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Review Article

Microbes Drug Delivery System- A Comprehensive Review

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ABSTRACT

This review article focuses on the Microbes Drug Delivery System. The Microbial drug delivery system is an emerging form of drug administration characterized by the use of commensal microbes that have been genetically modified to produce medications for chronic diseases in humans. The drug delivery system now a days, very popular for its therapeutic effects and prolonged action. The most prominent route of administration used for it, is topical route of administration due to which it avoids first pass metabolism. There are various forms available for drug delivery system, which contributes to enhance the patient compliance. Drug delivery system is a method of administration for pharmaceutical medication to achieve a therapeutic effect in humans or animals. There are various routes available for drug delivery such as the oral, topical, parentral, inhalation, transdermal, transmucosal and implantable systems. The drug delivery system further divided into two types, Conventional drug delivery system is the classical method for the delivery of drug into the body and Novel drug delivery system is a new approach that utilizes new technologies, innovative ideas and methodologies to deliver the active molecules in safe yet effective concentration to produce desired pharmacological action. The human microbiome is known to play an essential role in influencing host health. Extracellular vehicles (EVs) have also been reported to act on a variety of signaling pathways, distally transport cellular components such as proteins, lipids, and nucleic acid, and have immunomodulatory effects. In this review article we have discussed about the Microbes based drug delivery system by taking the examples of Human microbiome and extracellular vesicles.

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INTRODUCTION

Microbes Drug Delivery System is an evolving form of drug administration considered by the use of commensal microbes that have been genetically modified to yield medications for chronic diseases in humans. Only protein containing drugs can be yield by microbes, as DNA encodes for protein. Research into microbial drug delivery bring up to this route of administration as topical, since the microbes release the drug directly to the surface of affected tissues, namely the gastrointestinal (GI) epithelium. Microbial drug delivery is not currently used as a standard route of drug administration due to its experimental nature. During clinical trials, it has been used to treat forms of inflammatory bowel disease (IBD). The most prominently studied vehicles of microbial drug administration are the bacterial species, Lactococcus lactis and Bacteroides ovatus. Since more than 10 years, pharmaceutical researchers attempt to develop an effective, safe and target-specific drug delivery system to potentiate the therapeutic actions and reduce the side effects. The conventional drug delivery systems (DDSs) show the enhancement in the lifestyle of the patients suffering from non-communicable diseases, autoimmune diseases but sometimes, drug resistance developed during the treatment is a major concern for clinicians to find an alternative and more advanced transport systems. Advancements in drug delivery facilitate the development of active carrier for targeted action with improved pharmacokinetic behavior. This review article focuses on microbe-based drug delivery systems to provide safe, non-toxic, site-specific targeted action with lesser side effects. Pharmaceutical researchers play a vital part in microbe-based drug delivery systems as a therapeutic agent and carrier. The properties of microorganisms like self-propulsion, in-situ production of therapeutics, penetration into the tumor cells, increase in immunity, etc. are of interest for development of highly effective delivery carrier. Lactococcus lactis is therapeutically helpful in Inflammatory Bowel Disease (IBD) and is under investigation of phase I clinical trial. Moreover, bacteria, anti-cancer oncolytic viruses, viral vectors (gene therapy) and viral immunotherapy are the attractive areas of biotechnological research. Virus acts as a distinctive candidate for imaging of tumor and accumulation of active in tumor [1]

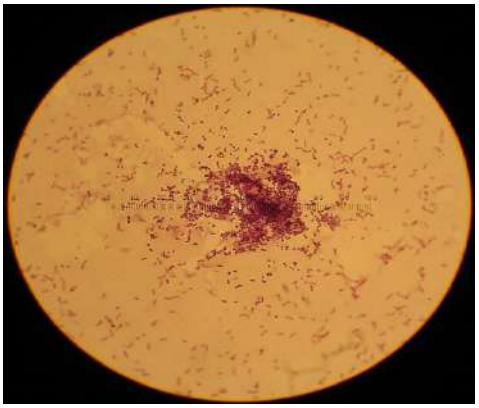


Fig 1- Lactococcus lactis, a species used in microbial drug delivery[2]

Introduction of Microorganism-

Microorganisms take most of the part of our earth as they are found around us and also inside our bodies. These complex communities of microbes that include bacteria, fungi, viruses and other microbial and eukaryotic species provide a tremendous enzymatic capability and play a vital role in controlling most aspects of host physiology. Over the past few years, the field of immunology and microbiology has been revolutionized by the growing understanding of the fundamental role of the microbes in the induction, education and function of the human immune system. Some of them are pathogenic and some are useful. Microbes help to maintain the atmosphere of our environment [3]. Each organism has their own type of cellular composition, morphology, mode of nutrition, movement and reproduction. Most of the organisms live as free living, parasitic or as host. Micro-organisms require basic nutrients for

their growth and development. Some microbes are beneficial in decomposing organic material, providing nutrition, production of oxygen and etc. Microorganisms have paved the way for the future in medicine,industry and research [4].

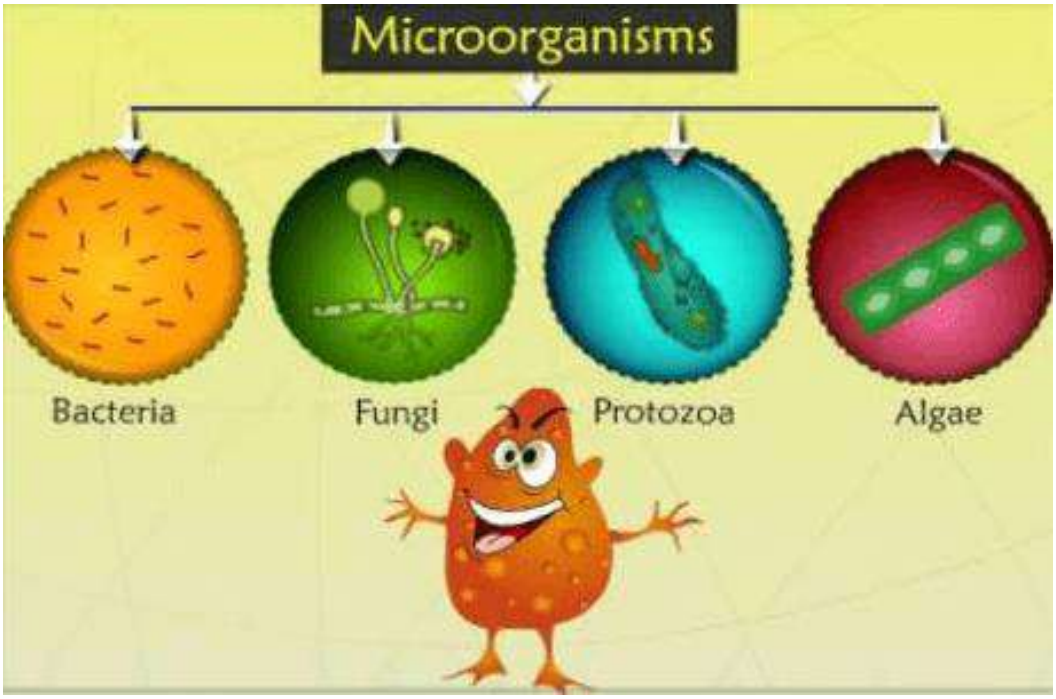


Fig 2- Various types of Microorganisms[5]

Introduction of Drug Delivery System-

To obtain a given therapeutic response, the suitable amount of the active drug must be absorbed and transported to the site of action at the right time and the rate of input can then be adjusted to produce the concentrations required to maintain the level of the effect for as long as necessary. The distribution of the drug-to-tissues other than the sites of action and organs of elimination is unnecessary, wasteful, and a potential cause of toxicity. The modification of the means of delivering the drug by projecting and preparing new advanced drug delivery devices can improve therapy. Since the 1960s, when silicone rubber was proposed as an implantable carrier for sustained delivery of low molecular weight drugs in animal tissues, various drug delivery systems have been developed. At the beginning of the era of controlled drug delivery systems, a controlled release system utilizes a polymer matrix or pump as a rate-controlling device to deliver the drug in a fixed, predetermined pattern for a desired time period [6]. These systems offered the following advantages compared to other methods of administration:

- The possibility to maintain plasma drug levels a therapeutically desirable range.
- The possibility to eliminate or reduce harmful side effects from systemic administration by local administration from a controlled release system.
- Drug administration may be improved and facilitated in underprivileged areas where good medical supervision is not available.
- The administration of drugs with a short in vivo half-life may be greatly facilitated.
- Continuous small amounts of drug may be less painful than several large doses.
- Improvement of patient compliance.

- The use of drug delivery systems may result in a relatively less expensive product and less waste of the drug.

Fig 3- Design requirement for a drug delivery system[7]

Classification of Drug Delivery System-

- Localized Drug Delivery
- Targeted Drug Delivery
- Sustained Drug Delivery
- Modulated Drug Delivery
- Controlled Drug Delivery

1. **Localized Drug Delivery-**
2. **Targeted Drug Delivery-**

The best controlled mechanism would be delivery of drug exclusively to the targeted cells or cellular components. That means the development of delivery mechanisms that would equal or surpass the selectivity of naturally occurring effectors (e.g., peptide hormones). As in the case of hormone action, drug targeting would probably involve a recognition event between the drug carrier mechanism and specific receptors at the cell surface. The most obvious candidates for the targetable drug carriers are cell-type specific immunoglobulins. The concept of targeted drug delivery is different than localized drug delivery. The latter simply implies localization of the therapeutic agent at an organ or tissue site, while the former implies more suitable delivery to specific cell types.

3. **Sustained Drug Delivery-**

Injected or ingested drugs follow first-order kinetics, with initial high blood levels of the drug after initial administration, followed by an exponential fall in blood concentration. Toxicity often occurs when blood levels peak, while efficacy of the drug diminishes as the drug levels fall below the therapeutic range. This profile and the drug kinetics is undesirable, especially in the case where the margin between toxicity and required therapeutic concentration levels is small. The importance of controlled-release drug delivery systems may be argued with reference to the goal of achieving a continuous drug release profile consistent with zero-order kinetics, wherein blood levels of drugs would remain constant throughout the delivery period. The therapeutic advantages of continuous release drug delivery systems are thus significant, and encompass: in vivo predictability of release rates on the basis of in vitro data; minimized peak plasma levels, and thereby reduced risk of toxic effects; predictable and extended duration of action; reduced inconvenience of frequent dosing, thereby improving patient compliance [8,9]. Illustrates the constant plasma concentration that is desired for many therapeutic agents. The

controlled release aspect of sustained drug delivery systems pertains to a reliable and reproducible system whose rate of drug delivery is independent of the environment in which it is placed. This requirement emphasizes the need for precision of control and elimination of undesired contribution associated with the drug delivery[10].

4. Modulated Drug Delivery –

A significant challenge in drug delivery is to create a delivery system that can achieve manipulable nonzero-order release profile. This could be pulsatile or ramp or some other pattern. In some cases, it is also required that the release should be immediate. A pulsatile release profile within the therapeutic window[11].

5. Controlled Drug Delivery-

The ideal drug delivery system is the feedback-controlled drug delivery system that releases drug in response to a therapeutic marker. This can be classified into two classes: modulated and triggered device. A modulated device involves the ability to monitor the chemical environment and changes drug delivery rate continuously in response to the specific external marker, while in a triggered device no drug release takes place until it is triggered by a marker. These different approaches of drug delivery can have different routes of administration. Some of the most preferred routes are oral, pulmonary inhalation, transdermal, transmucosal, and implantable systems [12].

Classification of microbe-based drug delivery system-

The human microbiome is known to play an essential role in influencing host health. Extracellular vehicles (EVs) have also been reported to act on a variety of signalling pathways, distally transport cellular components such as proteins, lipids, and nucleic acid, and have immunomodulatory effects. Here we shall review the current understanding of the intersectionality of the human microbiome and EVs in the emerging field of microbiota-derived EVs and their pharmacological potential. Microbes secrete several classes of EVs: outer membrane vesicles (OMVs), membrane vesicles (MVs), and apoptotic bodies. EV biogenesis is unique to each cell and regulated by sophisticated signalling pathways. EVs are primarily composed of lipids, proteins, nucleic acids, and recent evidence suggests they may also carry metabolites. These components interact with host cells and control various cellular processes by transferring their constituents. The pharmacological potential of microbiome derived EVs as vaccine candidates, biomarkers, and a smart drug delivery system is a promising area of future research. Therefore, it is necessary to elucidate in detail the mechanisms of microbiome-derived EV action in host health in a multi-disciplinary manner [13]. Upon the initial discovery that eukaryotic cells release bi-layered vesicles into the extracellular environment in 1983, their function was not well understood and EVs were written off as the cellular equivalent of a garbage disposal. However, extensive research conducted over the past several decades have revealed that EVs are expressed in prokaryotes, eukaryotes, and archaea at varying levels of environmental stress. This evidence suggests that EV secretion is an evolutionarily conserved, necessary function in cells across all domains of life [14,15].

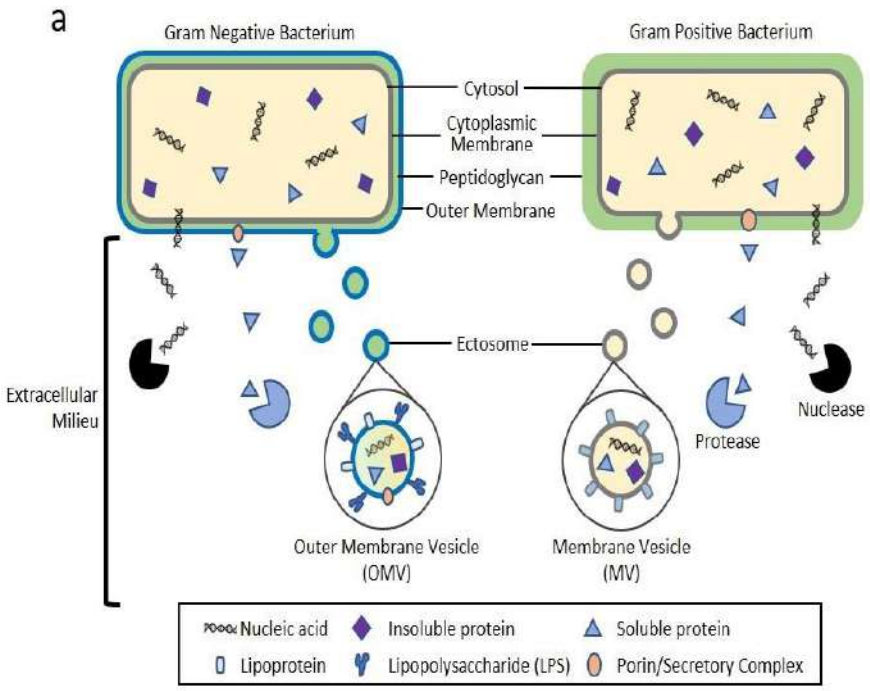
Microbiome- Derived EVS (Impactful mode of Microbe based Drug Delivery System)-

EVs are released from all three domains of life including our own eukaryotic human cells, so why is special interest warranted to EVs originating from our commensal bacteria? Three decades ago the foundation of human genetics was based on the assumption that the vast, complex biological functions of the human body were carried out primarily by the genetic information contained in our own cells. Thus, launched the groundbreaking Human Genome Project in 1990 which sought to

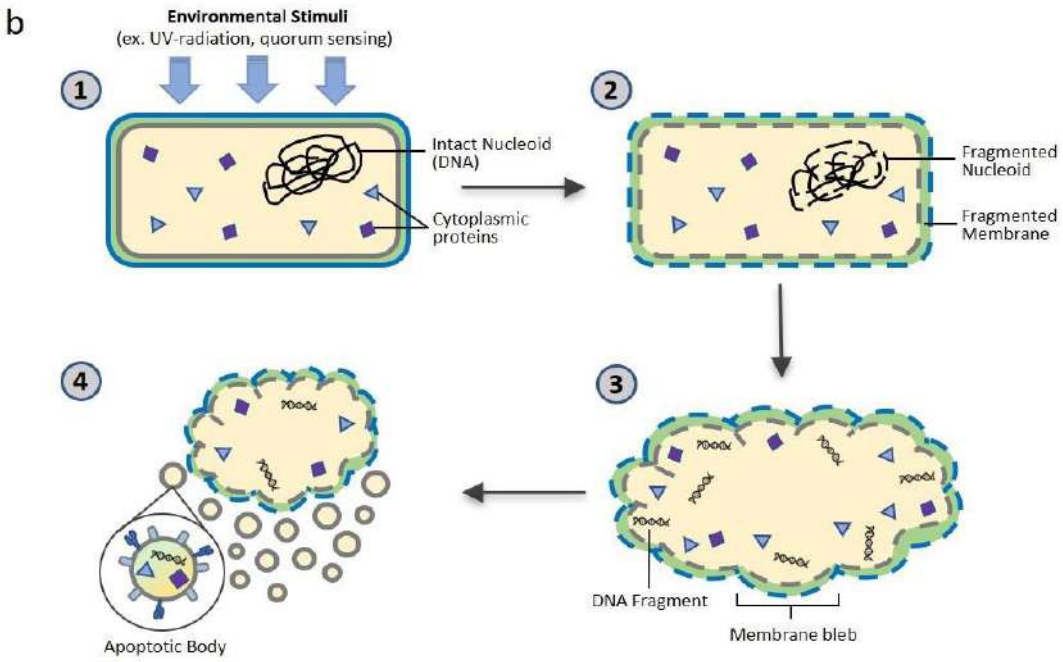
sequence and map the entire human genome in order to elucidate our genetic makeup. Early estimates of the number of genes contained in the human genome ranged from 50,000 upwards to 140,000. However, at the HGP's completion in 2003 it was revealed that the human genome contained drastically fewer genes than previously estimated. At present, the human genome is estimated to encode approximately 20,500 genes, barely surpassing the genetic content of Caenorhabditis elegans, a 1 mm roundworm [16, 17].

EV biogenesis -

The biogenesis of EVs is a very tightly regulated process governed by multiple signalling molecules and begins with receptor activation unique for each cell type. Though eukaryotic EV biogenesis is well characterized, the mechanisms of bacterial EV biogenesis have only recently begun to be elucidated. Here we will describe the current understanding of the biogenesis of ectosomes, also called shedding vesicles, in gram-negative and gram-positive bacteria as well as bacterial release of apoptotic bodies. Additionally, we will briefly discuss the well-defined mechanisms underlying eukaryotic exosome release that can offer insights into the process of EV biogenesis [18]. As shown in Fig 4 (a) [19] below, Gram negative and positive bacteria secrete ectosomes, or outer membrane vesicles (OMV) and membrane vesicles (MV), respectively biogenesis through budding of the outer membrane is well characterized, however the mechanism of MV biogenesis through the thick peptidoglycan cell wall of gram-positive bacteria is not yet fully understood.



As shown in Fig 4(b) [20] below, Bacterial cells also undergo apoptosis, a conserved self-destruct mechanism instigated by environmental stimuli such as quorum sensing or UV damage. After the apoptotic pathway is initiated, nucleoid DNA is degraded and subsequently fragmented, followed by cell membrane fragmentation. Finally, blebbing of the cell membrane occurs, resulting in release of bacterial apoptotic bodies containing bacterial cellular components.



Gram-negative bacteria: Outer Membrane Vesicles (OMV) -

Gram-negative bacteria produce ectosomes, known as outer membrane vesicles (OMVs), that contain periplasmic constituents including proteins, lipoproteins, phospholipids, and lipopolysaccharide (LPS). The first step in OMV formation is outward bulging of the outer membrane (OM). Links between the OM and the peptidoglycan are lost, either by movement of linking protein or by breaking the connection directly in various areas. This process can result in the incorporation of peptidoglycan fragments and parts of OM-peptidoglycan bridging proteins in the OM [21].

Gram-positive bacteria: Membrane Vesicles (MV)-

Unlike gram-negative bacteria, gram-positive bacteria lack an outer membrane and have a much thicker peptidoglycan cell wall outside of the cell membrane, which led to the initial assumption that gram-positive bacteria could not release EVs. However, increasing evidence has shown that many species of gram-positive bacteria release EVs, or membrane vesicles [22].

Microbial apoptotic bodies-

Another development in the field of microbial membrane dynamics is the recent attention given to prokaryotic programmed cell death (PCD), or apoptosis. It was originally presumed that possession of a genetically coded cellular self-destruct mechanism would confer no evolutionary advantage to single-celled organisms. However, recent evidence suggests that bacteria undergo apoptosis in an altruistic manner for the benefit of the entire colony rather than the individual cell in order to respond to environmental stress, biofilm formation, and genetic transformation [23, 24].

Microbial EV Components and functions-

Microbial EV components and functions Despite their nanosized dimensions, microbial EVs contain a variety of functional components including microbe-derived lipids, luminal and membrane proteins, nucleic acid (DNA, RNA, mRNA, tRNA, and sRNA), and possibly metabolites. After these components are released extracellularly within a spherical phospholipid bilayer, they have a variety of functional roles in host health. Here we will discuss these functions including drug delivery, targeting, immunomodulation, and gene transfer as they relate to the pharmacological potential of microbial EVs [25, 26].

CONCLUSIONS

Once when we discuss about the novel drug distribution structure, the Microbes based drug delivery scheme is an impactful method in this segment now these days and in upcoming future. Commonly, the microorganisms are very impactful in our society in a good and bad way both. The microorganism can act as food, medicines and can also spread various infections, but by their correct use in an accurate amount can help in the treatment of various diseases. We can determine from this review article, that if we merge the accurate amount of microorganism with our drug in novel drug delivery system, it can lead to bind the drug at targeted site more rapidly and effectively. On the basis of above discussion, we can conclude that the Microbes based drug delivery system is going to be very promising in future of health care system.

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CONFLICT OF INTEREST-

The authors of this paper declare no conflict of interest

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