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Batteries applications in the biomedical industry: A review

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Abstract

In today's rapidly advancing world of technology, batteries have become crucial components of life-saving devices in the biomedical industry. From cardiac pacemakers to implantable cardioverter-defibrillators (ICDs), batteries play a pivotal role in ensuring these devices operate effectively, reliably, and safely. These batteries are distinguished by their high power and energy density, ensuring robust performance, and they uphold unwavering reliability and safety standards to safeguard patient well-being. Their adaptability and flexibility enable seamless integration into diverse medical applications, complemented by predictable discharge voltage, low self-discharge rates, long service life, and critical end-of-life indication mechanisms. Within the domain of cardiac rhythm management, batteries empower critical devices like pacemakers, leadless pacemakers, ICDs, cardiac resynchronization therapy (CRT), and cardiac implantable electronic devices (CIEDs), ensuring the maintenance of optimal cardiac function. This paper investigates various battery types utilized in the medical industry, with a particular focus on the prevalence of lithium-based batteries, known for their reliability and high energy density. Moreover, this contribution provides insights into the thriving biomedical battery market, driven by technological advancements and the escalating demand for innovative medical solutions. This review also underscores the indispensable nature of batteries in modern healthcare, catalyzing groundbreaking medical innovations and enhancing patient care.

Keywords: *Biomedical batteries, Medical device power, Lithium batteries, Energy harvesters*

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1. Introduction

Batteries are electrochemical devices that transform the energy of chemical bonds into electricity and power a wide range of electrical devices. Typically, a medical battery is composed of a cell or connected group of cells designed to receive, store and deliver electric energy when needed. Since the introduction of batteries in medicine, they have contributed to many devices for use either external or internal in the human body. Internal devices are implanted in vivo in humans and animal models not only for the purpose of treatment but also for diagnosis, prognosis, and biological investigations. The implanted biomedical devices, powered by batteries, include neurostimulator, cochlear implant, pacemaker, cardiac defibrillator, bone growth generator, cardiac resynchronization device and drug delivery system. The non-implantable batteries are those employed in diagnostic imaging devices, patient monitoring devices, in vitro diagnostic instruments, therapeutic devices, prosthetic devices. Depending on the type of device and treatment, the performance requirements for medical batteries used to power these devices vary. Although nowadays, there are attempts at other strategies for supplying power sources in these implants, such as bio-fuel cells, thermoelectricity, piezoelectricity, electromagnetic generators, and even battery-free and wireless technologies, batteries are still the dominant source of power in these devices, especially in cardiovascular implants [1,2].

There are two categories of battery systems powering implantable devices, including primary batteries and secondary batteries. The primary systems are composed of lithium metal anodes accompanying a variety of cathodes including iodine, manganese oxide, silver vanadium oxide, carbon monofluoride and hybrid cathodes. These batteries provide the proper power levels for a specific medical device, ranging from microampere to ampere level currents. Moreover, they can provide ultrahigh energy density, theoretically 50% higher than secondary batteries. As a result, primary batteries are more widely used compared to secondary batteries. For example, Lithium-carbon monofluoride (Li-CFx) batteries have an open circuit voltage of 3.0 V and a theoretical energy density of 2119 Wh/kg, which is much higher than ~500 Wh/kg of Li-ion batteries (secondary batteries). Lithium-silver vanadium oxide (Li-SVO), Lithium-iodine (Li/I_2), and lithium manganese dioxide (Li/MnO_2) are other examples of implantable batteries in this category broadly used in the industry, as they have ultrahigh energy densities. Despite such advantages, primary batteries have also drawbacks, such as their high unit cost and restricted lifespan. Secondary batteries are lithium-ion chemistry-based, developed for when the batteries need to be charged while remaining implanted [3]. Since during the cycle of charging and discharging inside the body they

generate heat and lose their capacity, secondary batteries are of more limited use. Recently, studies have investigated high-performance and sustainable lithium secondary batteries (LSBs) by using biomass-derived materials as diverse components for LSBs. Biomass is the most abundant energy storage product from sunlight and provides great opportunities for fabricating systems of ‘‘green battery’’. They indicate that some sustainable biomolecules/biopolymers such as starch, cellulose, lignin, natural gums, proteins, and furfural can be regenerated and used to fabricate functionalized binders, separators, or solid-state electrolytes, and some other natural chemicals derived from fungus or tomato can be modified to serve as electrolyte additives to effectively improve the battery performance.

Implantable batteries, compared to batteries applied in electronics and electric vehicles, need more consideration in terms of safety and stability as they are in contact with human organs. First, the size of the battery determines the size and operating service longevity of an implantable medical device. Although a small battery will minimize overall device size, it couldn’t provide a relative long service life for the devise otherwise they have high energy density in order to have as little volume and weight as possible in the limited space of the human body [4]. Moreover, due to the great risk of chemical contamination inside the human bodies they need to be properly packed with no possibility of leakage. Another critical characteristic of medical batteries is their self-discharge rate. They normally need to have a safe uninterrupted operation for a battery life of 8-10 years [5].

The global market size of medical devices batteries in 2021 was USD 2700.1 million and is expected to reach a revenue CAGR of 6.3% by 2030. The main drivers of revenue growth in the global medical devices batteries market concern rising the global prevalence of cardiovascular and chronic diseases, and increasing public and private spending on upgrading current healthcare infrastructure. Among these ranges of batteries, the lithium batteries segment accounted for the largest revenue share in this market in 2021, and due to a rising demand, this segment is anticipated to grow at a considerable revenue rate by 2030. This is mainly because lithium batteries are preferable in size, weight, and energy density. So, many medical devices are powered by lithium and lithium ion batteries. On the other hand, despite this growth, there are also some factors restraining the global medical devices batteries market from expanding further such as a shortage of battery manufacturers, particularly for non-implantable devices, and the rapid miniaturization of implantable integrated electronic components [6].

This review aims to highlight the properties and applications of batteries used in medical industry. In this regard, the limitations, advantages, and practicality of recent innovations and developments are deliberated. This paper presents a review on battery maintenance, replacement and recharging process as well as their manufacturing and commercial processes.

2. Features of batteries used in medical industry

Batteries for biomedical applications are often used to support device operations that require frequent or continuous power, such as cardiac sensing and pacing, neuromodulation therapy, or simply maintaining power to the electronic circuits. Radio frequency telemetry is a function that requires a moderate amount of power from the battery. Implantable cardiac pacemakers and defibrillators now commonly include this feature. High-rate discharges, such as those used for cardiac defibrillation, may be short in duration and infrequent. Battery designs may incorporate thin anodes and cathodes with large superficial electrode areas to accommodate the high-power pulses required by devices such as implantable defibrillators [7].

Medical device batteries frequently use chemistries commercially available in other shapes, such as coin and cylindrical cells. Medical devices often require battery designs, features, and manufacturing processes explicitly tailored to their unique applications. The development of medical device batteries requires careful consideration of various fundamental features to ensure optimal performance. These critical characteristics encompass high power and energy density, reliability, safety, flexibility, predictable discharge voltage, low self-discharge rates, long service life, and end-of-life indication (Figure 1). The incorporation of these features is essential to guaranteeing the efficiency and effectiveness of implantable medical device batteries, thereby advancing the quality of patient care [8].

Figure 1. Main features of batteries used in medical industry

2.1 High power and energy density

In medical device batteries, high power and energy density play a crucial role in enhancing battery performance, lifespan, and size. Due to their compact size and high volumetric energy density, implantable medical devices have been predominantly powered by lithium-based batteries. Researchers have been working on enhancing the energy density of non-rechargeable batteries, such as those used in pacemakers, to increase their useful lifetime by up to 50% and decrease their size and weight [2]. The shrinking size of solid-state batteries, which feature a solid electrolyte, high energy density, and thin packaging, facilitates the implantation of devices in various body parts. High energy density batteries are crucial for medical devices that require a small and unobtrusive design, such as implantable devices, as they can provide a significant amount of energy output in a compact and lightweight package. Batteries that possess high energy density can operate for a longer duration in proportion to their size. This characteristic broadens the scope of medical devices that such batteries can power. Batteries with higher energy density can deliver the same amount of energy as those with lower energy density but in a smaller size. Lithium-sulfur dioxide batteries have the capability to provide high pulses, particularly at low temperatures. However, their low energy density adds bulk [9-11]. Therefore, high power and energy density are significant for medical device batteries because they may extend working life, decrease size and weight, and improve performance. These considerations are especially critical for implanted medical devices, which must be compact, long-lasting, and high-performing.

2.2 Reliability and safety

Biomedical implantable devices rely on batteries for their operation. These batteries are crucial as any malfunction or failure to perform as expected can pose a direct physical threat to the patient. Biomedical cells typically come into close or direct contact with the patient and must function safely under all circumstances. Replacing a device due to battery depletion can be risky and expensive, even if the cells function as expected [12,13]. Reliability and patient safety are inseparable when it comes to implantable cells. Cells that are created for implantable biomedical applications are subject to regulation by various national and international bodies. These regulations pertain to their classification as hazardous materials, electrical components, and medical device components. In addition to regulatory agency-mandated safety testing, cells typically go through qualification and design assurance testing. During production, a combination of sampling, destructive testing, and nondestructive testing is utilized to monitor and confirm the product's safe, consistent, and predictable performance [8].

Primary lithium anode chemistries have been used in the most demanding biomedical applications, while some newer applications have started using secondary lithium-ion-based cells. Lithium-based systems possess high power and energy density; however, they become hazardous when exposed to temperatures around or exceeding 180°C, which is the melting point of the highly reactive lithium metal constituent. Ultimately, the risk was traced back to two root causes, each originating from a different manufacturer. The first design had a flaw that could result in a short circuit, while the second supplier experienced a fabrication issue that led to a welding defect. Both issues caused short circuit conditions that could potentially lead to battery ignition [8].

The FDA (Food and Drug Administration) in the United States acknowledges specific standards, referred to as "consensus standards," to ensure

reasonable safety and effectiveness for various aspects of medical devices. Lithium-based chemistries bring several particular safety problems. The first of these is that molten lithium metal is highly reactive. Excursions above this temperature can result in the battery violently venting with fire [8].

As previously stated, guaranteeing patient safety in a biomedical battery application necessitates going above and beyond typical safety norms. Failure of life-sustaining biomedical equipment to work as expected might result in the patient's death or severe health effects, including those caused by premature device replacement. Levy's previous research on the reliability of lithium anode-based systems focused on lot analysis, individual cell reliability, and postmortem analysis [14-16]. To avoid this failure mechanism, chemistries that can potentially encounter significant resistance in the middle of life, such as silver vanadium oxide, must be correctly developed. Several failure modes are unique to rechargeable lithium-ion chemistry. Accelerated life testing is permitted to support dependability claims; however, at least three years of battery data are necessary to support a 9 to 10 years longevity claim. In 2013, the FDA expanded its "case for quality" program to include a focus on batteries and battery-powered devices, emphasizing those components of the device design and manufacturing process that are critical to ensuring device quality and, ultimately, patient safety [8].

2.3 Flexibility

Conventional intelligent biomedical devices always include inflexible power sources, complex circuit designs, brittle chips to enable real-time data processing and transmission, and intelligent feedback, which are not stretchable and reduce the whole system's flexibility. As a result, completely stretchable intelligent gadgets with stretchable power sources and self-adaption mechanisms for close-loop health monitoring and therapies are required [17]. Furthermore, with current battery technology's rigid encasings and non-biocompatible materials, devices used to treat cutaneous injuries are challenging to deploy. As a result, there is an apparent demand for flexible, portable, and biocompatible batteries that can continue to operate in the presence of biological fluids, corrosive chemicals, or infectious by-products produced during battery operation [18].

Silver (Ag) and zinc (Zn) are known for their antibacterial characteristics and biocompatibility among the several materials available for battery electrodes. Moreover, Ag-Zn batteries were known for their dependability and safety compared to the currently widely utilized rechargeable lithium-ion batteries (LIBs). Current flexible battery research has concentrated on rechargeable batteries such as lithium-ion power sources and flexible LIBs; nevertheless, challenges remain for utilizing these in biomedical applications with biofluid or infectious agent contact, which may necessitate the use of disposal primary batteries. Encapsulation was also utilized in some flexible LIBs to prevent fluid interaction, although the issue of biocompatibility remains [18,19].

Besides operating in potentially corrosive or hazardous conditions, the battery must be flexible enough to adhere to the curved surfaces of human or animal anatomy without impeding current flow. In addition, due to the high power needs of most biomedical applications, earlier flexible batteries utilized "stacked" designs [20]. However, cell stacking, which is common in traditional batteries for biomedical applications, limits battery flexibility, and the lamination necessary to keep the stacked layers together adds to fabrication complexity. Inflexible batteries often have adequate power but can produce power interruptions and safety hazards when bent, twisted, stretched, or folded [21].

2.4 Predictable discharge voltage

The importance of having a predictable discharge voltage for medical device batteries cannot be overstated, as it serves several essential purposes. Initially, it guarantees that the battery will offer a steady and dependable power supply for the device. Medical devices require batteries with a flat, predictable, and reliable discharge profile. Lithium-based batteries are a suitable choice for this purpose [22]. Additionally, it aids in prolonging the lifespan of the battery. Using up all the energy stored in a battery during discharge is not advisable. Typically, a certain amount of reserve energy is intentionally left behind after the equipment is turned off. Manufacturers opt for this voltage threshold to conserve energy to minimize

battery usage [23]. Thirdly, ensuring that the device functions correctly and safely is crucial. Furthermore, it helps prevent any potential damage or excessive battery use. High-current power tools and medical devices tend to cause the battery voltage to drop prematurely, resulting in an early cut-off. Even after the cut-off, these batteries might still have significant capacity remaining. Using a battery analyzer at an average load, you can discharge them and often find that 30 percent of residual capacity is still left [23].

2.5 Low self-discharge rate

When choosing a battery for medical devices, it is crucial to consider the battery's self-discharge rate. Self-discharge is the term used to describe the gradual reduction in the charge level of a battery when it is not in use. It is often impossible to completely eliminate self-discharge [24]. Medical devices must have a battery with a low self-discharge rate, as they may not be utilized frequently or for extended periods. This ensures that the battery will retain sufficient charge when required. LIBs designed for industrial use have an impressively low self-discharge rate. This feature allows medical devices to remain unused for long periods without losing their charge [25,26]. Numerous factors, such as battery type, state of charge, charging current, and ambient temperature, can influence a battery's self-discharge rate [27]. Lithium batteries have a low self-discharge rate, which is one of their advantages. By keeping the battery storage voltage above the minimum voltage and storing the battery at lower temperatures, the self-discharge rate can be minimized. Design engineers can construct a model that increases battery longevity by examining how the discharge profile will change over time [28]. As a result, a low self-discharge rate is critical for the dependability and lifetime of medical device batteries, particularly in applications where the battery is not used frequently or for extended periods.

2.6 Long service life

When choosing a battery for medical devices, it is critical to consider the service life of the battery. The term service life refers to the amount of time a device is expected to be functional after being built, installed, and maintained as stated. Medical devices are frequently required to operate for extended periods, and the battery must supply a consistent power source throughout the device's service life. In order to guarantee that the battery will supply a consistent and reliable power source during the device's service life, design engineers must evaluate the impact of chemistry on the discharge behavior of the battery [3]. LIBs have a nominal voltage of 3.6V or 3.7V. The battery should be charged to a maximum of roughly 4.1V and discharged to a low point of 2.7V. Industrial grade LIBs have a meagre self-discharge rate, allowing medical devices to be stored for long periods without losing their charge. Passivation is necessary for decreasing self-discharge in batteries, but too much of it might prevent energy from flowing when it is most needed [29,30].

2.7 End-of-life indication

The end-of-life indication for medical device batteries is crucial for the equipment's proper operation, safety, and lifespan. The battery must give accurate state-of-charge information and be highly reliable with predictable discharge profiles to guarantee the device functions correctly and safely throughout its service life. The end-of-life signal indicates when the battery can no longer give sufficient power to the device and must be replaced. The battery must offer a clear and precise end-of-life notification so the device does not fail abruptly and the battery can be replaced on time [31,32]. The discharge profile and battery chemistry may have an impact on the end-of-life indicator. It is crucial to clearly indicate when medical device batteries reach the end of their life. This is important for the device's proper functioning, safety, and longevity [33].

3. Types of batteries used in medical industry

Artificial cardiac pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) are both medical devices used to treat arrhythmias or irregular cardiac rhythms [34,35]. These gadgets are surgically implanted within the body and ensure that the heart pulses at a constant rate that meets the requirements of the individual [36]. Learning how these devices operate and what they can accomplish for you can assist you in making decisions and preparing for life with the new gadget.

Since the mechanisms and structure of these devices are nearly identical, we shall evaluate PMs efficacy. PMs are tiny electronic devices [34], about the size of a matchbox and weighing 20–50 g, that sense intrinsic heart rhythm and transfer electrical impulses, if necessary, to stimulate the heart and replace the defective sinus node or some other [37]. In 1958, Dr. Ake Senning and his colleagues were the first to implant a PM in a human; however, it only endured a few hours. Since then, PMs have been the treatment of choice for some heart diseases for more than 50 years [37-40]. The annual rate of implants is increasing. In the UK, the 10-year average growth rate for PMs is 4.7%, while the rate for implantable cardioverter defibrillators (ICD) is 15.1% [41]. Cardiac activity originates inside the sinus node, where intrinsically automatic cells serve as pacemaker cells. Then, electrical wave fronts propagate across the atria to the atrioventricular node, where they infiltrate the His-Purkinje system and swiftly depolarize the ventricles [42].

When the intrinsic conduction integrity of the heart is lost, the electrical excitement of the cardiac tissue permits a small and external electrical stimulation to drive myocytes to the threshold, resulting in the depolarization of neighboring myocytes via energy-consuming biological processes and the propagation of an electrical wave front with near-simultaneous muscular contraction using excitation-contraction coupling. Pacemakers act as external stimulation [42].

Pacemakers are composed of a generator of pulses or can, containing the battery and electronic components, and leads [43], which flow from the can to the myocardium to hand over a depolarizing pulse and to detect intrinsic cardiac activity [44]. The conductor connections and the lead point electrodes are separated by insulating materials. According to the relationship between these cables, the leads may be coaxial, which refers to a tube within a tube, or coradical, which refers to coils placed side by side [43]. Active (electrically active helix at the apex for mechanical stabilization) or passive (electrically inert tines) fixation of the lead to the myocardium is possible. High impedance (fracture) and low impedance (insulation breach) result from the disruption of conducting elements and insulation materials, respectively. Pacing occurs when a voltage difference is created between the two electrodes [43].

Medical devices continue to advance, and the most recent generation of devices is more compact, has a longer battery life, and offers enhanced functionality compared to older models. The evolution of electronic devices will likely continue in the future. The battery is a crucial part of these devices, and the characteristics of the batteries used in them are improving as technology advances.

These devices' internal batteries have a limited lifespan. For instance, cardiac pacemakers operated by lithium iodine batteries have a lifespan of 7 to 10 years, while implantable cardioverter-defibrillators (ICDs) have a lifespan of 4 to 6 years [45,46]. Periodically, after the battery is discharged, these implantable medical gadgets must be replaced, and replacing them with surgery is invariably accompanied by several complications, such as infection and bleeding [47-50]. Hence, extending the longevity of implantable medical devices maintains the primary challenge for their development and clinical application. The heart in the body of a human produces a significant amount of hydraulic power [51], suggesting that generators can harvest the heartbeat's natural energy indefinitely. In the past, various groups of researchers have investigated the possibility of converting such kinetic energy into electrical energy [47,48,50,52-54]. Electromagnetic induction [55,56], electrostatic [57], piezoelectric [47,48], and triboelectric nanogenerators [50,53,58] are some of the intracorporeal energy scavenging technologies. However, the in vivo outputs of the previously stated devices are insufficient for use as a power source for implantable medical devices.

Self-powered medical implants may be able to circumvent the battery replacement problem, for example, by recharging the battery with biomechanical energy extracted from the movements of body organs, like cardiac motions. Due to their remarkable ability to convert mechanical energy into electrical energy, piezoelectric nanogenerators (PNGs) [59,60] and triboelectric nanogenerators (TENGs) [61,62] have garnered considerable attention over the past decade. PNGs have emerged as a basic method for generating voltage in vivo and in vitro from low-frequency mechanical sources, such as human activities [63,64] and cardiac motions [65]. Ceramics are the highest-performing piezoelectric materials. However, the stringent requirements for flexibility and toxicity

restrict the use of piezoelectric ceramics containing lead [66]. Poly(vinylidene fluoride) (PVDF) is a semi-crystalline, flexible, biocompatible, piezoelectric polymer [66] with five distinct polymorphs [67,68], of which the phases exhibit the greatest piezoelectric charge coefficient, d_{33}, between 30 and 40 pV/m [69]. The piezoelectric PVDF films are commercially available but have a very low power output. By producing nanofibers that are easily polarized in the piezoelectric phase using the electrospinning of PVDF, PNG efficacy can be increased by up to four times [70]. Composites of PVDF fibers including nanofillers have been produced to increase efficacy. These nanofillers can be carbon-based (grapheme [71] and carbon nanotubes [72]), or ceramic ceramic nanoparticles ($BaTiO_3$ [73], $NaNbO_3$ [74], and ZnO [75]).

Electromagnetic induction is a principle used to harvest energy from endocardial contractions. It consists of copper coils that are serially aligned and encircle a linear arrangement of permanent magnets (PM stack) [76]. The PM stack situated between two flexures (also known as spiral springs) begins to oscillate in response to an external acceleration, providing the efficacy of mechano-electrical conversion. Devices have been developed to harvest energy from endocardial contractions, and these devices can be implanted in a favorable location to increase the longevity of electronic cardiac implantable devices [76].

The VCES generator is an implantable cardiac pacemaker powered by a variable-capacitance electrostatic (VCES) generator that utilizes the movement of a living body [77]. It is possible to increase the energy density of the variable capacitor by increasing the surface area of the electrodes per unit volume and decreasing the distance between the electrodes. The ventricular wall is the most optimal source of vibration in the living body due to its relatively significant motion persisting throughout the day, but the vibration frequency for generating electricity is only 1 to 2 Hz. To achieve a high driving rate for the generator, it must resonate with a harmonic component of vibration [78].

Chemical batteries are an important energy source in cardiac implantable electronic devices (CIEDs) [79]. Chemical batteries are a type of battery that is composed of one or more cells. They consist of an anode and a cathode, with electrolytes between the electrodes to prevent electron transport between the poles. A porous insulator allows ions to travel between the two poles [42].

The PM was first powered by a rechargeable nickel-cadmium (NiCad) battery, but this was soon swapped out for an unstable, transient mercuric oxide cell. In the early 1970s, the lithium-iodine cell became the predominant power source for certain types of pacemakers. In the early 2000s, significant advancements in pacemaker technology necessitated that the power source provides milliampere current for data logging, telemetric communication, and programming [79]. To provide medium power, other lithium anode chemistries were developed, including lithium-carbon monofluoride [80], lithium-manganese dioxide [81], and lithium-silver vanadium oxide/carbon monofluoride hybrids [82].

Modern batteries developed for CIEDs have to be hermetically sealed to avoid internal leakage or moisture ingress, while the original zinc-mercury cell was not hermetically sealed and frequently released sodium hydroxide, leading to catastrophic failure of the power source. Without electrolytes, predominantly positive and negative charges would accumulate adjacent to the anode and cathode, rendering the cell inoperable [79].

Betacel was the first beta voltaic battery to be commercially viable, developed by Larry C. Olsen at McDonnell Douglas in the early 1970s. It employed the radioisotope Promethium-147 as the beta-electron source linked to silicon semiconductor cells [83]. The Betacel-Biotronik heart pacemaker incorporated this power source, which is more reliable than chemical batteries due to its ability to store more energy per unit volume. To accommodate certain varieties of nuclear and chemical batteries, the pacemaker must contain voltage amplification devices (dc-dc converters) or additional circuitry [83,84]. However, due to its short lifespan [85] and Harmful effects of radioactive materials on the human body [86], it was not extensively adopted.

4. Heart failure (Cardiac Rhythm Management)

Heart failure (HF) is a medical syndrome that has historically been described as a condition marked by a

decreased capacity of the heart's ability to pump and/or blood capacity, or possibly as an irregularity of cardiac function or anatomy causing an inadequate cardiac output or an adequate cardiac output as a result of corrective neurohormonal stimulation and elevated filling pressure of left ventricle. Major international scientific organizations advocated a consensus on a global classification and description of HF, in 2021. From this year, the term "HF" had been used to describe a clinical illness characterized by symptoms and/or signs associated with structure-related and/or functional cardiac abnormalities, which were supported by high natriuretic peptide levels and/or conclusive signs of respiratory or systemic congestion [87]. According to recent studies, HF prevalence and incidence vary greatly by geography, however, among older adults, HF still has a high prevalence and a significant risk of death after one year [88]. Moreover, this disease is considered one of the deadliest illnesses in developed countries like the USA, thus it is crucial to tackle this disease with effective treatment approaches including early revascularization, pharmacological base treatments, and devices [89].

Due to advancements in technology, expanded indications, expertise, and population aging, the implantation of cardiac implantable electronic devices (CIED) has considerably increased globally during the past 20 years [90]. Nowadays, CIEDs become important treatment approaches against HF. Approximately more than 1,000,000 CIEDs including pacemakers (transvenous and leadless), implantable cardioverter-defibrillators (ICDs), and device-related cardiac resynchronization therapy (CRT), were implanted in patients with HF worldwide [91,92]. According to clinical trials done in the past few years, CIEDs are reliable for resynchronization therapy or avoidance of sudden cardiac death (SCD) [93,94], however, the choice of reliable therapy for patients is still challenging, thus, some guidelines are designed to select the best treatment approach for patients, and it seems essential that physicians carefully study and implementation of these guidelines in order to save individuals life [95,96].

4.1 Pacemaker (transvenous pacemakers or TV-PMs)

Pacemaker (also called a pulse generator) was implanted in 1958 for the first time. This device consists of a pulse generator (only 20 g and 20 cc in size) and leads [97]. The main part of pacemakers is responsible for pulse generation. This responsibility can be done by setting up 3 circuits called communication, logic, and output circuits [98]. On the other hand, leads work by sending electrical signals from the heart back to the pacemaker through an insulated cable (covered in polyurethane or silicone). It has a connector for connecting to the pacemaker and a fixation mechanism for connecting to the heart [97]. Despite the effectiveness of electronic pacemakers, there are still significant flaws to consider such as lead breakages, interference from electromagnetic fields, insufficient autonomic responsiveness, short battery life, pacing-induced remodeling, negative impacts on the durable survival of patients, and difficulties in treating pediatric patients [99,100]. However, with making cautious clinical analysis [101], the emergence of so-called smart pacemakers [102], leadless pacemakers [103], and the help of novel approaches like machine learning, some negative outcomes of implanting pacemakers can be reduced [104].

4.2 Leadless pacemakers (LLPMs)

Despite significant positive effects of TV-PMs on individuals with severe HF conditions, including decreasing mortality rate and improving quality of life in these patients, up to 20 percent of short and long-term combined system failures at five years, also pocket and lead-related complications are still significantly attributed to TV-PMs [105]. In order to avoid these negative effects, LLPMs were developed by related companies [106]. An appropriate LLPM should be small, light, able to accommodate several devices in the long term if or when necessary, and simple to implant and remove. Moreover, Both mechanical ectopy and major thromboembolic events shouldn't be brought on by the device [106]. The first leadless pacemaker was the Nanostim LLPM made by Abbott Laboratories (Chicago, Illinois, United States) [107], this LLPM consists of 4 major parts including the docking button, battery, electronics part, fixation part [108]. Nowadays, besides Nanostim, other LLPMs like the Micra TPS (Medtronic) achieved FDA approval [107]. Figure 2 and figure 3 show a

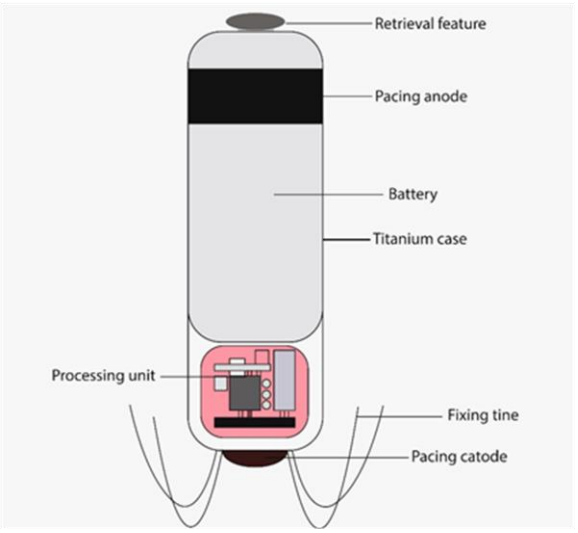

Figure 2. The basic components of a leadless pacemaker [109].

schematic depiction of a pacemaker device and a leadless pacemaker, respectively.

4.3 ICD

[109] Globally, more individuals are getting CIEDs such as ICDs, which increase heart-related diseases like atrial fibrillation [110,111]. Also, since ICDs' first utilization in 1985, it's considered a crucial treatment for heart conditions including ischemic cardiomyopathy and Systolic dysfunction as well as a significant increase in patients' quality of life (QOL) [112-115]. ICD implants are now a lot easier to perform than before, and the number of complications is declining. Nevertheless, ICDs remain susceptible to all cardiac pacing-related issues (such as infection, improper shock, erosion, conductor/insulation breakage, and over-and understanding), and many of these complications could demand a surgical revision or even device replacement, which can be a significant undertaking, along with this, ICD is high-cost technology [116], Despite that, due to its effectiveness against severe heart conditions like SCD, ICDs are still practical and used [117,118], also, next-generation ICDs that is called Subcutaneous ICD (S-ICD) were developed in last few decades in order to avoid complications that mentioned above. The location of the lead is the primary distinction between the two devices. The lead is inserted inside the heart when using a typical ICD, on the other hand, the lead of an S-ICD is positioned beneath the skin of the chest, and it's not touching the heart [119,120]. Generally, like pacemakers, ICDs consist of two parts: a pulse generator (in order to generate pulses) and leads or lead (as a connector) that is connected to a pulse generator [121]. In addition, leads are equipped with shock coils and pacing electrodes [121]. A single-chamber ICD system is depicted in figure 4.

4.4 CRT

CRT is a biventricular pacing therapeutical approach and it's a well-known treatment for HF, and studies have indicated that it has considerable therapeutic advantages, including lowered mortality, fewer hospitalizations for HF, and improved signs and QOL [122,123]. Biventricular pacing can be included in either an ICD or a pacemaker and typically comprises parallel pacing from the right and left ventricles. As the name suggests, the right ventricle receives a pacing-ICD lead, and the left ventricle receives a second pacing lead. In order to be coupled with the left ventricles lateral wall, the left ventricular (LV) lead is often routed into the coronary sinus (CS) and a reachable branch of the CS. CRT aims to enhance physiological dyssynchrony among the LV lateral wall and the ventricular septum by electrically resynchronizing the left and right sides of the heart. CRT has been related to increased ejection fraction (EF), fewer heart failure occasions, an improvement in heart failure class, and a decrease in mortality [124].

4.5 Power sources of CIEDs

It is essential to provide a suitable energy source for CIEDs. In fact, this in turn is challenging and requires many studies in order to produce a device with a longer

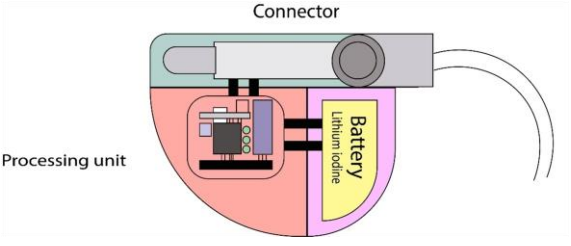

Figure 3. The main components of a pacemaker device [109].

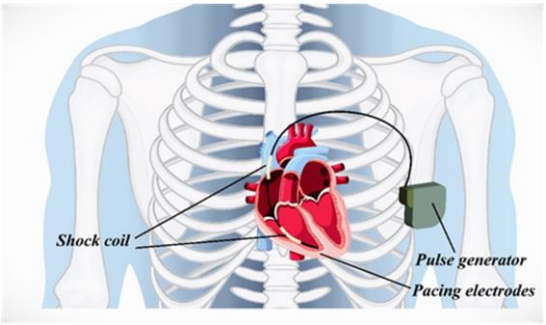

Figure 4. Schematic illustration of a single-chamber implantable cardioverter-defibrillator system [121].

lifespan and better performance. Simultaneously with the many changes that occurred in these devices, the energy sources of CIEDs have also undergone many changes. The energy sources of these devices have evolved from very large primary batteries to small lithium batteries and recently sources other than batteries to provide energy for these devices [125]. Important factors for all batteries used to power implantable medical devices include the following:

- Safety
- Performance predictability (current, voltage, and time correlations)
- High power density
- Lightweight and compact sizes
- Minimal self-discharge
- Life ending notifications

Alongside the previous characteristics, rechargeable cells also need to take charging safety and long cycle life into consideration.

4.6 Lithium-based batteries

Since lithium primary batteries provide the required endurance, minimal current drainage, and voltage features, the mercury-zinc battery was replaced by a lithium iodine battery in 1975, and it is considering extending the pacemaker battery lifespan (up to 10 years for certain variants). The normal average lifespan of initial lithium batteries is equal to a 10% capacity reduction over five years. In contrast, alkaline batteries contend with a related loss after just one year. Lithium batteries have an extended shelf life because the electrolyte's reaction with the lithium metal causes the surface to become passivated. All lithium systems are thought to be kinetically stable but thermodynamically unstable. Since they don't produce any gas, they are capable of being sealed securely. Additionally, the battery's terminal voltage decline profile is well-behaved, declining gradually enough to allow for the anticipation of battery end-of-life (EOL) during routine follow-up [46].

Lithium/iodine (Li/I_2) batteries, in which iodine is combined with poly-2-vinyl pyridine and used as a cathode, are one effective and well-researched energy technology. Due to its great reliability and biosafety, this variety of cells is still the chosen source of energy for numerous implantable pulse generators. The battery's output voltage, which is typically quite constant at 2.8 V, progressively decreases to 1.8 V as the battery nears its EOL. The energy loss curve enables us to calculate the battery's lifespan and choose the ideal interval for pulse generator replacement. The power capacity of these batteries improves from 2 to 3.5 Ah with a reduced size thanks to ongoing advancements in cell design and material innovation. Several varieties of lithium-based batteries, notably lithium-bromine, lithium-lead iodide, and lithium-copper sulfide batteries, disappear from the market with the development of the Li/I_2 battery, even with the emergence of batteries like Lithium/thionyl chloride ($Li/SOCl_2$) and lithium/carbon monofluoride (Li/CF_x), which provided more power than Li/I_2, but again due to some shortcomings, Li/I_2 was preferred to the mentioned batteries, although, $Li/SOCl_2$ and Li/CF_x batteries still used in cardiac monitoring devices [126].

Since its creation in the 1970s, lithium/manganese dioxide (Li/MnO_2) batteries have become the most popular choice for consumers and military purposes [127]. Due to their unique power-providing features, stable voltage operating, and estimable life span, nowadays, these batteries eventually became the ICDs', PMs, CRT related devices' power sources [3].

During the early stages of the development of ICDs, lithium/silver vanadium oxide (Li/SVO) batteries dominated the market since they offered high energy and power densities to overcome the shortcomings of earlier power sources. The Li/SVO battery discharge curve has two straight voltage phases which are followed by a steep decrease as the battery's lifespan

approaches its end. Li/SVO batteries are still used as power sources in some innovative ICDs and CRT gadgets. However, a new battery technology with an SVO and CF_x hybrid or dual cathode is increasingly replacing it. In 1999, the Li/SVO-CF_x battery was created by combining the greatest qualities of SVO and CF_x, resulting in a synergistic effect. These two battery architectures have comparable power capacities. Nowadays, most cardiac rhythm management devices utilize Li/SVO-CF_x batteries [81,128].

4.7 New energy sources (energy harvesters or self-powered devices)

Self-powered implanted devices offer the potential to decrease the need for high-risk recurring replacement surgery and increase the device lifespan within the body. Nevertheless, in order to achieve such practical technology, we need to conduct many studies and improve the current technology. But in spite of that, few harvesters have been introduced in recent years [129,130]. Energy harvesters divided into biomechanical energy harvesters that convert the energy of the body into electricity (including triboelectric nanogenerators (TENGs), piezoelectric nanogenerators (PENGs), and Hybrid nanogenerators (HNGs)), Thermic harvesters that convert thermal energy into electricity (including Pyroelectric nanogenerators (PyENGs)), biochemical energy harvesters such as biofuels that convert chemical energy from compounds found in biofuels into electrical energy by utilizing enzymes as catalysts, and finally solar energy harvesters that provide energy via interaction between light and the components in the solar cell [131,132].

5. Biomedical battery market

Recently, the medical devices market presented a promising part of the healthcare industry in general. It deals with prevention, diagnosis, and treatment of illnesses and diseases [133]. Hospitals, diagnostic centers, and patients at home are different types of users. Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) reported that only in USA market there are around 175000 different categories of medical devices. In detail, it can be mentioned that nearly 55 new medical devices have been approved by USFDA. Besides, 7000 clinical trial studies have been focusing on various medical devices as their data has been registered. Among those various devices wearable medical devices and implants had critical roles. Hearing aids and gadgets, implantable cardioverter defibrillators, cochlear batteries, neurostimulators, infusion pumps, diagnostic imaging device batteries, patient monitoring device batteries, critical care support batteries, in vitro diagnostic instrument batteries, therapeutic devices, prosthetic device batteries, pain management, and pacemakers are some examples of these categories [133-135]. The point is that the more these devices are important and popular, the more safety and economic price are needed. So, there is a need to achieve technology which help us to have safe, light-weight, compact, and high energy density and longer life cycle batteries for these medical devices [136].

Reports illustrates according to various applications of batteries in medical-related industries, there is a valuable growth in this market. Nowadays, different medical devices, in particular, in cardiovascular diseases, orthopedic, patient monitoring (home and hospital) and home healthcare are needed to batteries. Statics described the global battery market in medical scope will reach to $2.6 billion by 2028 with a CAGR of 5.2% from 2023 to 2028 [137].

Increasing the number of patients in various diseases especially cardiovascular diseases, the emergency needs to advance the conventional therapeutic methods and devices, and crucial economic and environmental aspects (for instance the need of recycling lithium-ion batteries to have a reduction in wastes) are all important causes which result in battery market growth. Figure 5 shows the diagram of forecast for the global medical battery market. To discover the most applicable materials in this market, it was showed that there is a promising need to lithium as lithium-ion batteries are known as one of the most valuable power sources in this scope because of their promising benefits including their long service life, high energy performance, and of course being portable [138].

Moreover, applications of batteries in medical industries are included but not limited to [137]:

- Patient Monitoring Devices
- General Medical
- Cardiovascular Medical
- Orthopedic Devices

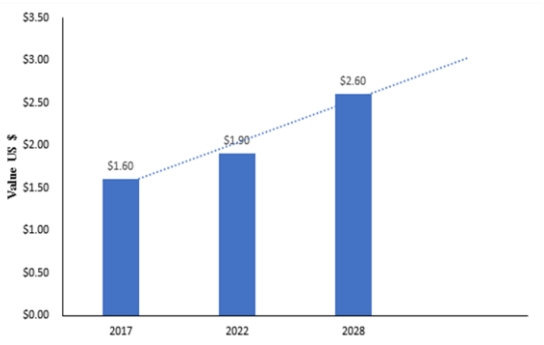

Figure 5. Trends and forecast for the global medical battery market.

- Home Healthcare Devices
- Other Devices

However, due to the increase in prevalence to chronic and vascular diseases, the application of cardiovascular medical batteries and devices will witness the highest growth rate [137]. Currently, medical device developers worldwide have been working on producing more than 930 medical device batteries for implants and wearable medical devices with different and novel types of batteries [136].

On the other hand, among implantable and implantable batteries, the non-implantable part is predicted to be the largest section as patients will need more portable medical batteries for various applications in particular self-awareness and diseases treatment [137].

Many companies in the world have been developing different types of medical devices batteries over the past decades. Publishing near to 450 patents in this field in the last 5 years is a witness of their efforts in this competitive market [136]. Ultra-life Corporation, Eagle-Picher Technologies LLC, EnerSys, Liberating Technologies, Inc., Panasonic Corporation, Tadiran Batteries Ltd., Saft Groupe S.A., Arotech Corporation, SHENZHEN KAYO BATTERY Co., Ltd, and Vitec Group plc., are some of the key players in the global medical batteries market [135].

From regional view, North America will be predicted to remain the largest market since it has high levels of technology and infrastructure in medical scope and generally healthcare. Also, APAC will have the largest growth rate in this market because of growing awareness and advancements in general healthcare [137].

6. Conclusion

The special characteristics and activities of micelles, particularly in recent decades, promoted great attention from the scientific society which resulted in the introduction of different types of micellar systems and various applications. Nano micellar delivery systems and micellar-based techniques have been emerged to increase the solubility, stability, and biological properties of many compounds with various applications as well as improve the functional processes on an industrial scale. Micelles by providing hydrophobicity and hydrophilicity at the same time are good options to be used for promoting materials' properties, especially insoluble drugs. Therefore, it is of great significance to engineer micelles, and take advantage of their unique structural properties to produce more applicable and smart compatible micellar systems for various industries.

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