatoid arthritis is the use of nonsteroidal anti-inflammatory drugs (NSAIDS). A chronic long-term treatment with NSAIDs leads to an extensive list of side effects and complications which adversely affects the patient's compliance and overall outcome. Its purpose was to achieve focused delivery of a celecoxib-loaded spanlastic Nano-vesicle based delivery system to the inflamed joints without requiring large doses to be administered systemically. For the development of spanlastic nanovesicles targeted for transdermal delivery of celecoxib, the modified injection technique using Tween 80 or Brij as edge activators was used. The prepared nano-vesicle was characterized for entrapment efficiency, vesicle size, morphology, ex vivo permeation, and for other additional parameters. Carbopol gels containing the selected formulations were prepared and their clarity, pH, rheological parameters, and ex vivo permeation were determined. For comparative purposes celecoxib loaded niosomes and niosome containing gels were prepared and the niosome containing gels tested. The efficacy in vivo of the formulated gels was tested in a rat model of Freund's complete adjuvant induced arthritis. Various inflammatory markers such as TNF-α, NF-κB and COX-2 were measured in the paw tissue before and after treatment and evaluation. The spanlastic Nano-vesicle-containing gel represents a more efficient site-specific treatment for topical treatment of chronic inflammation like Rheumatoid arthritis, compared to commercial and other conventional alternatives.

Antioxidant agent[30]

L-Ascorbic Acid (LAA) protects the skin from aging and is categorized as a strong antioxidant. Staying on top of maintaining the stability of vitamin C is the most difficult undertakement in the world of cosmeceuticals. Objective is to maximize the stability and efficacy of vitamin C by encapsulating it in spanlastic vesicles. By employing the ethanol injection technique, LAA-loaded spanlastics were made and then tested on entrapment efficiency (EE%), particles size (PS), polydispersity index (PDI), zeta potential, deformability index (DI) and skin permeation. Selected spanlastics formula made from span 60 and tween 60 (5:1) showed the highest EE% of 89.77±3.61% (w/w), high deformability of 11.13±1.145 and stability, both physical and chemical for 6 months. Spanlastics outperformed the LAA topical solution in terms of drug penetration into the stratum corneum (SC). MMP2 and MMP9 levels were significantly supressed in response to LAA spanlastics treated rats 30.4% and 65.3% respectively when compared to control group after exposure to UV illumination. Real time quantitative PCR confirmed these results. Application of LAA-loaded spanlastics compared to UVB and LAA solution has shown to provide greater protection to the skin as observed from histopathological study of rat skin post UV irradiation.

F. OTOTOPICAL DELIVERY[31]

Ear infections are treated using conventional dosage forms such as solutions, suspensions, tablets, and capsules, which are designed for systemic action. However, in ailments affecting the middle ear such as acute otitis media, localized action is important. The local delivery of drugs to the site of infection in the middle ear can be achieved by ototopical delivery of antibacterial agents through the tympanic membrane. This method will assist in the eradication of pathogens while also averting antibiotic resistance. One of the obstacles to trans-tympanic delivery of antibiotics to the middle ear is the stratum corneum of the tympanic membrane and its impermeability. Therefore, this emphasizes the need for an elastic nano vesicular system capable of focusing through the tympanic membrane to the middle ear for treating infections.

Antibiotic agent

This research focused on attempting to develop a method for the ototopic treatment of acute otitis media through non-invasive trans-tympanic delivery by attempting to incorporate ciprofloxacin, a wide range fluoroquinolone antibiotic, into Span 60 based nano-elastic vesicles, nano-spanlastics. For this goal, ciprofloxacin-loaded nano spanlastics were produced using a thin film hydration technique with a number of non-ionic edge actuators as per full factorial design. The Study of the impact of formulation parameters on the characteristics of nano-spanlastic and the selection of the optimal formula were conducted in Design-Expert software. The selected formulation was also tested for comparative ex-vivo permeation through tympanic membrane of rabbits. The results indicated that the best nano-spanlastic formulation, which consists of 20% Brij 35 as an edge activator, was stored at 4- 8ºC over six months and maintained good physical stability. *Ex-vivo* permeation studies showed the higher efficiency of the optimal nano-spanlastic formulation in comparison to marketed Ciprocin drops. The obtained results indicates that spanlastics can be promising for enhancing trans-tympanic delivery of ciprofloxacin.

G. UNGUAL DELIVERY[32]

Human Nails are exposed to fungal infections like onychomycosis which is caused by fungus Trichophyton rubrum. Various treatment options have been deduced for onychomycosis. Nail is the main barrier to the entry of any foreign material. It therefore, forbids the permeation of antifungal agents via topical formulation. The delivery of antimicrobial agents via nail plate to achieve desired therapeutic action is quite a challenging task for research scientists and pharmacologists. In order to achieve the desired action, the antifungal agent should reach the target site. This highlights the need of developing a novel topical formulation for effectively delivering the drug via trans-ungual route to eliminate the infection.

Antifungal agent[33]

Efinaconazole is a new compound with poor solubility and low permeability as an antifungal triazole drug. Spanlastics are new-generation surfactant nanovesicles which possess fluidity and enhance drug permeability. The Plackett-Burman definite screening design applied to eight formulating and processing parameters that influence particle size, particle size transmittance, relative deformability, zeta potential, entrapment efficiency, and dissolution efficiency. Using Pareto charts, the top three contributors were identified as vesicle builder (Span), edge activator (Tween), and mixing time. Formulation- by- design (FbD) approaches were used to assess three important variables that were optimized to minimize efinaconazole spanlastic nanovesicles and maximize the transmittance, relative deformability, entrapment efficiency, and dissolution efficiency. The optimal efinaconazole spanlastic vesicles showed a particle size of 197 nm, transparency of 91%, relative deformability of 12.5 min, and dissolution efficiency of 81.23%. The spanlastic formulation was incorporated in to gel and evaluated in ex vivo for trans ungual delivery. This exploratory study provides an example of the application of risk management, statistical multivariate analysis, and the FbD approach in developing efinaconazole spanlastic nanovesicles.

CONCLUSION

Spanlastics are utilized to achieve site specific action for both lipophilic and hydrophilic drugs. They address the challenges of insolubility, poor bioavailability, instability and rapid degradation of medications. These systems hold the potential to make a significant contribution to advancements in nano vesicular drug delivery systems. This study mainly focuses on the application of spanlastics in delivering drugs to most of the organs and achieves site specific delivery. Elastic carriers have found a lot of usefulness in transporting drugs via numerous paths such as ocular, oral, topical, trans ungual, nasal and even to the middle ear for managing auditory and vestibular diseases, for eye treatment, systemic absorption, skin surface, nail fungus, and direct nose access.

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