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A Brief Review on Light Responsive Drug Delivery System as Personalized Medicine of Photodynamic Therapy and Over Years of Advancement on the Therapeutics

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KEYWORDS

Personalized Medicine, Light Responsive Drug Delivery System, Photosensitizer, Photofrin, Photodynamic Therapy

ABSTRACT:

Introduction -This review dredge into the foreground of personalized medicine within photodynamic therapy (PDT), focusing on the pivotal role played by light-responsive drug delivery systems. The exploration surrounds fundamental principles, spanning nanotechnology, biomaterials, and controlled release mechanisms. Beyond theoretical talks, interesting case examples covering a wide range of medical diseases are provided, highlighting the revolutionary potential of combining light-responsive medication delivery with personalised therapy.

Objectives-These studies highlight the adaptability and effectiveness of this strategy, especially when it comes to cancer therapy. To put it briefly, the purpose of this article is to provide researchers, clinicians, and pharmaceutical pioneers who are navigating the rapidly evolving field of light-responsive drug delivery systems with a succinct resource.

Methods - This is the comprehensive evaluation of literature from national and international journals. In this review ,we have used Elsevier, Science Direct ,Springer Link and website like Pub Med and Google Scholar to conduct literature search. The discussion covers the principles of PDT, emphasizing the importance of precise drug targeting and controlled release triggered by light. Most important factor that is the used of photosensitizer in the formulation of LRDDS is also mentioned and along with the carrier which is embed in it .Various strategies and technologies developed to enhance the efficacy and specificity of PDT through light-responsive drug delivery are reviewed.

Results- Photodynamic therapy (PDT) uses light-sensitive drugs to treat conditions like skin cancers, esophageal cancer, and lung cancer by targeting and destroying cancer cells when activated by specific light. This therapy disrupts tumor blood vessels and can stimulate the immune system against cancer cells. Designing effective light-responsive drug delivery systems requires optimizing drug and light properties to minimize tissue damage while ensuring precise drug release upon light activation. Overcoming challenges like phototoxicity is essential for safe and effective use of these systems in therapy.

Conclusion- In summary, the progress in light-responsive drug delivery systems signifies a significant advancement in personalized medicine, particularly in photodynamic therapy (PDT). This evolution reflects the dynamic synergy between research and innovation in therapeutics. These sophisticated drug delivery systems exemplify the precision and customization achievable in modern medicine, as

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they are designed to respond to specific light triggers. By enhancing treatment effectiveness and minimizing off-target effects, the integration of light responsiveness into drug delivery offers a more patient-centered approach to therapy.

1. Introduction

The variety of investment in the world of basic science has made many opportunities for important progress in the medical field. Many researchers have found out varieties of gene disorders going through the survey report and also identified genetic variation in patients.[1] Personalized medicine reduces the dosing frequencies of the patient and depends on patients pathophysiology along with the combination of pharmacogenomics, environment and lifestyle.[2] It is functions has been spread through variety of fields of medical background which is informed by each person unique genetic, genomic information etc, personalized medicine also takes advantage to take genomic medicine to understand molecular understanding of the disorders to optimized health care.[3] (As Mentioned in Figure 1)

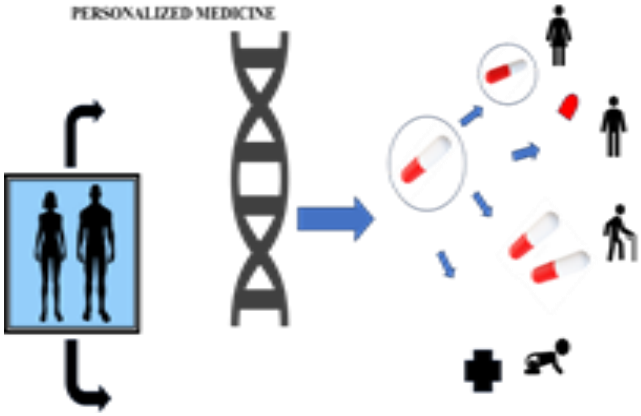

Figure 1: Graphical representation of personalized medicine

A light-responsive drug delivery system is a specially designed mechanism designed to release medication in response to light stimulation from the outside environment. Light-sensitive materials or components are frequently integrated into medicine transporters or containers using this state-of-the-art technology. These materials undergo modifications upon exposure to certain light wavelengths, which triggers the release of encapsulated medications at predetermined times and locations. With its precise and on-demand medication delivery, treatment may be tailored to meet specific needs and achieve better results while reducing the risk of adverse effects. By taking light as source for stimuli for various advantages including not invasive, high resolution and temporal control due to these reasons it has been extensively spread in medical field. Many light-based delivery systems can utilize non ionizing radiation and it is also categorized into three types Photo triggered system (PTS), Photothermal system (PS), Photo-isomerization system (PIS).[4]

History of LRDDS

In ancient times, first use of the light as therapeutic agent was used by various ancient Egyptians, Chinese & Indians to treat disorders like vitiligo, rickets, skin cancers.[5] One of the earliest with most effective therapeutic effect was Heliotherapy, which introduced by the Greeks somewhere about 3000 years ago, from late 18th century, Sun therapy was effective in rickets disorder and in 19th century a physician named Cauvin stated that sunlight is the curative factor for Scurvy, Rickets etc. Through the work of Danish physician Niels Finsen, phototherapy was recognised widely and became a formalised scientific field. He was the first to treat lupus vulgaris with carbon arc phototherapy, and in 1903, he was granted the Nobel Prize in recognition of his revolutionary achievement.

2. Objectives

The following are the objectives of this review:

1. To provide a brief overview of medication delivery systems that respond to light.
2. To look into the application of these systems in personalised medicine, especially with regard to photodynamic treatment.
3. To examine the advancements made in light-responsive therapies throughout time, emphasising their efficacy and potential for use in clinical settings.

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3. Methods

This is the comprehensive evaliuation of literature from national and international journals.In this review ,we have used Elsevier, Science Direct ,Springer Link and website like Pub Med and Google Scholar to conduct literature search.

The most important requirement of LRDDs is the photosensitizers .

Photosensitizer

There are 3 main components- Chromophore, Linker, Reactive group, apart from light source and oxygen as main components. Photosensitizer has the ability to absorb light at specific wave length and triggers photochemical reactions.[6] (as mentioned in the figure 2)

The basic photosensitizer property:

1) Exceptional chemical purity
2) Stable at room temperature
3) Shows photochemical effect on specific wavelength
4) Simple in synthesis process and easily available.[7]

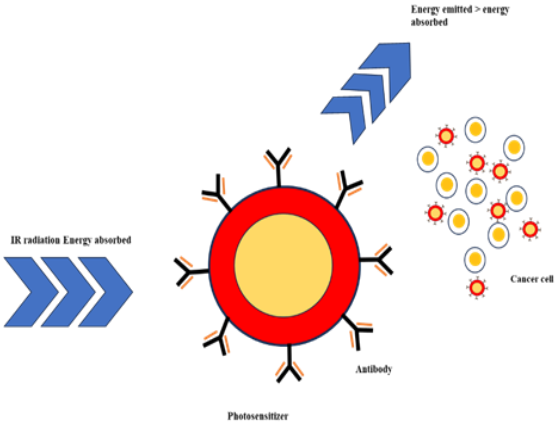

Figure 2: Graphical representation of Photosensitizer

Generation of Photosensitizers

1. 1st Generation:

First-generation photosensitizers refer to the initial compounds or agents that were used in early research and clinical applications of photodynamic therapy (PDT) and related light-based treatments. These early photosensitizers laid the groundwork for the development of more advanced and effective agents used in modern photodynamic therapy. Some notable first-generation photosensitizers include:

a) Hematoporphyrin derivative (HPD): Hematoporphyrin derivative (HPD), a complex combination of hematoporphyrin-derived porphyrins, has been employed for tumour localization and photo radiation treatment.8 Photofrin (a hematoporphyrin derivative combination containing different dimers) and Foscan are the most often used sensitizers in oncologic PDT and are approved for a wide range of malignancies.[9] Hematoporphyrin, in particular, has been shown to have an affinity for malignant tumours and to undergo a photodynamic response when exposed to light. Lipson and Baldest reported a hematoporphyrin derivative (HPD) produced via an acetic acid sulfuric acid preparation of hematoporphyrin in 1960. This substance has been proven to be more selective for malignant tissue than pure hematoporphyrin in terms of both amount and retention time as measured by fluorescence. It has also been demonstrated that when HPD is activated by 405-nm violet light, it emits red light with peaks at 630 and 690 nm and has cytocidal effects on red light activation.[10] The 630-nm laser generated by hematoporphyrin derivatives may significantly hinder the growth of human pulmonary adenocarcinoma xenograft tumour in nude mice, the mechanism of which has been associated with tumour angiogenesis inhibition via down-regulation of VEGF and HIF-1 gene expression and tumor apoptosis promotion via up-regulation of Bax, Caspase-3, and down-regulation of Bcl-2 gene expression.[11]

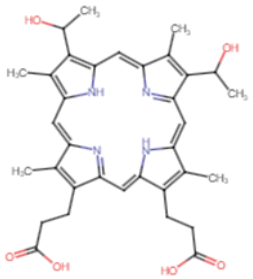

Figure 3: Hematoporphyrin

b) Photofrin®: Based on Dougherty's pioneering work, a more active substance, dihaematoporphyrin diether or Porfimer Sodium, was licensed for clinical usage under the brand name Photofrin® in 1993.[12] Photofrin is a complex combination of monomeric and aggregated porphyrins linked together by ether and ester bonds that is employed as a photosensitizing agent in tumor photodynamic treatment. Photofrin's anticancer impact is dependent on the presence of light and oxygen. The initial step is to provide an intravenous injection of photofrin. Tumors, skin, and reticulo endothelial system

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organs (including the liver and spleen) store photofrin for a longer amount of time. Tissues are irradiated with laser light at 630 nm wavelength in the second stage.[13]

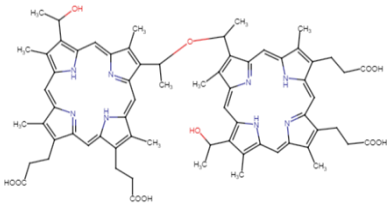

Figure 4: Photofrin® (Ether form)

2nd Generation:

Second-generation photosensitizers refer to newer compounds developed with enhanced properties and improved characteristics as compared to their earlier counterparts. These advancements aim to address limitations observed in first-generation photosensitizers, such as higher specificity, reduced side effects, improved targeting, and increased efficacy in generating reactive oxygen species upon light activation. Here are examples of second-generation photosensitizers:

1. 5-aminolevulinic acid: The prodrug idea provides an alternate route to the direct delivery of a photosensitive agent. A prodrug, according to Dr. Adrien Albert is a non-active molecule that is metabolically transformed to a pharmacologically active agent after delivery. Dr. James C. Kennedy introduced one such prodrug, 5-aminolevulinic acid (5-ALA), into PDT in 1992. They demonstrated that photosensitization with protoporphyrin IX (PpIX) is detected following exogenous injection of 5-ALA in aqueous solution to individuals with superficial cutaneous diseases.[14] They discovered that 5-aminolevulinic acid could be converted in cells into protoporphyrin IX, a highly photoactive endogenous porphyrin derivative. Protoporphyrin IX can be triggered for tissue damage by either a red or a blue light source.[15]

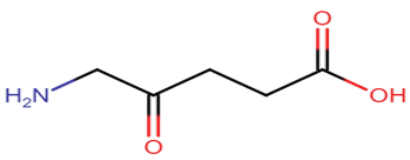

Figure 5: Aminolevulinic

2. Benzoporphyrin derivatives: One of the most promising photosensitizers for photodynamic treatment (PDT) is the so-called 'benzoporphyrin derivative' mono-carboxylic acid (BPD-MA). BPD-MA has a significant absorption peak at 700 nm, which may allow for more tissue penetration and activation than Photofrin®.16 Benzoporphyrin derivative monoacid ring A (BPD-MA, verteporfin) is a second-generation photosensitizer with significant advantages over Photofrin® for use in PDT (Levy, 1994). This substance is chemically pure and is activated with light at long wavelengths (690 nm), allowing light to penetrate deeper into the treatment region. Because benzoporphyrin derivatives have fast plasma and tissue pharmacokinetics, they are swiftly removed from tissues, resulting in a shorter time of skin photosensitivity when compared to other medications such as Photofrin®.[17]

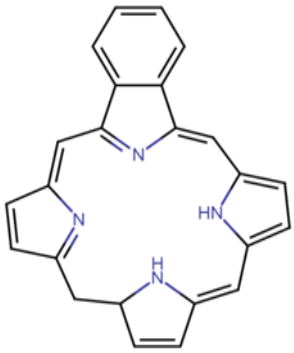

Figure 6: Benzoporphyrin

4. Phthalocyanines: Phthalocyanines are second generation photosensitizers that are extended macrocyclic structures. This generation was created in an attempt to address several concerns with first generation medications.[18] Phthalocyanines are benzoporphyrin congeners with nitrogen atoms instead of carbon. In contrast to porphyrins, phthalocyanines display strong and acute absorption in the red spectral window and high fluorescence quantum yields.[19] Phthalocyanines have two primary electronic absorption bands: the Q band (usually 600-700nm) and the Soret band (300-400nm). Because of excitonic interaction between overlapping molecules, these bands usually break into at least two components in the solid state.[20]

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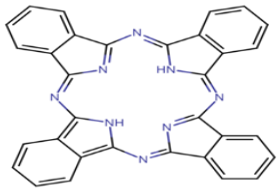

Figure 7: Phthalocyanines

3. 3rd Generation:

In the field of photodynamic treatment (PDT), the classification of third-generation photosensitizers was not as well defined or universally agreed upon as the distinctions between first and second generations. Third-generation photosensitizers, on the other hand, often relate to additional developments and innovations in photosensitizer design aimed at overcoming limits of previous generations while improving efficacy, specificity, and safety.

The research for potential third-generation photosensitizers is still in its early phases. Several essential elements must be met in order to produce a new PDT employing a next generation photosensitizer with the following ideal properties:

1. Should selectively accumulate in cancer cells.
2. Should be rapidly metabolized and excreted from the body.
3. Should have an optimal wavelength for excitation longer than 650 nm, allowing deeper penetration into the tissue.
4. Should be hydrophilic, which is preferable for clinical use.[21]

Carriers used in light responsive drug delivery system (LRDDS)

Although LRDDS is precisive and effective it is also dependent on some carriers at the time of delivering the drug into target tissues. It is the integral component of LRRDs which plays an important role in controlled release therapeutic medicine. LRDDS is versatile where different customization of the materials is needed like polymer, nanoparticles, etc.[22]

Liposome-

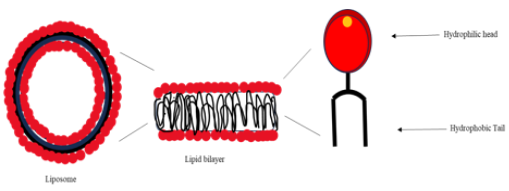

Figure 8: Systematic diagram of Liposome

Photodynamic therapy (PDT) stands as an evolving modality for treating superficial tumors. This technique involves the systemic administration of a photosensitizer, succeeded by the irradiation of the tumour site with non-thermal light after a predefined time interval. In the pharmaceutical sector, liposomes have garnered significant attention as carriers for Long-Acting Release Drug Delivery Systems (LRDDS). These diminutive vesicles consist of lipid bilayers mimicking cell membranes, showcasing a unique structure that facilitates the encapsulation of both hydrophobic and hydrophilic medications, rendering them versatile carriers. In LRDDS, liposomes play a pivotal role in enabling delayed and controlled drug release. The engineering of the lipid bilayer allows for the fine-tuning of the release rate, resulting in a depot effect. Additionally, alterations to the liposomal surface contribute to improved stability, extended circulation time, and enhanced site-specific targeting, thereby mitigating systemic adverse effects. Employing liposomes as carriers in LRDDS presents a promising avenue for refining treatment outcomes by tailoring drug release profiles and augmenting drug delivery efficiency.[23]

Polymeric Nano Particle: Polymeric nano particle has the fascinating way of pulling towards interest over the years due to its small nano size properties, it acts as drug carriers which is used for potential controlled drug release, many polymeric nano particles have the ability to protect the drug along with the molecules against the environment.[24]

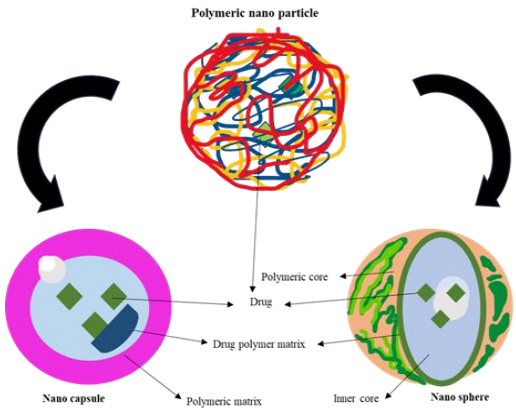

Figure 9: Graphical representation of Polymeric nano particle

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Gold nano particle –

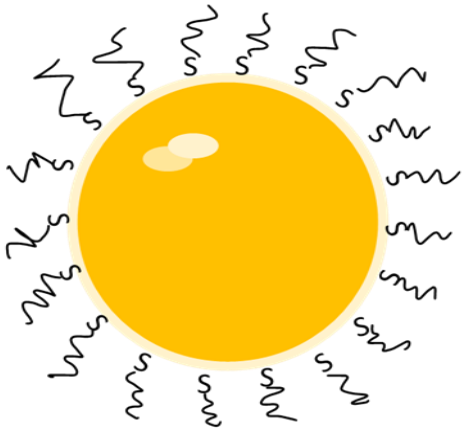

Figure 10: Gold nanoparticle

Physical or chemical methods can be used to create gold nano particles, and either a top-down or bottom-up strategy can be used. Bottom methods are basically nucleation of chemical. For targeted therapeutics, Light-Responsive Drug Delivery Systems (LRDDS) utilising gold nanoparticles present a viable route. By using their distinct optical characteristics and stability, these nano particles allow for targeted medication administration with few adverse effects. Adding gold nano particles to LRDDS improves treatment effectiveness, demonstrating how they may be used to further personalised medicine.

Components of LRDDS

In order to initiate drug release in a spatiotemporal manner, these systems frequently employ light-sensitive compounds.

The components of a Light-Responsive Drug Delivery System (LRDDS) include:

1. Photosensitive Material: Photosensitive materials, like nano particles or polymers, are crucial constituents. When exposed to light, these materials change in structure or characteristics, causing the medicine to be released from its capsule.[25]
2. Light Sources: The external stimulus required to cause the drug's release from the photosensitive materials is provided by light sources, such as lasers or light-emitting diodes (LEDs).[26]
3. Encapsulation of Drugs: The photosensitive polymers encapsulate the drug of interest, allowing for regulated release upon exposure to light.[27]
4. Targeting Ligands: To improve the specificity of medication delivery to the intended spot, targeting ligands may be added. These ligands have the ability to activate at specific sites in response to light.[28]
5. Responsive Mechanism: It is essential to comprehend the mechanism by which light induces medication release, be it via photothermal effects, photoisomerization, or other mechanisms, in order to develop light-responsive drug delivery systems. [29]

Types of LRDDS

Light-responsive drug delivery devices, also known as photo responsive drug delivery devices, employ light as an external stimulus to trigger the release of drugs at a preset location or time.

1. **Photo-chromic System**: Photochromic molecules exhibit conformational changes in reaction to light, which consequently alter the drug's release from the encapsulation.[30]
2. **Photo-thermal System:** When light is absorbed by nano particles, it is transformed into heat, which causes the medicine to release or enhance its release from thermosensitive carriers.
3. **Photo-dynamic Therapy System (PDT)**:When exposed to light, photosensitizers produce reactive oxygen species, which cause localized drug release and cell death. [31]
4. **Photo-responsive Nano particles**: Light-responsive materials such as nanogels or photoactive polymers are discovered in nano particles containing drugs that release when exposed to light.[32]
5. **Light-triggered Liposomes**: Photoactive lipids, for example, are light-sensitive components found in liposomes that cause medication release when exposed to light.Techniques used in LRDDS: Photo-responsive materials, which change their structure or other properties in response to light and release therapeutic compounds under controlled settings, are commonly used in these systems.

1. Photochemical Release System: The structure of the drug carrier is altered by photochemical processes such photolysis and photoisomerization, which result in drug release.[33]
2. Photo-responsive Nano particles: Photo-responsive polymers or light-absorbing moieties in nano particle form are examples of light-responsive components for controlled medication release.[34]

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3. Photo-responsive Hydrogels: Hydrogels that react to light by changing their structure, porosity, or volume results in drug release.[35]
4. Up conversion Nano particles: Nano particles that can be activated with near-infrared (NIR) light to release drugs under control by converting lower-energy photons into higher-energy ones. [36]
5. Photo-responsive Liposomes: Liposomes have photo-responsive elements that, when exposed to light, alter their membrane permeability.[37]
6. Light-triggered Carriers: Nanocarriers with controlled medication release that react to particular light wavelengths. [38,40]
7. Photothermal Therapy: When exposed to light, materials that absorb it produce heat, which can be used as a therapeutic modality or for medication release. [38]

Description on photodynamic therapy

Photodynamic therapy: A light-activated medication called a photosensitizer or photosensitizing agent is used in photodynamic treatment to kill cancer cells. A laser or other devices, such as LEDs, can be used as the light source. This therapy, also known as PDT, is mostly administered locally, focusing on a particular body part. [39]

5. Results

Cancers and pre cancers are treated by the photodynamic therapy:

The FDA has approved photodynamic therapy to treat:

1) Actinic keratosis
2) Advanced cutaneous T-cell lymphoma
3) Barrett oesophagus[40]
4) Basal cell skin cancer
5) Oesophageal (throat) cancer
6) Non-small cell lung cancer
7) Squamous cell skin cancer (Stage 0):

Photodynamic therapy is also used to relieve symptoms of some cancers, including:[41]

i. Oesophageal cancer when it blocks the throat

ii. Non-small cell lung cancer when it blocks the airways

Photodynamic therapy treats cancers

Photosensitizer-saturated cells react negatively to light of a certain wavelength because the photosensitizer produces oxygen radicals, which are oxygen molecules that destroy the cells. In addition, photodynamic treatment damages blood arteries inside the tumour, preventing it from getting the vital nutrients it needs to keep growing. Moreover, it has the ability to incite the immune system to attack tumour cells, even in remote parts of the body.[42]

Photodynamic works in cancer cells

There are two steps in the photodynamic treatment procedure. First, a photosensitizer is applied topically, orally, or intravenously (IV), accordingly on the body where the tumour is located. The medication mostly leaves normal cells within 24 to 72 hours; however, it still remains in cancerous or precancerous cells. The tumour is then subjected to a light source. The way that light is applied depends on where the tumour is located. The light is focused on the malignant region of skin tumours. When a doctor has to treat a tumour in the throat, airways, or lungs, they can thread a fibre optic cable that provides illumination to the affected areas by inserting an endoscope through the throat. One particular kind of photodynamic treatment that treats aberrant white blood cells that cause skin problems in people is extracorporeal photopheresis (ECP).[43]

Clinical consideration of Light

The qualities of the medication and the vehicle, as well as the external light's strength and wavelength, are all crucial to the effectiveness of light-triggered drug delivery systems. These variables affect tissue toxicity by affecting the depth of light penetration.

Light penetration

There are two main ways that light interacts with tissues: absorption and scattering. Variations in the tissue's refractive index cause dispersion of photons.[44] When the energy of the incoming photon and the ground state energy difference of a molecule are equal, absorption occurs.[45] With distance, the irradiance (surface power density) of the transmitted light decreases exponentially due to scattering and absorption. The deep penetration of NIR light makes it a desirable tool for the activation of drug delivery vehicles in living systems.

Phototoxicity

One major issue in the development of light-responsive medication delivery devices is phototoxicity. This happens when light, which is utilised to release the medicine, produces reactive species that damage the tissues around it. Researchers work to overcome this by choosing safe light wavelengths, optimising

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photochemical characteristics, and carefully choosing materials. In order to ensure safe and effective therapeutic applications, the objective is to build systems that release medications upon light activation without causing injury.[46]

Mechanism of light responsive

All systems used in photo triggered medication delivery have one thing in common: the materials they use absorb electromagnetic light and convert it into various types of energy. A particle's sensitivity to light depends on its quantum yield (the number of events, such chemical processes or emitted photons, per absorbed photon for each particle) as well as its absorption cross-section, which shows the probability of photon absorption for each particle.**[47]**

UV light

Photochromic groups such as azobenzene and spiropyran have been shown to undergo reversible transitions when exposed to UV/visible photons, which can trigger photochemical reactions in photo responsive nano particles. These changes in polarity and hydrophobicity, such as photoisomerization, affect the organisation of nano particles. Additionally, chemical groups like those based on o-nitro benzyl and coumarin may be permanently cleaved by light, which makes them valuable for altering parameters that impact particle integrity. Furthermore, nano particles are disrupted by light-induced rearrangement processes, such as the Wolff rearrangement of the hydrophobic 2-diazo-1,2-naphthoquinone (DNQ) group caused by UV radiation. Drug release is facilitated by photo crosslinking, which is demonstrated by the [2 + 2] photo cycloaddition of coumarin groups. This process shrinks the nanostructure or tampers with the uniform packing. The material supplied does not go into depth about how NIR light is converted to UV or visible light. [48]

Drug release from Nano particle

Inorganic particles, including plasmonic nanoparticles and upconverting nano particles (UCNPs), can transport drugs covalently attached to their surfaces. Mesoporous silica nano particles house drugs within their porous structures. Organic vesicles like liposomes and polymersomes, formed through self-assembly, possess a hydrophilic core and hydrophobic bilayer, facilitating the delivery of both hydrophobic and hydrophilic drugs. Polymeric micelles and solid organic nano particles primarily convey hydrophobic drugs within their hydrophobic cores, though covalently attached hydrophilic drugs can also be transported. Nanogels, structured from crosslinked hydrophilic polymers, can physically entrap drugs based on properties like charge and size, or have drugs covalently attached to the polymers. Whenever possible, we have used data from the literature to outline the irradiation circumstances, such as wavelength, power, and duration.[49]

Applications of LRDDS

Medicine can use light-responsive drug delivery systems (LRDDS) for a variety of purposes as they provide accurate control over drug release.

1. Cancer Therapy: Using light-responsive nanocarriers, tailored drug delivery to cancer cells can be controlled both spatially and temporally. [50]
2. Photodynamic Therapy: Photosensitizers released in response to light for use in photodynamic therapy of cancer. [51]
3. Ocular Drug Delivery: Systems that react to light to deliver drugs under regulated conditions for eye disorders. [52]
4. Diabetes Management: Insulin delivery devices that react to light to release insulin when needed. [53]
5. Neurological Disorder: Systems that respond to light to deliver drugs to the central nervous system specifically. [54]
6. Infectious Diseases: Delivery of antimicrobial drugs that react to light to treat infections.
7. Wound Healing: Growth factors and therapeutic chemicals are released in response to light, which promotes wound healing.

Timeline of PDT-

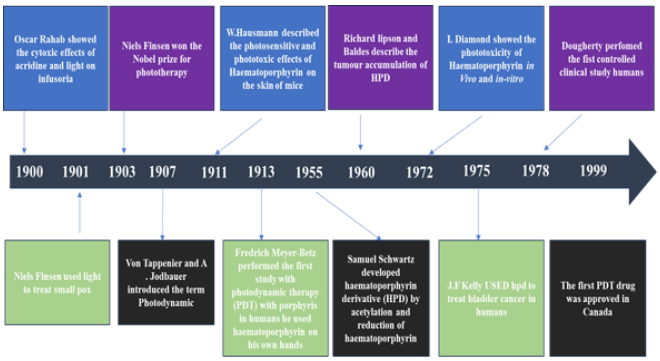

Figure -11 Timeline of PDT

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Example of photodynamic therapy -

1. PDT, which uses the photosensitizer Photofrin, a commonly used photosensitizer in clinical practice, was originally approved in Canada in 1993 for the preventive treatment of bladder cancer. Thomas Dougherty's discovery in 1983 that crude hemoporhyrin included a variety of porphyrins is credited with the invention of photofrin. Additional porphyrins such as protoporphyrin and hydroxyethylvinyldeuteroporphyrin were produced by acetylating them. Dihaematoporphyrin ether (DHE), which is made up of two porphyrin units connected by an ether bond, was subsequently determined by Dougherty to be the active ingredient. Mono-, di-, and oligomers of photofrin—a partly purified HPD—all have the essential porphyrin moiety present. [55]

6. Conclusion

To sum up, the development of light-responsive drug delivery systems represents a noteworthy advancement in the field of personalised medicine, especially with regard to photodynamic treatment (PDT). Over the years, the field of therapeutics has seen significant developments that demonstrate the dynamic interaction between research and innovation. These advanced medication delivery devices are prime examples of the accuracy and customisation possible in modern medicine, since they are calibrated to react to light cues. In addition to improving treatment efficacy, the combination of light responsiveness and medication delivery reduces off-target effects, opening the door for a more patient-centered strategy. The customised treatments for a wide range of illnesses. This complex meeting point of science and medicine represents the possibility of revolutionary effects on patient outcomes and the ongoing quest of excellence in the field of therapy.

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