Journal of Advanced Biomedical and Pharmaceutical Sciences

Journal Homepage: http://jabps.journals.ekb.eg

SPANLASTICS: A Unique Formulation Strategy in the Delivery of Pharmaceuticals-Carbapenems as a Model

Shadwa Abdelfattah Ahmed Mousa [1,2], Milad Reda Qelliny [1*], Reham Ali Ibrahem [3], Safy Hadiya [4], Hatem A. Sarhan [1], Fatma Mohamed Mady [1]

[1] Department of Pharmaceutics, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt
[2] Department of Pharmaceutics, Faculty of Pharmacy, Merit University Egypt (MUE), Sohag, Egypt
[3] Department of Microbiology and Immunology, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt
[4] Assuit International Center of Nanomedicine, Al-Rajhy Liver Hospital, Assuit University, 71515, Egypt

Received: June 23, 2024; revised: August 4, 2024; accepted: August 22, 2024

Abstract

Drug delivery systems based on nanotechnology have been significant in surpassing the challenges associated with traditional dose forms. A promising drug delivery vehicle is spanlastics, an elastic nanovesicle that can transport a variety of drug compounds. Spanlastics have shown an increasing amount of interest in various forms of administrative pathways. They may squeeze themselves through skin pores because they are elastic and malleable, making them ideal for transdermal delivery. Non-ionic surfactants or mixtures of surfactants make up spanlastics. Numerous studies have demonstrated how spanlastics greatly improve drug toxicity, drug bioavailability, and therapeutic efficacy. Our future goal is to evaluate the spanlastic-encapsulated carbapenem's antibacterial and anti-biofilm characteristics. Following the isolation of Staphylococcus epidermidis isolates and the assessment of their microbiological sensitivity, the plate microtiter test was employed to investigate their capacity to form biofilms.

Keywords
Nanoparticles, Spanlastics, Spans, Edge activators, Drug Delivery System, Carbapenems.

Introduction

The method or strategy of delivering a drug in such a manner that it has a therapeutic effect on humans or animals is referred to as medicine delivery [1]. Medications are enhanced by transitioning from traditional forms to innovative delivery techniques. The utilization of advanced medication delivery systems—quick-to-respond, sustained, and cost-effective—known as Advanced Medication Delivery Systems, serves as cornerstones of Traditional Medicine's rejuvenation [2]. Pharmaceutical companies are developing innovative pharmaceutical delivery methods due to the increasing demand for faster, less harmful, and more potent medication administration to individuals. The method of drug administration significantly affects its efficacy. For certain substances, precise dosage may be crucial to achieve optimal benefits, as doses outside this range can be ineffective or even hazardous [3]. Moreover, treating severe illnesses requires a multifaceted approach to pharmaceutical distribution to precisely target affected areas, as evidenced by advances in successful medicines. Pharmacokinetics, potency, immunogenicity, bio-recognition, and nonspecific toxicity are all complex factors influencing pharmacological effects [4, 5].

Drug degradation and loss are being managed and reduced through the study and testing of more therapeutic targeting and delivery techniques [6,7]. Different types of drug carriers include soluble, insoluble, synthetic, or naturally occurring varieties, as listed in [7-10]. These carriers can be designed to degrade gradually in response to environmental cues such as acidity or basicity of the surrounding environment, light, or voltage response, and to selectively release additional medication molecules (e.g., using smart nanoparticles). Targeting medication delivery to specific locations is essential. Two primary techniques for targeting drug delivery sites are: I. Passive techniques; II. Directive techniques [11]. These systems can be categorized as controlled medication release systems or targeted drug delivery systems. Some therapeutic benefits of these advanced systems include increased drug efficacy, site-specific administration, and reduced toxicity/side effects. Additional advantages include enhanced patient compliance, effective treatments for once-incurable diseases, potential preventive applications, and broader applicability. It's important to note that medication delivery systems are not universally applicable.

Certain dosage forms are commonly believed to have significant drawbacks, such as increased harmful effects and reduced potency. The importance of the route of administration (X) and the type of medication formulation (Y) has grown with the expansion of the healthcare industry. In this context, "drug delivery mechanism" refers to any element of the Cartesian product (X.Y). Pharmacological delivery mechanisms include vesicles, aqueous polycrystalline stage dispersions, and particle dispersion forms, which are examples of medication transport systems where particles range in size from 1 to 1000 nm. All these systems have shown considerable potential as methods for delivering medications. Improving dosage forms aims to create substances with desirable properties such as prolonged potency,

**** Correspondence:*** *Milad Reda Qelliny*
Tel.: *01228281799*
Email Address: *mila_reda@mu.edu.eg*

safety, and effective pharmaceutical outcomes. Advanced systems like controlled medication release or targeted drug delivery systems offer therapeutic benefits including increased drug efficacy, site-specific administration, and reduced toxicity and side effects.

Enhanced patient compliance, effective treatments for diseases once considered incurable, potential preventive applications, and expanded applicability are among the advantages of advanced medication delivery systems. It is recognized that certain dosage forms have significant drawbacks, such as increased harmful effects and diminished potency. The importance of the route of administration (X) and the type of medication formulation (Y) has intensified with the expansion of the healthcare industry. In this context, "drug transport mechanism" refers to any element of the Cartesian product (X.Y). Pharmacological delivery mechanisms include vesicles, aqueous polycrystalline stage dispersions, and particle dispersion forms, which are examples of medication transport systems containing particles ranging in size from 1 to 1000 nm. All of these systems have demonstrated considerable potential as methods for delivering medications. This improvement in dosage forms aims to produce substances with desirable properties such as prolonged potency, safety, and satisfactory pharmaceutical outcomes.

The addition of cross-linkable groups to block copolymers enhances particle stability and temporal control. Substituting specific ligands for block copolymer micelles is a highly promising method for improving targeting and specificity at specific sites of action. Controlled-release devices were authorized by regulatory bodies during their initial development in the 1950s. Spansule (Smith, Kline & French Laboratories) became the first FDA-approved controlled-release medication delivery device. In the 1950s, the primary drug-release mechanisms employed by first-generation drug delivery techniques included regulated dispersion, regulated osmosis, regulated ion exchange, and regulated dissolution. Before the 1950s, most conventional products used a breakdown-based release mechanism, often combined with a distribution mechanism. The approval of the first sustained preparation for intravenous drugs in the early 1990s marked a new phase in drug development. A stable intravenous preparation using PLGA microparticles was developed to extend the shelf-life of polypeptide and protein-based therapeutic agents [12].

Adjusting the proportion and particle size [4], and PEGylation—a process where polyethylene glycol (PEG) polymers are bonded with protein substances [4]—represent significant advancements of the second generation. This procedure extends the circulation time of protein molecules in the bloodstream. Nanomedicine employs nanoscale particles, such as biocompatible nanoparticles [13] and miniature robotic devices [14], across a broad spectrum of applications including diagnosis [15], drug delivery [16], sensing [17], and locomotion within living organisms [18]. Integrating nanotechnology into medication delivery systems has the potential to overcome these limitations.

Nanotechnology's most cutting-edge application lies in the development of therapeutics at the nano scale, offering potential benefits such as modifying properties like solubility, pharmaceutical release profiles, diffusivity, biological absorption, and immune system activity. This advancement could lead to more effective and convenient administration methods, along with a reduced toxicological profile, fewer side effects, improved distribution throughout the body, and an extended medication lifetime cycle [19]. Proposed drug delivery methods aim either for targeted delivery to specific sites or for controlled release of pharmaceutical compounds [20]. However, these methods must overcome challenges such as opsonization and sequestration by the mononuclear phagocyte system [21].

Medication delivery also involves targeting, which can be active or passive, utilizing nanostructures or nanotechnologies for drug delivery processes. Active targeting integrates drug delivery systems with specific moieties like antibodies and peptides, facilitating binding to receptor structures expressed in the target area. In contrast, passive targeting transports the drug carrier complex to the intended site through affinity or binding mechanisms influenced by various variables in the surrounding environment as it circulates within the bloodstream. The primary targets in the human body include receptors or antigens embedded in the outermost layers of cells [22]. Currently, the majority of medications administered via nanotechnology are designed for disease treatment.

Advancements in the design of drug delivery methods and mechanisms have been driven by developments in nanotechnology, drug discovery/design, and drug transportation technologies. Recently, novel approaches in pharmaceutical transportation have aimed to enhance targeted drug action, reduce side effects, and improve drug absorption [23]. Drug delivery systems and nanomedicine are considered pivotal for the future of medicine [24]. Oncology serves as a notable example of a life-threatening disease where advancements in technology have significantly impacted both diagnosis and treatment, as discussed earlier. Researchers have repeatedly explored methods to enhance the permeability of herbal medications by utilizing common colloidal carriers [22,23].

The rigid and flexible properties of current carriers for pharmaceutical transport across biological membranes limit their utility. Current studies are focused on enhancing the adaptability of typical carriers to improve therapeutic efficacy. Therapeutic vesicular drug delivery stands out as a prominent approach in medication delivery, enabling targeted release and enhanced drug penetration. These systems transport both water-soluble and lipophilic drug molecules. Spanlastics, an adaptive nanovesicle transporter, combine a non-ionic surfactant with an edge activator to achieve their versatile properties. This allows spanlastics to deliver both hydrophobic and hydrophilic medications effectively. Additional layers can be incorporated to further tailor their properties.

Lipid Based Nano-Drug Delivery System

The development of multiple strategies utilizing nanoscale delivery systems has made it feasible to transport pharmaceuticals to specific sites, providing pharmaceutical investigators with new avenues to explore in enhancing drug delivery to brain cells [25]. These innovative drug carrier technologies hold promise for various medical applications beyond brain and spinal cord delivery. For medications with a short half-life, nanotechnology offers the potential to reduce dosing frequency.

Ligand-based selective targeting has proven to be an effective strategy for delivering therapeutic agents to cancerous growths. Advances in medical imaging devices and biotechnology are continually revealing new and unique targets for treatment [26]. However, these points of interest can present challenges for certain medication transport systems using nanotechnology approaches. Therapeutic vesicles typically consist of spherical liposomes—vesicles with either a single lipid bilayer or a multilamellar lipid bilayer comprising at least one inner and one outer lipid layer [27]. Traditional vesicle structures like liposomes and niosomes have demonstrated the ability to

enhance gastrointestinal absorption of pharmaceuticals and improve vaccination effects [28]. Nevertheless, the instability of conventional vesicles in the gastrointestinal tract has limited their effectiveness, necessitating modifications to their bilayer structures to enhance in vivo stability [29].

Liposomes

Liposomes, a form of nanotechnology, can encapsulate both hydrophilic and lipophilic drugs. Hydrophilic drugs reside within the aqueous core of phospholipid bilayer systems, while lipophilic drugs are encapsulated within the bilayer itself. To enhance drug delivery, scientists worldwide are utilizing various advanced liposome formulations such as PEGylated liposomes—liposomes containing linear polymer chains of polyethylene glycol—targeted liposomes conjugated with ligands, and liposomes incorporating medications [30]. These advancements have led to numerous nano-formulations across disciplines including anti-cancer, anti-bacterial, anesthesia, gene therapy, and anti-inflammatory agents. However, these formulations ultimately require clinical investigation to evaluate their efficacy [31].

Niosomes

Niosomes are gaining attention as effective transdermal drug delivery vehicles due to their enhanced capability for drug penetration. Various pharmacologically active substances, including chemotherapy for cancer, antioxidants, and antimicrobial compounds, can be delivered transdermally using niosomal carriers [32]. Proniosomes refer to niosomes that are dehydrated; upon addition to a warm aqueous medium, they rapidly disperse to form niosomes.

Proniosomes

Proniosomes are dehydrated forms of niosomes. Rehydrating proniosomes in a warm aqueous medium results in rapid niosomal dispersion within minutes. These surfactant-coated, water-based carrier particles are physically more stable during storage and shipping compared to niosomes. They directly encapsulate the substances they transport, prolonging drug circulation time. Proniosomes also exhibit reduced toxicity and enhanced penetrability at the target site [33]. Transferosomes, another type of lipid-based vesicle, contain an aqueous core surrounded by a lipid bilayer that includes an edge activator. They are effective drug delivery vehicles for transdermal applications. Unlike liposomes, transferosomes can deliver higher amounts of active compounds to deeper layers of intact skin due to their flexibility and ability to squeeze through narrow pores [34]. Transferosomes are evaluated based on parameters like drug entrapment efficiency and drug content. They have versatile applications, including delivering vaccines, proteins, anesthetics, anticancer drugs, and herbal remedies. They offer advantages such as improved patient compliance, enhanced bioavailability, and site-specific delivery [35]. Modified liposomes, such as ethosomes, have been developed to address challenges like size, drug entrapment efficiency, and surface charge. Ethosomes are newly modified lipid carriers composed of ethanol, phospholipids, and water [36, 37].

Spanlastics

Spanlastics are biodegradable, non-immunogenic, and benign vesicular transporters. Researchers have utilized common colloidal carriers such as microemulsions and liposomes to enhance the permeability of botanical medications. Numerous studies have demonstrated that spanlastics can improve treatment efficacy, patient adherence, medication absorption, and minimize adverse effects. These vesicular carriers offer advantages over niosomal colloidal delivery technologies and are more chemically stable than liposomes due to their flexibility. The incorporation of an edge activator in the vesicle membrane acts as a disruptive agent, enhancing the vesicles' deformability to overcome biological barriers [16]. The term "Spanlastic" (Span + Elastic) was introduced in 2011, marking a milestone in pharmaceutical development. These deformable vesicular carriers exhibit higher permeability compared to medication solutions [16]. Spanlastics are extremely small and contain medication within amphiphilic vesicles formed by an anionic surfactant. They excel where liposomes may falter, such as in chemical instability attributed to oxidative breakdown and varying phospholipid purity. This family of vesicular carriers enables the delivery of drugs for ocular, oral, topical, nasal, and transungual applications to specific body sites [16].

The Advantageous Effects of Spanlastics

Spanlastics are biodegradable and non-immunogenic. They enhance bioavailability by providing protective support to medications, ensuring they reach targeted areas intact. Through a lipid bilayer structure, spanlastics enable hydrophilic or lipophilic drugs to traverse physiological membranes, including those of the eye. This shielding effect protects drugs from the biological environment, enhancing therapeutic efficacy by minimizing their degradation and maximizing their impact at the intended site. Spanlastics are osmotically active and stable, thereby contributing to the prolonged stability of encapsulated medications. This feature is crucial for extending the duration of drug molecules in systemic circulation during prolonged medication use [34].

Categories of Spanlastics

Spanlastic is categorized according to the variety of layers it possesses, as demonstrated below [38].

1. **1. Multi Lamellar Vesicles (MLVs):** MLVs are structures composed of numerous lipid bilayers. They typically range in size from half to one micron in diameter. MLVs are widely used due to their simplicity in manufacturing and their ability to remain stable over long periods of storage.
2. **2. Large Unilamellar Vesicles (LUVs):** LUVs range in size from the hundred nanometer range to one micron. They have a high ratio of aqueous to lipid components, which allows them to encapsulate more medication within their core.

3. Small Unilamellar Vesicles (SUVs): SUVs are produced by the sonication process from multilamellar vesicles. They are smaller in size, typically ranging between 20 nm and 50 nm.

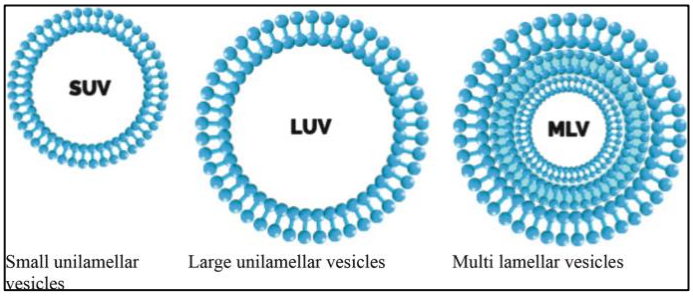

Figure 1. Classification of spanlastic [38]

Spanlastic Compositions

Surface-active compounds, also known as surfactants, serve to reduce the surface tension between two liquids. They lack ionicity. A non-ionic surfactant's head does not contain an electrically charged molecule sorbitan esters (also known as Spans) are nonionic surfactants. The formation of concentrically arranged bilayers by spans produces the vascular component that is spanlastic. There are a few different variations of the polyoxyethylene sorbitan, also known as the span, which is a component of the molecule. These variations by analyzing the varieties of Span, it is possible to predict the stability of the vesicular formulation to a large extent.

Vesicles exhibit significant disruption, aggregation, and inconsistency based on the Span 80 and Span 40 values. In contrast, the addition of saturated alkyl chains to Span60 enhances its durability. Edge activators are substances that modify the lipid bilayer, such as biocompatible surfactants, to which an amphiphilic substance is added to enhance its permeability and flexibility. By decreasing their interfacial tension, the bilayer becomes more deformable. The tendency of EAs to generate larger spherical vesicles results in the diminution of particle size. Tween 80 is an edge activator that enhances vesicle elasticity. Any vesicle larger than the biological membrane's pore size can readily migrate from the outside to the inside due to the tween80's transient increase in pore size. In addition, this promotes increased drug transfer and greater drug penetration into the vesicles. Ethanol optimizes the nano vesicular particles. It's useful since it condenses membranes. It helps to improve vesicle persistence and capture of drugs. The vesicular membrane's total thickness is reduced.

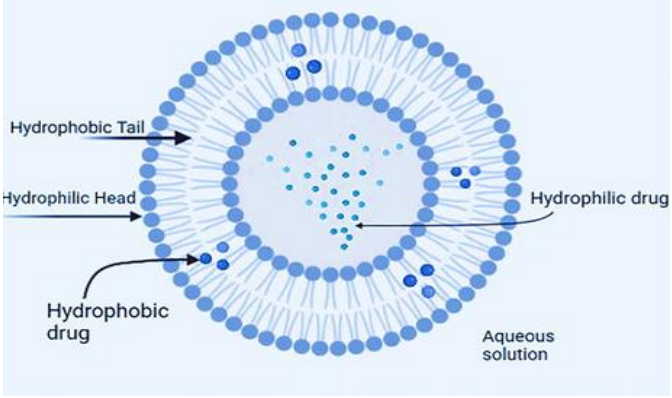

Figure 2. Structure of spanlastic [35]

Spanlastic Penetration Mechanism

Medications can infiltrate the body via two distinct routes [39]. Intercellular lipid lamellae undergo alteration by the contacts and penetration-enhancing activities of elastic particles with the epidermal cell membrane. Flexible vesicles can serve as drug-carrier structures allowing drug-carrying vesicles to pass through intercellular barriers and overcome biological boundaries. These carriers' efficient travel is aided by the following factors: The vesicle bilayers' very stress-dependent flexibility. There is an osmotic gradient. In higher concentrations, the surfactant causes solubilization (lysis). Edge activator (EAs) boosting flexibility.

- Spanlastic and layers of the organ are seen in (Figure 3)
- The connection between the spanlastic system and the epidermis as well as the development of pores within the organ's layers. Is seen in (Figure 3)
- The penetration of the spanlastic system through the layers is seen in (figure 3)
- The drug release from the spanlastic system inside the organ is seen in (figure 3). As a result, the medicine that has become stuck in the system contacts the affected area directly .

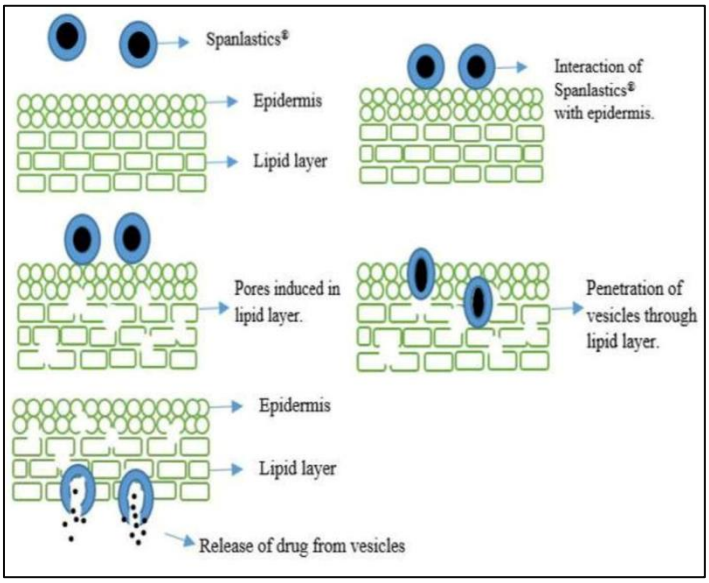

Figure 3. The mechanism for achieving penetration of the spanlastic system deep inside the skin's epidermis and the membrane of lipids [36].

Method of preparation

1. Using ether injection as a method of preparation

Using a 14-gauge needle, surfactant in ether is slowly injected into a 4 mL aqueous phase heated to 60 ºC. Using a rotary evaporator, the solution will evaporate. After the organic solvent has evaporated, monolayer vesicles will form. [37].

2. Method for injecting ethanol

This method permits the production of spanlastics with a specific ratio of non-ionic surfactant to edge activator. The intended medication is dissolved in ethanol as the solvent and then distributed. The lipid solution is sonicated for five minutes. This solution is then continuously injected into a heated aqueous solution containing an edge activator (such as Tween), which has

been agitated for twenty minutes at 80 ºC with a magnetic stirrer. To reduce the concentration of the final formulation to ten millimoles, use distilled water. [39].

3. Technique for hydrating thin films

In a round-bottom flask, Span 60 is weighed and dissolved in chloroform. As the organic liquid is evaporated using a rotary evaporator under vacuum, a thin layer will form on the inner surface of the flask. Using the selected edge activator, a specific amount of the substance will dissolve in the aqueous phase. This phase will be added to the thin layer deposition. After reattaching the flask to the evaporator, it will be rotated for thirty minutes at normal pressure, 60 ºC, and 90 revolutions per minute to completely remove the lipid coating from the flask's walls. After remaining undisturbed for over two hours, the resulting dispersion will be left overnight [40].

4. Modified spraying methodology

Additionally, spandex is manufactured using this method. This method creates the organic phase by dissolving non-ionic surfactants in 2 to 3 mL of ethanol, which is then sent to a misting apparatus. The aqueous phase is heated to 55 to 60 ºC. The organic phase is then sprayed onto the liquid phase. [41].

Characterization Techniques of Spanlastics

1. Using a transmission electron microscope: Morphological analysis is carried out on spanlastics to ascertain their lamellarity, homogeneity of size and shape, and physical stability.
2. Consider the vesicle's PDI and size: The movement of light can assess the formulation particle dimension as well as the PDI [41].
3. Zeta's potential: The instrument is used to determine the spanlastic formulation's zeta potential. It aids in the identification of the factors that lead to flocculation, aggregation, or dispersion [42].
4. V/mm3 (vesicles/millimeter3): The hemocytometer was used to determine the density of vesicles in a sample that had been adequately diluted with water [43].
5. Effectiveness of entrapment: To measure how well trapping worked, we turned to centrifugation. A 10 ml sample of the spanlastics dispersion may be centrifuged then collect the supernatant. The use of ultraviolet light assessed medicine in the supernatant [44].
6. Evaluation of Elastic Properties: As a surrogate for elastic qualities, the deformability index (DI) is useful. Nanospanlastics' elasticity may be measured using an extrusion technique. nanospanlastics were fabricated and extruded for 10 minutes under constant vacuum pressure [45, 46].
7. Differential scanning calorimetry's practical use: Differential scanning calorimetry is used to analyze the thermal properties of a given sample. A sample of the extrudate, weighing between 5 and 10 milligrams, is placed in a 40-milliliter aluminum crucible and precisely weighed before being sealed. All tests are conducted in a nitrogen atmosphere with heating rates of 10 ºC/min and temperatures ranging from 20 to 150 º C [47].
8. Experiments on drug release in vitro: Researchers used Franz diffusion cells to study drug release in vitro. The donor chamber and the receptor chamber were separated by a cellophane divider. The receptor chamber was filled with buffer at pH 6, and a weighed quantity of spanlastic was placed on one side of the dialysis membrane. The solution was then magnetically stirred at 500 rpm to maintain a temperature of 37 ºC [47].
9. Analysing Stability: The spanlastic formulation was subjected to a stability test by being stored for three months at 4 ºC in a glass vial at room temperature. Samples were extracted from the system at scheduled intervals. After 30, 60, and 90 days in storage, the encapsulation efficiency (EE%), particle size, size distribution, and drug release were analyzed.

Bacterial Infections and Bacterial Resistance

Despite medical advances such as vaccinations, antibiotics, enhanced hygiene, and the prevention of vector-borne illnesses, infections continue to be the leading cause of sickness worldwide. Infectious diseases kill around 13 million people each year. Numerous bacterial infections, especially those affecting the respiratory and gastrointestinal systems, have been linked to non-airborne chronic illnesses such as insulin resistance, gastrointestinal ulcers, cardiovascular disease, asthma, and cancer . The advent of antibiotics to address these bacterial infections has lowered morbidity and mortality, but antibiotic usage has drawbacks. Low concentrations in infection areas, the necessity for repeated high doses to achieve the required concentrations, severe adverse reactions and morbidity, and significant side effects and toxicity have left doctors with limited treatment options. One major issue is insufficient intracellular penetration [48-49].
Furthermore, the rise of antibiotic-resistant bacteria has rendered the most routinely used antibiotics ineffective. There is an urgent need to investigate alternative treatments for bacterial infections and prevent the spread of antibiotic resistance. This is due to the difficulty in accessing antibiotics, the emergence of new multi-drug-resistant bacterial strains, and the decreasing development of new antibiotic classes. Nanosystems, with their unique physical properties and excellent surface-to-volume ratio, can more easily penetrate barriers and interact with bacteria. This suggests that they could potentially overcome the limitations of conventional antibiotic treatments [50-54].

Nanosystems and Antimicrobials

Advantages of Nanosystems for Infection Treatments

1. Higher levels of the drug inside the cell, which leads to improved outcomes [55].
2. Greater pharmaceutical bioavailability due to improved cellular absorption and extended- release.
3. Lower dose and schedule of administration.
4. More uniform distribution and improved patient compliance.
5. Also, it has been demonstrated that some nanosystems used as routes of administration may be able to get around resistance by attacking diseases in different ways at the same time [56]

Spanlastics and Antimicrobials

Due to the lack of traditional medicines, vesicular systems such as spanlastics are now the subject of intensive investigation. Vesicular systems have been used as drug delivery systems because they are less harmful and more effective than free drugs at the same dosage. A bilayer of edge activator and surfactant is found in spanlastics. They are more stable than liposomes because they lack oxidatively degradable phospholipids. Vesicles are an appealing method of drug administration for the treatment

of antibiotic infections due to their lower toxicity and increased effectiveness.

Bacteria have been linked to a variety of serious diseases and early deaths. Due to their efficiency and low cost, antibiotics are the primary therapy for bacterial infections. However, several studies have shown that the misuse of antibiotics has led to the rise of bacteria resistant to a wide range of antimicrobial treatments. As a result of widespread pharmaceutical usage, superbugs have evolved in recent years. In these bacteria, the super-resistance gene NDM-1 was discovered. The principal targets of the most commonly used antibiotics are cell wall construction, translation machinery, and DNA replication machinery. Nanoparticles (NPs) are unlikely to produce antibiotic-dependent bacterial resistance mechanisms because they work by making direct contact with the bacterial cell wall rather than entering the cell. This is why newly discovered antibacterial nanoparticle materials have piqued the public's curiosity [57-60].

The majority of bacteria live in multispecies biofilms where they interact with their environment and with one another. Biofilms are bacterial colonies that grow on solid surfaces and are composed of extracellular polymeric substances (EPS) [61]. When bacteria create EPS, they become permanently attached to the surface. Once bacteria have established themselves, flagella development stops, allowing for rapid multiplication and biofilm formation. At this point, the bacteria have established an antibiotic-resistant barrier, allowing the systemic infection to persist over time [62,63]. As a result, biofilms represent a substantial threat to human health. Biofilm bacteria may create superantigens to further evade the immune system. Bacterial infections remain widespread, despite the availability of numerous antibiotics and other novel therapies. Planktonic bacteria and biofilms, both of which are resistant to medicines and the body's natural defenses, can cause persistent illnesses that are notoriously difficult to cure. Fewer antimicrobials are effective against biofilms compared to planktonic bacteria [64].

Carbapenems as a Model

Carbapenems are the most recent generation of β-lactam antibiotics [65]. They are the ultimate choice for long-term in-patient care against dangerous infectious microorganisms. Carbapenems boast excellent hydrolysis resistance. However, carbapenem-resistant bacteria typically possess β-lactamases. Gram-negative microbes such as Enterobacteriaceae and Pseudomonas have exhibited global distribution. The incidence of this resistance is linked to bacterial production of carbapenems, enzymes that hydrolyze carbapenems and increase efflux of multiple drugs [66, 67]. This newly acquired resistance spreads rapidly through species segregation involving integrins, plasmids, and transposons [68].

A broad spectrum of antimicrobials, including aminoglycosides, quinolones, and cephalosporins, have been found in recent studies to be ineffective against carbapenem-resistant bacteria [68]. In response to this therapeutic challenge, several carbapenem formulation and delivery strategies have been developed with two primary goals. One approach to prevent carbapenem degradation by bacteria is to stabilize its molecular structure [69]. The second approach involves enhancing carbapenem absorption and penetration into bacteria to improve the drug's therapeutic efficacy against resistant strains. Ongoing research is focused on achieving these objectives. The efficient delivery of antimicrobial compounds is believed to be achievable using nano-sized carriers that provide essential chemical protection and targeted action [70].

These include solids and liposomes as nano-carriers, self-assembling micelles [71-74], lipid nanoparticles, polymer nanoparticles, metal nanoparticles, and quantum dots. These nano-carriers have been shown to effectively reduce microbial resistance [73-77]. Comprehensive reviews provide further details on various nano-carrier delivery strategies that enhance antibacterial effectiveness against numerous pathogenic bacteria [75, 76]. Nanoparticles have significantly enhanced the delivery of antibiotics in recent years, garnering attention for their potential in combating microbial resistance and preventing biofilm formation [75, 76]. The thermodynamic stability of self-assembled nano-sized polymeric nanoparticles makes them a viable method for delivering antibiotics. These particles enhance antibiotic efficacy against multidrug-resistant bacteria, as demonstrated in animal studies. They also protect antibiotics from degradation, allowing for reduced therapeutic doses and extended circulation [77]. Polymeric nanoparticles aid in the targeted delivery of antibiotics, reducing the frequency of administration and minimizing side effects. Various biodegradable polymers such as alpha-hydroxy acid-based polyesters (e.g., alginate, chitosan, polylactide, polyglycolide, and polycaprolactone) and polyamino acids are commonly used for medication delivery in medical literature [78-85].

Fazli *et al*. reported on the delivery of imipenem using a chitosan-polyethylene oxide nanofiber mat incorporating ZnO nanoparticles to physically entrap imipenem/Cilastatin within nanopores [79]. They successfully maintained the release of imipenem/Cilastatin, although concerns persist regarding the potential toxicity of ZnO nanoparticles [80]. Polyhydroxy-acid esters biodegrade effectively and have been utilized for sustained release of antimicrobials [20]. Modifying certain polymer characteristics such as molecular weight and hydrophilicity/hydrophobicity can customize nanoparticles for specific delivery functions [81]. However, no studies have specifically investigated the safety of carbapenem delivery using polyhydroxy-acid esters. Niosomes are nonionic surfactant nanoparticles that mimic the characteristics of liposomes. Composed of amphipathic lipids and nonionic surfactants, niosomes are widely used in drug delivery. They can dissolve in both fat and water [82]. Niosomes are more stable, less prone to oxidation, and more cost-effective than liposomes because they utilize nonionic surfactants instead of lipids for membrane formation. They remain stable at room temperature and carry no net electrical charge. Noisome particles have demonstrated effectiveness in various delivery routes including inhalation, oral ingestion, ocular administration, dermal application, and intravenous injection.

Niosomes, derived from the cosmetics industry, are valued for their osmotic nature, biocompatibility, and anti-inflammatory properties, making them excellent vehicles for medication delivery [83, 84]. These amphipathic structures have an aqueous core surrounded by a hydrophobic membrane, facilitating the delivery of both hydrophobic and hydrophilic therapeutic substances due to their high water permeability and neutral charge [85]. Niosomes, composed of water-soluble bilayers containing nonionic surfactants, are capable of carrying large doses of medication, making them ideal for drug encapsulation [86, 87]. They have recently garnered attention as potential carriers for antibacterial agents [88].

Spanlastics (SPLs) are elastic nanovesicles developed by Kakkar and Kaur [40], consisting of ethanol, an edge activator, and a nonionic surfactant. Spanlastics can deliver drugs that are both

hydrophilic and hydrophobic, utilizing compartments with hydrophilic and lipid layers [89]. These vesicular carriers are non-immunogenic, biodegradable, and non-toxic, significantly enhancing therapeutic efficacy, medication absorption, patient compliance, and reducing adverse effects [39]. Spanlastics are chemically stable due to their elasticity, offering advantages over liposomal and niosomal delivery systems [40]. The presence of an edge activator in spanlastics disrupts the vesicle's lipid membrane, increasing permeability and deformability across biological membranes [39].

Recent studies have explored various applications of spanlastics, such as enhancing the delivery of ciprofloxacin trans-tympanically [90], treating fungal keratitis with clotrimazole intraocularly [91], and improving terbinafine hydrochloride penetration through nails [92]. Spanlastics have also been used for topical delivery of fenoprofen calcium to treat arthritis [93]. Research specifically evaluating spanlastics for carbapenem delivery is limited. In this study, meropenem was formulated into spanlastic nanoparticles using span and an edge activator. The nanoparticles were then tested for their antibacterial efficacy in vitro against meropenem-resistant bacteria. Meropenem, a broad-spectrum antibacterial drug in the carbapenem family, is used in both adults and children to treat severe infections empirically until the causative organisms are identified. It is approved in the US for treating complicated intra-abdominal infections (cIAI), complicated skin and skin structure infections (cSSSI), and bacterial meningitis in children over 3 months old. Meropenem exhibits broad in vitro activity against both Gram-positive and Gram-negative pathogens.

Conclusion

In conclusion, the evolution of advanced medication delivery systems represents a significant leap forward in pharmaceutical technology, particularly through the integration of nanotechnology. These innovative systems, including spanlastics, liposomes, and niosomes, offer remarkable improvements over traditional methods by enhancing drug efficacy, targeting precision, and minimizing side effects. Advanced delivery techniques such as controlled-release and targeted systems facilitate more effective and site-specific medication administration, addressing key challenges like drug degradation and resistance. While spanlastics, with their flexible and stable characteristics, show promise in overcoming biological barriers and enhancing therapeutic outcomes, the broader application of nanosystems in combating antibiotic resistance highlights their potential to revolutionize infection treatment. As research and development continue, these advanced drug delivery systems will likely play a pivotal role in optimizing medication efficacy and patient compliance, ultimately advancing the field of medicine.

References

1] Tiwari, G., et al., *Drug delivery systems: An updated review.* 2012. 2(1): p. 2.

2] Patel, R.J.I.J.o.S. and Technology, *Overview of industrial filtration technology and its applications Rakesh Patel, Devarshi Shah, Bhupendra G. Prajapti and Manisha Patel.* 2010. 3.(10)

3]Tamargo, J., J.-Y. Le Heuzey, and P.J.E.j.o.c.p. Mabo, *Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide.* 2015. 71: p. 549-567.

4]Glassman, P.M., V.R.J.J.o.P. Muzykantov, and E. Therapeutics, *Pharmacokinetic and pharmacodynamic properties of drug delivery systems.* 2019. 370(3): p. 570-580.

5]Vugmeyster, Y., et al., *Pharmacokinetics and toxicology of therapeutic proteins: advances and challenges.* 2012. 3(4): p. 73.

6]Ulbrich, K., et al., *Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies.* 2016. 116(9): p. 5338-5431.

7] Liechty, W.B., et al., *Polymers for drug delivery systems.* 2010. 1: p. 149-173.

8] Patel, V.M ,.B.G. Prajapati, and M.M.J.A.P. Patel, *Effect of hydrophilic polymers on buccoadhesive Eudragit patches of propranolol hydrochloride using factorial design.* 2007. 8: p. E119-E126.

9]Patel, R.P., et al., *Formulation and evaluation of sustained release matrix tablet of Tizanidine Hydrochloride by direct compression technique.* 2015.

10]Patel, S., et al., *Solubility enhancement of benfotiamine, a lipid derivative of thiamine by solid dispersion technique.* 2012. 4(Suppl 1): p. S104.

11]Adepu, S. and S.J.M .Ramakrishna, *Controlled drug delivery systems: current status and future directions.* 2021. 26(19): p. 5905.

12]Makadia, H.K. and S.J.J.P. Siegel, *Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier.* 2011. 3(3): p. 1377.1397-

13]McNamara, K. and S.A.J.P.c.c.p. Tofail, *Nanosystems: the use of nanoalloys, metallic, bimetallic, and magnetic nanoparticles in biomedical applications.* 2015. 17(42): p. 27981-27995.

14]Saadeh, Y. and D.J.A.j.o.r.s. Vyas, *Nanorobotic applications in medicine: current proposals and designs.* 2014. 1(1): p. 4-11.

15]Oliveira Jr, O.N., et al., *Nanomaterials for diagnosis: challenges and applications in smart devices based on molecular recognition.* 2014. 6(17): p. 14745-14766.

16]Mosallam S, A.R ,.Abdelbari MA. Advanced Vesicular Systems For Antifungal Drug Delivery. AAPS Pharm Sci Tech, 2022; 23: 1-11, 2022. 3(2): p. 133-149.

17]Holzinger, M., A. Le Goff, and S.J.F.i.c. Cosnier, *Nanomaterials for biosensing applications: a review.* 2014 :2 .p. 63.

18]Golovin, Y.I., et al., *Towards nanomedicines of the future: Remote magneto-mechanical actuation of nanomedicines by alternating magnetic fields.* 2015. 219: p. 43-60.

19]Mirza, A.Z. and F.A.J.I.N.L. Siddiqui, *Nanomedicine and drug delivery :a mini review.* 2014. 4: p. 1-7.

20]Lu, H., et al., *Recent progress on nanostructures for drug delivery applications.* 2016. 2016.

21]Blanco, E., H. Shen, and M.J.N.b. Ferrari, *Principles of nanoparticle design for overcoming biological barriers to drug delivery.* 2015. 33(9): p. 941-951.

22]Kumari, A., V. Kumar, and S.J.T.M.R. Yadav, *Nanotechnology: a tool to enhance therapeutic values of natural plant products.* 2012. 7(2): p. 34-42.

23]Mignani, S., et al., *Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: a concise overview.* 2013. 65(10): p. 1316-1330.

24]Pandit A, Z.D.T.-f.y.o.n.-b.-m.h.w.r.h.F.M. *Pandit A, Zeugolis DI. Twenty-five years of nano-bio-materials: have we revolutionized healthcare? Fut Med. 2016;11(9):985–7.*

25]Ahmed, S., et al., *In vitro and preclinical assessment of factorial design based nanoethosomes transgel formulation of an opioid analgesic.* 2016. 44(8): p. 1793-1802.

26]Woldu, M., *Design and Evaluation of Nanoparticulate Drug Delivery Systems for Imaging and Treatment of Malignant Brain Tumor.* The Global Journal of Pharmaceutical Research, 2014.

27]Mura, S., et al., *Penetration enhancer-containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil* .International Journal of Pharmaceutics, 2009. 380(1): p. 72-79.

28]Schwendener, R.A., *Liposomes as vaccine delivery systems: a review of the recent advances.* Ther Adv Vaccines, 2014. 2(6): p. 159-82.

29]Saifi, Z., et al., *Bilosomes nanocarriers for improved oral bioavailability of acyclovir: A complete characterization through in vitro, ex-vivo and in vivo assessment.* 2020. 57: p. 101634.

30]Mahtab, A., et al., *Quality by design driven development and optimization of teriflunomide loaded nanoliposomes for treatment of rheumatoid arthritis: An in vitro and in vivo assessments.* Journal of Drug Delivery Science and Technology, 2019. 51: p. 383-396.

31]Elsayed, M.M.A., et al., *Deformable liposomes and ethosomes: Mechanism of enhanced skin delivery.* International Journal of Pharmaceutics, 2006. 322(1): p. 60-66.

32]Ammar, H.O., et al., *Proniosomes as a carrier system for transdermal delivery of tenoxicam.* Int J Pharm, 2011. 405(1-2): p. 142-52.

33]Alsarra, I.A., et al., *Proniosomes as a drug carrier for transdermal delivery of ketorolac.* Eur J Pharm Biopharm, 2005. 59(3): p. 485-90.

34]https://rpbs.journals.ekb.eg/article_137621.html.

35]Ansari, M.D., et al., *Spanlastics a Novel Nanovesicular Carrier: Its Potential Application and Emerging Trends in Therapeutic Delivery.* AAPS PharmSciTech, 2022.s 23(4): p. 112.

36]Chauhan, M.K. and A. Verma. *SPANLASTICS-FUTURE OF DRUG DELIVERY AND TARGETING*. 2017.

37]Kaur, I.P., et al., *Development and evaluation of novel surfactant-based elastic vesicular system for ocular delivery of fluconazole.* J Ocul Pharmacol Ther, 2012. 28(5): p. 484-96.
38]Joshi, S., Bawage, S., Tiwari, P., Kirby, D., Perrie, Y., Dennis, V., & Singh, S. R. (2019). Liposomes: a promising carrier for respiratory syncytial virus therapeutics. *Expert opinion on drug delivery*, *16*(9), 969-980.
39]Mekkawy, A.I., et al., *Combinatorial Therapy of Letrozole- and Quercetin-Loaded Spanlastics for Enhanced Cytotoxicity against MCF-7 Breast Cancer Cells.* Pharmaceutics, 2022.(8)14 .
40]Badria, F. and E. Mazyed, *Formulation of Nanospanlastics as a Promising Approach for Improving the Topical Delivery of a Natural Leukotriene Inhibitor (3-Acetyl-11-Keto-β-Boswellic Acid): Statistical Optimization, in vitro Characterization ,and ex vivo Permeation Study.* Drug Des Devel Ther, 2020. 14: p. 3697-3721.
41]Kakkar S, Kaur IP. Spanlastics—A Novel Nano Vesicular Carrier System for Ocular Delivery. Int J Pharm, 2011; 413: 202–10. Drug Deliv Transl Res, 2011. 13(4): p. 1153-1.168
42]Abdelbari, M.A., et al., *Implementing Spanlastics for Improving the Ocular Delivery of Clotrimazole: In vitro Characterization, Ex vivo Permeability, Microbiological Assessment and In vivo Safety Study.* Int J Nanomedicine, 2021. 16: p. 6249-6261.
43]Sousa, F., et al., *Current Insights on Antifungal Therapy: Novel Nanotechnology Approaches for Drug Delivery Systems and New Drugs from Natural Sources.* Pharmaceuticals (Basel), 2020. 13.(9)
44]Alharbi, W.S., et al., *Spanlastics as a Potential Platform for Enhancing the Brain Delivery of Flibanserin: In Vitro Response-Surface Optimization and In Vivo Pharmacokinetics Assessment.* 2022. 14(12): p. 2627.
45]Saleh, A., et al., *Zolmitriptan Intranasal Spanlastics for Enhanced Migraine Treatment; Formulation Parameters Optimized via Quality by Design Approach.* 2021. 89(2): p. 24.
46]Sallam, N.M., et al., *Impact of the mucoadhesive lyophilized wafer loaded with novel carvedilol nano-spanlastics on biochemical markers in the heart of spontaneously hypertensive rat models.* Drug Deliv Transl Res, 2021. 11(3): p. 1009-1036.
47]Shahira F. El Menshawe, M.M.N., Heba M. Aboud, Rasha M. Kharshoum, Asmaa Mohammed M. Hussein Elkelawy & Doaa S. Hamad *Transdermal Delivery of Fluvastatin Sodium Via Tailored Spanlastic Nanovesicles: Mitigated Freund's Adjuvant Induced Rheumatoid Arthritis in Rats Through Suppressing P38 MAPK Signaling Pathway, Drug Delivery, 2019; 26(1): 1140-154.* . J Liposome Res, 2019. 30(1): p. 45-53.
48]Anderson, S.T., R .Laxminarayan, and S.W. Salant, *Diversify or focus? Spending to combat infectious diseases when budgets are tight.* Journal of Health Economics, 2012. 31(4): p. 658-675.
49]Hamburg, M.A., *Considerations for infectious disease research and practice.* Technology in Society, 2008. 30(3): p. 383-387.
50]Ogoina, D. and G.C. Onyemelukwe, *The role of infections in the emergence of non-communicable diseases (NCDs): Compelling needs for novel strategies in the developing world.* Journal of Infection and Public Health, 2009. 2(1): p. 14-29.
51]Huh, A.J. and Y.J. Kwon, *"Nanoantibiotics": A new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era.* Journal of Controlled Release, 2011. 156(2): p. 128-145.
52]Imbuluzqueta, E ,.et al., *Novel bioactive hydrophobic gentamicin carriers for the treatment of intracellular bacterial infections.* Acta Biomaterialia, 2011. 7(4): p. 1599-1608.
53]Beaulac, C., et al., *Eradication of mucoid Pseudomonas aeruginosa with fluid liposome-encapsulated tobramycin in an animal model of chronic pulmonary infection.* Antimicrob Agents Chemother, 1996. 40(3): p. 665-9.
54]Siegel, R.E., *Emerging gram-negative antibiotic resistance: daunting challenges, declining sensitivities, and dire consequences* .Respir Care, 2008. 53(4): p. 471-9.
55]El-Ridy, M.S., et al., *Biological evaluation of pyrazinamide liposomes for treatment of Mycobacterium tuberculosis.* International Journal of Pharmaceutics, 2007. 330(1): p. 82-88.
56]Pelgrift, R.Y. and A.J. Friedman, *Nanotechnology as a therapeutic tool to combat microbial resistance.* Advanced Drug Delivery Reviews, 2013. 65(13): p. 1803-1815.
57]Moazeni, E., et al., *Formulation and in vitro evaluation of ciprofloxacin containing niosomes for pulmonary delivery.* J Microencapsul, 2010. 27(7): p. 618-27.
58]Hsueh, P.R., *New Delhi metallo-ß-lactamase-1 (NDM-1): an emerging threat among Enterobacteriaceae.* J Formos Med Assoc, 2010. 109(10): p. 685-7.
59]Poole, K., *Mechanisms of bacterial biocide and antibiotic resistance.* J Appl Microbiol, 2002. 92 Suppl: p. 55s-64s.
60]Jayaraman, R.J.C.s., *Antibiotic resistance: an overview of mechanisms and a paradigm shift.* 2009: p. 1475-1484.
61]Romero, D., et al., *Amyloid fibers provide structural integrity to Bacillus subtilis biofilms.* Proc Natl Acad Sci U S A, 2010. 107(5): p. 2230-4.
62]Huh, A.J. and Y.J. Kwon, *"Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era.* J Control Release, 2011. 156(2): p. 128-4.5
63]Hajipour, M.J., et al., *Antibacterial properties of nanoparticles.* Trends Biotechnol, 2012. 30(10): p. 499-511.
64]Reyes, V.C., S.O. Opot, and S. Mahendra, *Planktonic and biofilm-grown nitrogen-cycling bacteria exhibit different susceptibilities to copper nanoparticles.* Environ Toxicol Chem, 2015. 34(4): p. 887-97.
65]Köhler, T., et al., *Carbapenem activities against Pseudomonas aeruginosa: respective contributions of OprD and efflux systems.* Antimicrob Agents Chemother, 1999. 43(2): p. 424-7.
66]Quale, J., et al., *Interplay of efflux system, ampC, and oprD expression in carbapenem resistance of Pseudomonas aeruginosa clinical isolates.* Antimicrob Agents Chemother, 2006. 50(5): p. 1633-41.
67]Meletis, G., et al., *Mechanisms responsible for the emergence of carbapenem resistance in Pseudomonas aeruginosa.* Hippokratia, 2012. 16(4): p. 303-7.
68]Ventola, C.L., *The antibiotic resistance crisis: part 1: causes and threats.* P t, 2015. 40(4): p. 277-83.
69]Fair, R.J. and Y. Tor, *Antibiotics and bacterial resistance in the 21st century.* Perspect Medicin Chem, 2014. 6: p. 25-64.
70]Brooks, B.D. and A.E. Brooks, *Therapeutic strategies to combat antibiotic resistance.* Adv Drug Deliv Rev, 2014. 78: p. 14-27.
71]Brown, A.N., et al., *Nanoparticles functionalized with ampicillin destroy multiple-antibiotic-resistant isolates of Pseudomonas aeruginosa and Enterobacter aerogenes and methicillin-resistant Staphylococcus aureus.* Appl Environ Microbiol, 2012. 78(8): p. 2768-74.
72]Roe, D., et al., *Antimicrobial surface functionalization of plastic catheters by silver nanoparticles.* J Antimicrob Chemother, 2008. 61(4): p. 869-76.
73]Zazo, H., C.I. Colino, and J.M. Lanao, *Current applications of nanoparticles in infectious diseases.* J Control Release, 2016. 22 :4p. 86-102.
74]Zhang, Z., et al., *Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases.* Wiley Interdiscip Rev Nanomed Nanobiotechnol, 2013. 5(3): p. 205-18.
75]Cheow, W.S. and K. Hadinoto, *Antibiotic polymeric nanoparticles for biofilm-associated infection therapy.* Methods Mol Biol, 2014. 1147: p. 227-38.
76]Samiei, M., et al., *Nanoparticles for antimicrobial purposes in Endodontics: A systematic review of in vitro studies.* Mater Sci Eng C Mater Biol Appl, 2016. 58: p. 1269-78.
77]Hofmann, D., et al., *Drug delivery without nanoparticle uptake: delivery by a kiss-and-run mechanism on the cell membrane.* Chem Commun (Camb), 2014. 50(11): p. 1369-71.
78]Turos, E., et al., *Antibiotic-conjugated polyacrylate nanoparticles: new opportunities for development of anti-MRSA agents.* Bioorg Med Chem Lett, 2007. 17(1): p. 53-6.
79]Fazli, Y., et al., *A novel chitosan-polyethylene oxide nanofibrous mat designed for controlled co-release of hydrocortisone and imipenem/cilastatin drugs.* Int J Pharm, 2016. 513(1-2): p. 636-647.
80]Rasmussen, J.W., et al., *Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications.* Expert Opin Drug Deliv, 2010. 7(9): p. 1063-77.
81]Forier, K., et al., *Lipid and polymer nanoparticles for drug delivery to bacterial biofilms.* J Control Release, 2014. 190: p. 607-23.
82]Saini, A., et al., *Encapsulation of functional ingredients in lipidic nanocarriers and antimicrobial applications: a review.* 2021. 19: p. 1107-1134.
83]Bartelds, R., et al., *Niosomes, an alternative for liposomal delivery.* PLoS One, 2018. 13(4): p. e0194179.
84]Marianecci, C., et al., *Niosomes from 80s to present: the state of the art.* Adv Colloid Interface Sci, 2014. 2 :05p. 187-206.
85]Abdelkader, H., et al., *Niosomes and discomes for ocular delivery of naltrexone hydrochloride: morphological, rheological, spreading properties and photo-protective effects.* Int J Pharm, 2012. 433(1-2): p. 142-8.
86]Ge, X., et al., *Advances of Non-Ionic Surfactant Vesicles (Niosomes) and Their Application in Drug Delivery.* Pharmaceutics, 2019. 11.(2)
87]Yeo, P.L., et al., *Niosomes: a review of their structure, properties, methods of preparation, and medical applications.* 2017. 11 :(4)p. 301-314.
88]Durak, S., et al., *Niosomal Drug Delivery Systems for Ocular Disease-Recent Advances and Future Prospects.* Nanomaterials (Basel), 2020. 10.(6)
89]Saleh, A., et al., *Zolmitriptan intranasal spanlastics for enhanced migraine treatment; formulation parameters optimized via quality by design approach.* 2021. 89(2): p. 24.
90]Al-Mahallawi, A.M., O.M. Khowessah, and R.A. Shoukri, *Enhanced non invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles :Fabrication, in-vitro characterization, and comparative ex-vivo permeation studies.* Int J Pharm, 2017. 522(1-2): p. 157-164.

91]Basha, M., et al., *Design and optimization of surfactant-based nanovesicles for ocular delivery of Clotrimazole.* J Liposome Res, 2013. 23(3): p. 203-10.
92]Elsherif, N.I., R.N. Shamma, and G. Abdelbary, *Terbinafine Hydrochloride Trans-ungual Delivery via Nanovesicular Systems: In Vitro Characterization and Ex Vivo Evaluation.* AAPS PharmSciTech, 2017. 18(2): p. 551-562.
93]Farghaly, D.A., et al., *Topical delivery of fenoprofen calcium via elastic nano-vesicular spanlastics: Optimization using experimental design and in vivo evaluation.* 2017. 18: p. 2898-2909.