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Cell Encapsulation Technology-A Futuristic Approach For Device Based Therapeutics Delivery

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ABSTRACT:
Cell encapsulation technology is projected to have a major significant part instead of conventional and innovative organ replacement in novel methods. Using the 3-D approach, cell encapsulation technology is developing from stem cell research to therapeutic delivery of morphogens and proteins in prolonged drug delivery. Recent advancements in the field have led to the development of biodegradable scaffolds that can hold and release cell content in various anatomical sites. Biomimetic scaffolds are advantageous in controlling cell and polymer interactions and have the accurate invention of devices that aid cell tracking. The current state of cell microencapsulation is summarized in this overview. It also covers the significant directions and difficulties this discipline faces as it works toward the controlled administration of biological therapies. Any pharmaceutical formulation has two ingredients: an excipient and an active component. Polymers which are cell encapsulation excipients aid in the production of dosage forms and enhance their physicochemical characteristics. Any dosage form uses polymers as excipients, which are crucial. They should be biocompatible, inert and non-toxic without affecting drug release. They fall into two general categories: synthetic polymers and natural polymers. Polymers are the initial choice to construct any dosage form because they have a wide range of applications. Nowadays, producers are leaning toward employing natural polymers due to several issues with drug release and side effects since organic polymers are essentially polysaccharides, which have both biocompatibility and have lesser adverse effects.

Keywords: Cell encapsulation; biomaterials; biocompatibility; immunosuppression; cell proliferation.

I. INTRODUCTION :

Cell encapsulation technology is a capable approach for medicinal applications in different body organs. A semipermeable membrane is used in cell encapsulation to enclose several living cell types, including myoblast, fibroblasts, neural stem cells, mesenchymal stem cells, and embryonic stem cells designed to create a therapeutic chemical. Drugs and metabolic waste products diffuse out of cells, oxygen and nutrition are the molecules diffuse into cell. This semipermeable membrane additionally shields the encapsulated cell from host immunity [1]. Cell encapsulation technology offers several advantages, like inhibition of administration of drugs repetitively. Encapsulation of cells in the biocompatible matrix is the primary approach in the cell encapsulation field. The viability and proliferation of cells can be maintained by the polymer used to formulate encapsulated cells. As this polymer membrane separates the immobilized cells from the activation

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of the immune system in the host body, it permits transplantation of the foreign cellular substances for clinical use. Because of its immunoisolation from the host immune system, genetically modified cells can be entrapped to express therapeutic effects [2]. In the past years, there has been progressing in encapsulation technologies for organ transplantation and allogenic tissue [3]. Cell encapsulation method based on microtechnology has been advanced in several aspects, such as the production of microcapsules which has accurate control on polymeric structure, enclosed cell membrane, and particle size [4]. Investigators can construct an encapsulated microcapsule that is structured by incorporating individual components. Cells or different molecules are encapsulated into separate chambers within the same structure [2] Porous structure and mechanical strength prevent cell encapsulation from damage [5]. Lack of porous structure in cell immobilization alters the efficacy of encapsulated cells [6]. By controlling the thickness, composition and structure homogeneity achieved in immobilization of cells [7]. Due to the versatility of polymer based encapsulation different techniques like microfluidics, micromolding, electrostatic droplet extrusion are used in cell immobilization [8].Hamilton gastight syringe is accurate in encapsulation technique optimization [9]. Size of drops should be controlled and maintained inorder to build efficient cell encapsulation structure [10].

II. HISTORICAL APPROACH :

Cell encapsulation technology had its roots in 1933. Scientist "Bisceglie" on the experiment of transplanting polymerized tumour cells encapsulated into the abdominal cavity of pig laid the basis for cell encapsulation technology. Upon administration into the host body, cells survived for long periods without destroying the host immune system. After thirty years, the experiment of encapsulating cells for immunoprotection aroused the "Artificial cells" term regarding cell encapsulation technology. This concept of artificial cells was continued to practice in the 1970s to encapsulate xenograft pancreatic islet cells to control glucose levels in animal models for diabetes. Since then, many studies have been done to move forward in the field of genetics, biology, pharmaceutical technology and polymer science. In this process of development, many microencapsulation devices have come into practice. Also, cell encapsulation technology substituted the limited supply of tissues with a broad range of suitable cell lines. These aid in systematically or locally distributing therapeutic peptides for long-term periods. As a result, cell encapsulation technology functions in medicinal applications for diabetes, hemophilia, renal failure diseases or disorders. Most recent preclinical trials on small animal models suggested the systematic basis for future scientific studies, including cell encapsulation of allogeneic pancreatic islets for diabetes treatment and cell encapsulation of cells expressing cytochrome P450 enzyme for the prevention of cancer. Nevertheless, with recent development in multidisciplinary studies, research is not progressing toward reaching the target of expectations. Though the scientists are equipped with all needed tissues and materials, the limitation in reaching the mark is based on reproducible tissue capacity. Significantly, many important questions remained unanswered, and this was the etiology of hindering the progress of cell encapsulation technology. Formerly, the "stepwise analysis" strategy is applied to essential research questions without following a trial and error approach. This strategy has shown positive results in cell-based encapsulation technology [2]. Immunomodulation, nanocoatings, novel materials in encapsulation technology provided a promising approach [11].

III. CELL ENCAPSULATION TECHNOLOGY :

Encapsulation is a type of technique in which volatile, easily degradable and bioactive substances are protected from in vivo conditions [12]. Encapsulation is an beneficial technology that offer various advantages than other conventional approaches [13] (Fig 1). Optimal delivery of encapsulated cells having therapeutic aspect is achieved with potency and biosafety. [14]. There is lack of developing of encapsulated cells with good stability and long term approach in in vitro and in vivo conditions[15]. Subjection of encapsulating cells to higher temperature during the preparation process results in aggregation of cells [16]. Cell based therapeutics are efficient tools in treating diseases when compared to potential aspects of other drug delivery systems [17]. Cells in encapsulation divide and this process of cell division can be controlled by altering the thickness of the encapsulated membrane [18]. To explain cell encapsulation technology in optimized conditions of culture medium, cell proliferation is

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studied. One daughter cell is produced upon cell division with parent cell properties. Signalling molecules are responsible for the regulation of cell proliferation and differentiation. The microenvironment of cell encapsulation can show similar physiological conditions in maintaining the phenotype of encapsulated cells. This encapsulation technology might support the long-term persistence of cells and the proliferation of encapsulated cells. The cells are encapsulated in a polymer. Its proliferation depends upon the medium's condition, the material used for cell encapsulation and the concentration of the polymer. For instance, cells encapsulated with optimum polymer concentration showed good cell proliferation and viability conditions compared to low or higher polymer concentration. Cells are differentiated based on several factors like the type of cell, cell culture medium and cell-cell interactions. Differentiation is affected by different signals that control cells' functioning in vitro and in vivo environments. To improve cell differentiation, scientists resemble in vivo environments in vitro conditions. Cell encapsulation could provide a proper environment for differentiating cells in vivo and in vitro environments—a research study on encapsulation of mesenchymal stem cells into various types of cells like insulin-producing cells. Multiple parameters are responsible for differentiating cells, including the concentration of alginate solution and preliminary concentration of cells. The optimum concentration of polymer results in optimum conditions for cell differentiation and proliferation. There are two types of cell encapsulation technology. It includes macro and microencapsulation. In macro encapsulation using macro-scale devices, cells are encapsulated into hollow fibers and hydrogels. Microencapsulation using micro moulding and microfluidic chip devices encapsulates cells into microfibers and microparticles [19]. To protect transplanted cells from rejection, encapsulated cells like micro and macro encapsulation are used as immunosuppressants [20]. Microfluids in single cell droplet are having higher efficiency in cell encapsulation technology [21].

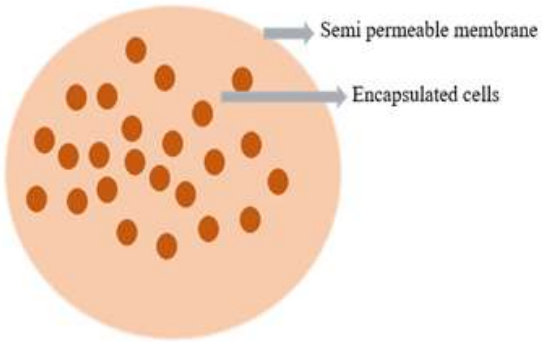

Fig 1: cell encapsulation technology

IV. TYPES OF CELL ENCAPSULATION :

4.1. Macroencapsulation :

In the synthetic hollow type of macroencapsulation for cell encapsulation, diffusion chambers with tubular shapes are used. Culture medium or hydrogel carries out the encapsulation and physical isolation of cells in fiber from adjacent tissues.

4.1.1. Construction of Hollow Fibers :

Through the nozzle of equipment, the polymer solution is pumped out as extrusion, and the aqueous solution flow by a central lumen, resulting in the fabrication of hollow fibers. In the aqueous water bath, hollow fibers are subjected, and the excess solvent is filtered out to collect pure hollow fibers. By "Sealing", hollow fibers are converted into encapsulated hollow fibers. For encapsulation of different cell types such as dopamine secreting cells, neuronal growth factor secreting cells, islets of pancreas, liver cells, and hollow encapsulation method is widely used. The procedure for gelation is easy in this method, and the gels made using this method can be quickly recovered. When cells are made by microencapsulation subjected to mechanical forces, they have more chances to break. This may result in fibrotic reactions. In this case, thin membranes are preferred for more minor diffusion barriers. The supply of oxygen and nutrients is based on diffusion, and there may be chances of accumulating encapsulated cells waste products in the capsules. Macrocapsules have a longer diffusion path to reach the centre core, which causes a central necrotic core due to deficiencies in oxygen and nutrient supplement. This limitation in size can be overruled by using hollow fibers that are smaller in size, which can improve the complement of nutrients. But, the fabrication of

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tiny hollow fibers requires many devices, decreasing patient compliance.

4.1.2. Macroencapsulation Beads :

In a study of probiotics encapsulation, Bacterial cells are encapsulated into a hydrocolloid bead matrix of culture medium. These bead encapsulated cells are protected from in vivo environments, and the survival of cells in the gastrointestinal environment is prolonged [6]. Coating of encapsulated cells with chitosan showed poor results when compared to microbeads [22]. Macroencapsulation technique aids in providing physicochemical and mechanical support to maintain cell therapeutic functions and cell expansion [23].

4.2. Microencapsulation :

Microencapsulation is suitable in protecting sensitive materials and provide conditions resembling to their natural environment [24]. Of Different types of cell encapsulation, microencapsulation is widely used in pharmaceutical field [25]. Because of the increase in consideration of microencapsulation with polymer matrix has resulted in a rise in applications in pharmacy, biotechnology, agriculture, industry and medicines. To protect from in vivo environments, microencapsulated cells are coated in the heterogeneous or homogeneous matrix. On application of microencapsulation, the core reactions with in vivo conditions could reduce, the transfer of core material to the external environment could be decreased, the easy handling of encapsulated cells, the release of the core material could be controlled, and the taste of core material is masked. The core material can be diluted into small amounts if needed. Chitosan microcapsules are widely used for cell encapsulation [26] (Fig 2).

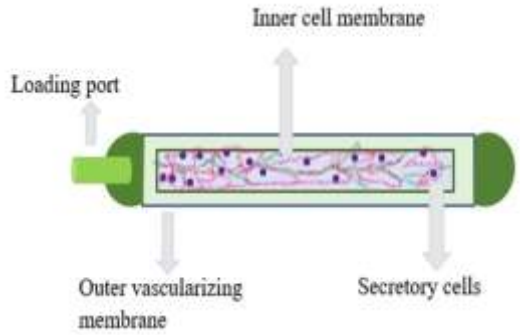

Fig 2: Marketed model of cell encapsulation technology

V. ADVANTAGES OF CELL ENCAPSULATION TECHNOLOGY :

1. Used to treat type1 diabetes mellitus, a disease that destroys the pancreas's beta cells that produce insulin.
2. Cell encapsulation therapy treats acute or chronic hepatic failure using allogeneic xenohepatocytes [2].
3. Cell encapsulation technology can be used to treat most age-related diseases and also desperately replace the scarcity of donor organs.
4. Compared with the lifetime of exogenous delivery of hormones or complete transplantation of organs, cell encapsulation therapy is favorable in the case of pharmacoeconomics. Insurance companies also raise the demand for cell-based transplantation to decrease the payments they need to pay hospitals for conventional therapies.
5. Cells that are fabricated into encapsulation could be transplanted into different types of organs and tissues by which cell encapsulation technology is applied for oral, regional(for example, Brain), local (for example, Solid tumours) or systemic (for example Intraperitoneal) therapeutics delivery[2].
6. Cell encapsulation technology is used as promising approach for controlled drug release [27].
7. Encapsulation technology aids in delivery of probiotics [28].
8. Immobilized cells are having improved performance in terms of stability and activity [29].

VI. PURPOSE OF CELL ENCAPSULATION TECHNOLOGY :

Encapsulation technology is applied not only to increase bioavailability but also to protect cells from host environment such as, presence of light and oxygen, high temperature [30]. Viability and stability of the encapsulated substances can be determined by polymer materials [31]. According to some studies, encapsulated cells are having good bioavailability than not encapsulated cells [32]. A microcapsule should satisfy a defined set of requirements to achieve the target of cell encapsulation-based therapies. Encapsulating capsule membrane should work as a device that protects from immunization. It should be able to keep immune system components from reaching living cells. Cell encapsulation membrane should allow oxygen, Nutrients like glucose and proteins like growth factors into encapsulated cells. The

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encapsulation membrane should be strong enough to endure in the human body's transplantation, handling, and in vivo environment. The encapsulating membrane used will be biodegradable in many cases. But, degradation of the biodegradable encapsulating membrane should not affect encapsulated cells. Two main characteristics involved in nutrition diffusion and host immune response are surface charge and diameter of the capsule.

Hydrogels, The selection of appropriate material in case of targeted delivery of cells to the host body or encapsulating them intended for sustained distribution of chemicals they make to the surrounding cellular region, is one of the essential design considerations for a microencapsulation method. The topic of cell microencapsulation has profited significantly from biomaterial advancements and optimization during the past few decades. Because these materials possess several desirable qualities, hydrogel-forming polymers are almost exclusively used to create microcapsules. Examples include hydrogels, made up of 3D networks of hydrophilic polymers and offer a hydrophilic environment for embedded cells. Hydrogels can also be made to deliver physical stimuli, biochemical and cellular that natural processes of cells such as cell attachment, differentiation and growth.

The simplest method of encapsulation involves encapsulating cells in bulk hydrogels, which involves three steps:

1) To the solution of pre gel, cells were suspended at the desired density.
2) Then, the suspension was injected into the cellular container.
3) Through a change in photocuring, temperature or chemical reaction, the gelling process is done using a pre-gel suspension of cells.

Another technique that quickens the kinetics of gelation is ultrasonication-induced gelation. Bulky hydrogel encapsulating materials are frequently made of manufactured polymers, such as PEG (polyethylene glycol)-based hydrogels. Gel formation depends on photoinitiators, monomers and crosslinkers. According to specific investigations, PEG hydrogels that develop through a temperature change outperform photopolymerization reactions when used in settings with scant light penetration. The recipient's immunological response and the survival of transplanted cells can be impacted by the sizes and forms of an encapsulating substance [33] [6].

VII. POLYMERS USED IN CELL ENCAPSULATION TECHNOLOGY :

7.1. Organic Polymers :

There exist natural polymers, but their usage in pharmaceutical applications is appealing due to their affordability, accessibility, and lack of toxicity. They are also biocompatible, chemically modifiable, and possibly biodegradable, with a few exceptions.

7.1.1. Alginate :

In marine algae and brown seaweed like Macrocystis pyrifera, Laminaria hyperborean and Ascophyllum nodosum, alginates, also known as alginic acids, are linear, unbranched polysaccharides. Alginate could be transformed into its salt form. One of its form-sodium alginate, which is the most widely utilized type right now. These polymers are made of two distinct monomers in various ratios, specifically blocks of L-glucuronic acid or -D-mannuronic acid in homopolymers or blocks that alternate the two in blocks of heteropolymer, linked in - or -1,4 glycosidic linkages (Fig 3). The molecular weights of alginates range from 20 to 600 kDa. Alginates have been used and researched as tablet binders, disintegrants, stabilizers in emulsions, and suspending agents [34].Using ionic cross linking technique with cations like calcium and barium, alginate is converting from solution to gel form [35].

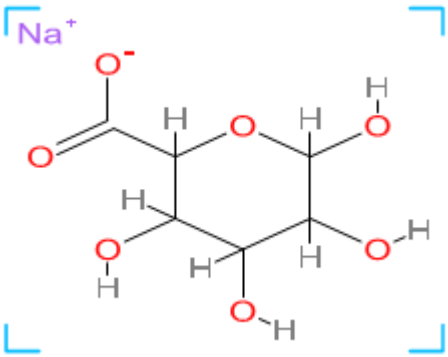

Fig 3: Chemical structure of alginate

7.1.2. Chitosan :

It is generally known that the mucopolysaccharide chitin, a naturally occurring component of crustaceans, insects, and other organisms, is composed of 2-acetamido-2-deoxy-b-D-glucose via beta (1 to 4) linkage (Fig 4). Chitinase can break down chitin. Despite the presence of nitrogen, it has very low

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immunogenicity. It performs naturally as a structural polysaccharide, much like cellulose. In coastal areas, chitin is the leading cause of surface pollution. The physical properties of chitin are white, rigid, inelastic, and nitrogenous polysaccharide.

Although this N-deacetylation is nearly never fully accomplished, chitosan is the N-deacetylated derivative of chitin. A precise terminology regarding the level of N-deacetylation has not been established between chitin and chitosan. Due to their higher nitrogen content than synthetically substituted cellulose, chitin and chitosan are of commercial interest (1.25%). Chitin is thus a practical chelating agent. Since most modern polymers are made of synthetic materials, they are far less biocompatible and biodegradable than natural polymers like cellulose, chitin, chitosan, and their derivatives.

However, the reactivity and processability of these naturally plentiful minerals are constrained. Because these natural polymers have excellent biocompatibility, biodegradability, non-toxicity, adsorption characteristics, etc., chitin and chitosan are acceptable functional materials. Chitosan has lately received its identity as a potential polysaccharide resource. Even though there have been numerous attempts to create active derivatives of chitosan through chemical alterations, relatively few have succeeded in making them soluble in common organic solvents and some binary solvent systems. Many researchers have reported that chitin and chitosan structures have been chemically altered, improving their solubility in common organic solvents [1].

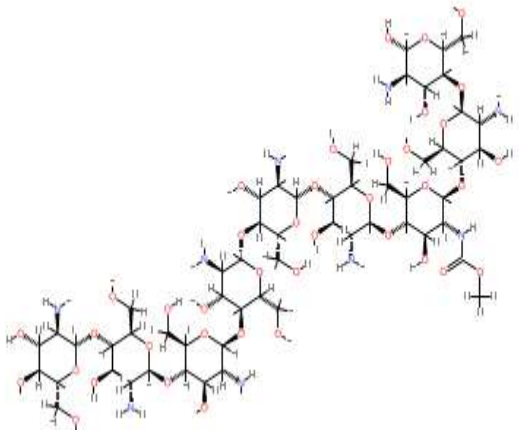

Fig 4: Chemical structure of Chitosan

7.1.3. Hyaluronic acid :

All living things naturally contain hyaluronic acid (in the short form designated as HA), a mucopolysaccharide and a type of carbohydrate. It may consist of thousands of sugars or other carbs. When unbound, it bonds to water, giving it a rigid viscous character akin to "Jelly" when other molecules are not connected to it. Hyaluronan (HA), a polysaccharide, is a disaccharide with a straight polyanion structure (Fig 5). Although it has been demonstrated that HA can occur intracellularly, it is most commonly found in the pericellular and extracellular matrix. The biological functions of HA include regulating the flow of water and moisture throughout tissues, supramolecular assembly of proteoglycans in the extracellular matrix, and various receptor-mediated functions in mitosis, cell detachment, migration, inflammation, and tumour growth. It also maintains the elastoviscosity of liquid connective tissues like joint synovial and vitreous eye fluid. Its role in the body includes binding water and lubricating moveable body parts, including joints and muscles. It works well as a moisturizer in skin-care products due to its consistency and tissue friendliness. In nature, hyaluronic acid is one of the most water-soluble (water-loving) compounds, and hyaluronic acid is sometimes referred to as "nature's moisturizer." Due to HA's distinct viscoelastic properties, biocompatibility, and non-immunogenicity, it is used in a variety of clinical procedures, such as the supplementation of fluid of joints in rheumatoid arthritis, as an eye surgery surgical aid, and to speed up the regeneration and healing of surgical wounds. Hyaluronic acid is approved for different drug delivery routes. Such as topical, ophthalmic, parenteral, pulmonary and nasal [36].

Due to its unique physicochemical characteristics, natural polysaccharide hyaluronic acid is used as a viscosity elastic substance in surgery related to ophthalmology. HA has a prominent role in cataract surgery, simplifying procedures and guarding the corneal endothelium. Hyaluronic acid is being researched as a treatment for osteoarthritis and, to a lesser extent, rheumatoid arthritis due to its lubricating and cushioning qualities as well as evidence of some in vitro anti-inflammatory activity and a potential disease-modifying effect in animals. Patients with osteoarthritis experienced reduced knee discomfort and improved joint motion after receiving weekly intra-articular injections of hyaluronic acid 20mg for 3 to 7 weeks. In most comparisons, this

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occurred to a greater extent than with placebo, although in the largest experiment, hyaluronic acid's benefits were comparable to those of placebo. Hyaluronic acid appeared identical to methylprednisolone 40mg (for three weeks) and a single injection of triamcinolone 40mg in the few studies that compared it to other treatments. The persistent effect hyaluronic acid offers beyond the remedy's end set it apart from other therapies. These characteristics and its excellent tolerability profile support future research on hyaluronic acid in osteoarthritis patients. Additional areas of interest for further research include some scant evidence of improvement in rheumatoid arthritis patients and a potential healing effect of hyaluronic acid on perforations of the tympanic membrane. In conclusion, hyaluronic acid has a proven track record as an adjuvant to cataract surgery and may provide patients with osteoarthritis with a feasible therapy choice. Its excellent tolerability encourages future investigation into its potential application in the broader range of ophthalmological and arthritic diseases, as well as in the healing of wounds [37].

For various prospective medicinal therapies, pure or modified HA can efficiently encapsulate proteins and enable their regulated release. For instance, growth factors can be encapsulated by hydrophilic HA particles, controlling their release and enhancing their biological effects. Recombinant human growth hormone incorporation led to a mass erosion or biodegradation after sustained protein release from these HA hydrogels. HAs are excellent building blocks for parenteral hydrogels. Proteins were released from stiff hydrogels more slowly than from softer ones. Negatively charged -amylase exhibited sustained release properties in phosphate buffer saline. The release of positively charged lysozyme, on the other hand, was inhibited after 4 hours as a result of electrostatic interactions with HA. They also demonstrated that lysozymes from the hydrogels were continually and fully released into the subcutaneous environment in the presence of hyaluronidase, causing the gel network to break down quickly. These hydrogels are perfect for therapeutic protein delivery since the activities of the released proteins were preserved [38].

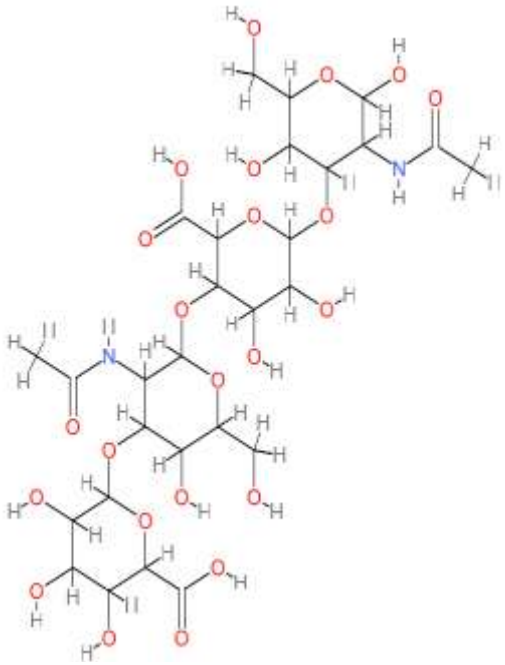

Fig 5: Chemical structure of Hyaluronic acid

7.1.4. Collagen :

Collagen based encapsulation have high rate of cell activating properties [26]. Assembly of collagen molecules during development of encapsulation is crucial step in viability of cells in collagen encapsulated matrix [39] (Fig 6). The presence of several cell-signalling domains in collagen gels, as well as other mammalian-derived protein-based polymers discussed in the following section, makes these substances efficient matrices for cellular growth. Due to its low immunogenicity, type I collagen is the most researched substance for tissue culture. Collagen gels have the benefit of being produced naturally without the use of chemicals. Still, the resulting collagen matrices have disadvantages, such as mechanical brittleness and weak resistance to enzymatic breakdown. Because of this, various procedures have been studied to improve the collagen's stability and mechanical properties, including chemical techniques like glutaraldehyde and the water-soluble carbodiimide and physical processes like dehydro thermal and UV radiation, enzymatic cross-linking approaches.

Self-assembled collagen microspheres, which are stable, can be injected into living organisms. They offer hMSCs (human mesenchymal stem cells) a protective, growth- and migration-supporting environment both in vitro and in vivo are examples of the promise held by

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collagen microcapsule technology. They also provide superior hyaline cartilage reproduction for the microencapsulation of hMSCs [33].

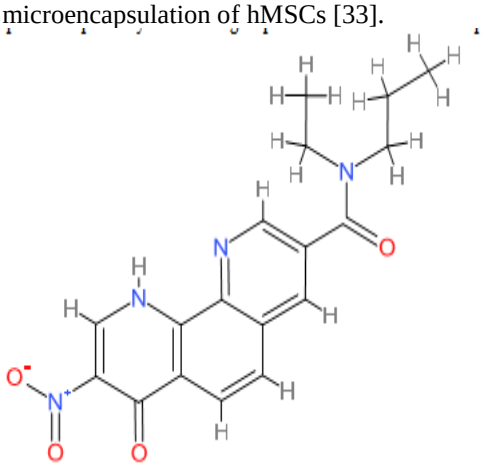

Fig 6: Chemical structure of collagen

7.2. Synthetic polymers :

For use in regenerative medicine, biodegradable synthetic polymers have a variety of benefits over non-degradable ones. They can be fabricated into various geometries with the appropriate bulk and surface properties, just like any synthetic polymers, and can be produced at predictable quality and purity. One benefit is the flexibility to adjust mechanical characteristics and degradation dynamics to suit different applications. Resorbable sutures, medication delivery systems, and orthopaedic fixation devices, including pins, rods, and screws, are just a few clinical uses for biodegradable synthetic polymers. Numerous artificial matrices for tissue engineering applications using synthetic biodegradables have been investigated. For these uses, the constitutive polymer-determined mechanical characteristics of the scaffolds must functionally resemble those of the tissue that needs to be rebuilt.

In the end, the polymeric support is intended to break down, whether via transplantation or invasion. The goal is to produce tissue that is mechanically, functionally, and histologically similar to the surrounding tissue. A wide variety of biodegradable polymers, including elastic, flexible compounds for bone regeneration and stiff, rigid materials for use in weight-carrying tissues such as bone, are needed to construct scaffolds suitable for various purposes. In addition to the mechanical characteristics, the scaffold's degradation kinetics must be adjusted to fit different applications. The possible applications in regenerative medicine are described after a brief discussion of the main kinds of synthetic, biodegradable polymers. Artificial matrices for tissue engineering applications, orthopaedic fixation devices, cosmetic and prosthetic implants, and nano, micro, and macroscopic drug and gene delivery systems are just a few of the biomedical uses for synthetic polymers[40].

7.2.1. Polyethylene glycol :

As injectable blood-persistent systems for the controlled release of pharmaceuticals, site-specific drug delivery, and medical imaging, biodegradable polyethylene glycol (PEG)-coated nanospheres have significant potential therapeutic applications (Fig 7). Polylactic acid (PLA) nanospheres have been shown to have a blood half-life of up to several hours in rats when coated with hydrophilic PEG. In contrast to PEG, which is hydrophilic and biocompatible (molecular mass less than 20 kgs per mole), R is hydrophobic and biodegradable (i.e., PLA, polylactide glycolic acid (PLGA), and PCL (poly-(e-caprolactone)). PEG-coated nanospheres have been made from diblock PEG R or multiblock PEG R copolymers. Due to their different affinities for the water and oil phases, these incompatible building blocks create a phase-separated structure when the oil-in-water emulsions are transformed into nanospheres.

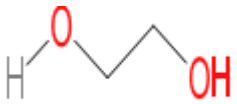

Fig 7: Chemical structure of polyethylene glycol

The final particle structure comprises a hydrophobic R polymer core that faces the dispersing aqueous phase and a hydrophilic PEG brush that meets it. PEG detachment, and complement activation by alkaline hydrolysis experiments have all provided proof of the PEG coating. The best conditions to prevent protein adsorption are a long PEG surface density and a high PEG chain length, according to mathematical modelling of PEG brushes on hydrophobic surfaces (Fig 8). The capacity to control the release of the encapsulated chemical and the shelf stability of PEG-coated nanospheres make them superior to other long-circulating systems. Only hydrophobic medications have so far been enclosed in PEG-coated nanospheres. Among them, the emulsion/solvent evaporation method traps high loadings of cyclosporin and lidocaine.

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Additionally, by carefully selecting the polymer composition and adjusting the nanosphere size, the release of the medicine that was encapsulated could be managed. Due to the need to enhance the administration of recently produced macromolecular drugs and antigens, protein distribution from biodegradable polymer systems has proven to be a challenging area of research. Due to the hydrophobic nature of their core, PEG-coated nanospheres may appear unsuited for encapsulating water-soluble compounds. In reality, it was anticipated that using a water-in-oil-in-water (w1/o/w2) emulsion technique, the water-soluble drug would diffuse toward the outer aqueous phase due to the large specific surface area of the oily nanodroplets (w2). If this happens, the poor entrapment efficiency could be a significant disadvantage, especially in the case of expensive medications. The need to enhance the delivery of recently created macromolecular medicines and antigens has made it a challenging area of research. The hydrophobic character of the PEG-coated nanospheres' core may at first appear to exclude their use for immobilizing compounds soluble in water. Given the high specific surface area of the oily nanodroplets, it was hypothesized that when using the water-in-oil-in-water (w1/o/w2) emulsion approach, the water-soluble medication would diffuse toward the outer aqueous phase (w2). If this occurs, the decreased trapping efficiency might be a severe drawback, especially in the case of costly drugs [41].

Comparable studies using liposomes containing DPPE-PEG 2000 found that, in contrast to the current study's findings, peak permeabilities were reached at around 4% mole DPPE-PEG 2000 in the mushroom area to brush chain conformation (It is projected that the height of polymers grafted to a surface will remain constant at low densities called mushroom transition and rise with the third root of the surface density of the polymer at high densities called brush transition). For a PEG chain with a mass of 5000 molecules, the change from the mushroom to the brush conformation is thought to occur at a rate of about 1.7 moles. As a result, the findings align with the depression of the lower PEG levels were consistent in mushroom to brush transition [42].

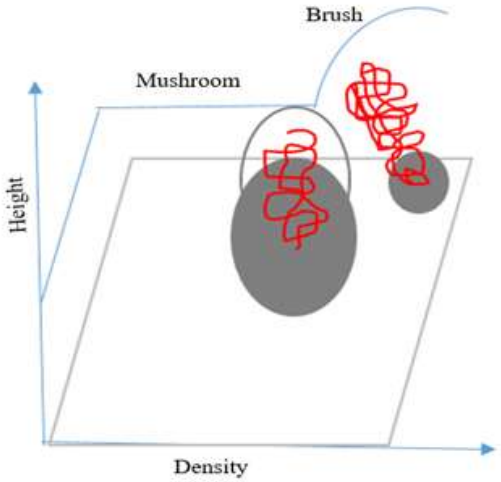

Fig 8: Mushroom and brush transitions of encapsulated cells

VIII. CELL-BASED DELIVERY SYSTEMS :

Due to distribution issues inside the organ and the probable short half-lives of the therapeutic molecules, the delivery of biological chemicals that might have medicinal benefits is sometimes challenging. Cell-based delivery systems have been developed to circumvent this issue, achieving continuous distribution by implanting cells that produce physiologically active chemicals. The immune system's rejection of the transplanted cells has limited the usage of such cells. The producer cells have been encapsulated in various methods to stop the immune cells from killing the transplanted cells. Cell encapsulation therapy has been promoted, particularly for treating diabetes, where the encapsulation of cells that make insulin minimizes the requirement for immunosuppression. Alginate microcapsules will increase the availability of nutrients and oxygen to the producer cells and have better mechanical strength, biocompatibility, and chemical stability. These beads can be injected into the body, where they might have a therapeutic effect. However, there are still unanswered questions regarding how the tissue receives the transplanted cells and how the immune system responds to them in treating diabetes. Alginates, organic polysaccharide polymers, encapsulate the extracellular matrix of the brown seaweed. Glycoside linkages bind the two anionic monomers (G blocks and M blocks) that make up the polymers. There are areas of mixed monomers interspersed throughout the polymers (MG blocks).

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In the presence of divalent and multivalent cations, the polysaccharides create heat-stable gels that can solidify at room temperature. Ions like Ba2+, Sr2+, and Ca2+ make potent connections to the G blocks via free carboxyl groups, but monovalent cations and Mg2+ do not cause gelation. In general, a higher G-content will result in a more potent gel. The gel's pore size can change based on the gelling solutions. However, it typically ranges from 5 to 200 nm. Depending on the cations utilized and the make-up of the gelling solution, alginates can be made more or less dense, stable, and biocompatible. Theoretically, it is possible to create some producer cells to emit many therapeutic proteins that are afterwards encapsulated in alginate. An electrostatic bead generator works best for producing beads of uniform size. Following encapsulation, the proteins can freely travel through the beads' pores, protecting the producer cells from immune-competent cells.

The actions of producer cells in the alginate bead's microenvironment have been studied in several research. A time of increasing cell proliferation is observed after an initial adaption phase, during which some cells experience cell death. In contrast, others begin to multiply, and tiny spheroids may form inside the gels. These spheroids then frequently create a steady state in the alginate where cell growth equals cell death. The CNS may be a good candidate for cell encapsulation therapy because it is an immune-privileged organ system. For instance, encapsulated mouse myoblasts have produced recombinant gene products such as human growth hormone (hGH). Up to 75 days of stable hGH expression have been shown by in vitro studies. Quantifying hGH using ELISA has demonstrated detectable levels up to 16 weeks after implantation, with a peak at eight weeks after implantation into the lateral ventricles of mice. Immunohistochemistry analysis of the hGH distribution reveals that there is hGH within 1.5 to 2 mm of the implantation site, with a gradient of decreasing concentration. The authors have evaluated the release of antibodies from encapsulated hybridoma cells in similar experiments. For 12 days, there was a continuous rise in antibody production, and then there was a stabilization. Immunoglobulins were found at a distance of 1 to 2 mm from the implantation site in the rat brain. As a result, producer cells that have been enclosed in a capsule may successfully adapt to the CNS milieu and continue to express a transgene for several weeks after implantation [43].

IX. MEDICINAL APPLICATIONS OF CELL ENCAPSULATION TECHNOLOGY :

When treating various diseases with encapsulated cells, cell type is crucial. While primary cells are safer but have a shorter lifespan than cell lines, the latter are more resistant, easier to cultivate, and capable of unpredictable behaviour. Due to the enormous number of cells needed, the cell supply is another limiting factor in addition to the cell type. For instance, obtaining human cells is challenging, expensive, and, most critically, constrained by moral and governmental health regulations. Because xenogeneic cells are immunoisolated by the capsule, their use in cell encapsulation research is expanded.

However, the chemokines and antigens generated by cells may cause the immune system to get activated and start an inflammatory process, which may ultimately result in graft rejection. Because of their hypoimmunogenic, immunoprotective, and plasticity characteristics, stem cells (SC), particularly mesenchymal SCs (MSC), are currently being employed as an alternative. The following section will summarise some of the therapeutic uses for microencapsulated cells [2] (Fig 9).

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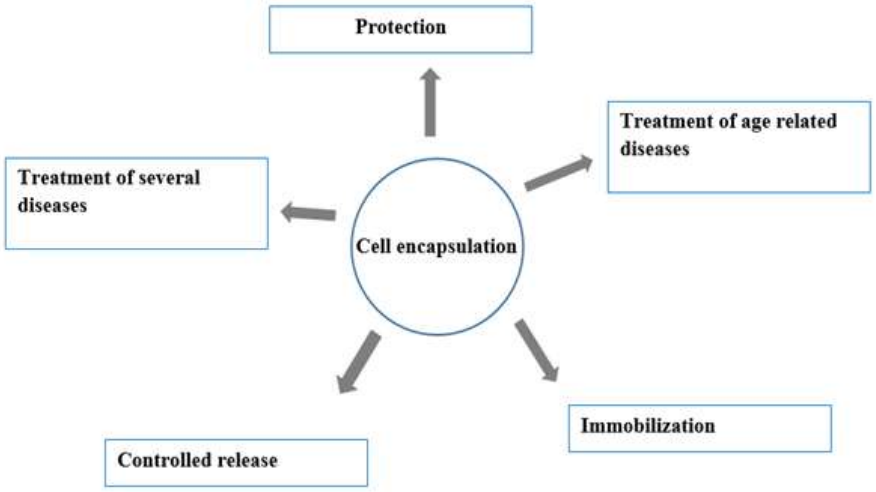

Fig 9: Medicinal applications of cell encapsulation technology

9.1. Cell encapsulation in chronic anaemia :

Blood loss, renal failure, dietary issues, and inflammation are a few of the various causes of anaemia. The therapy of anaemia in many human ailments has improved thanks to anaemia management in patients with chronic kidney disease. The most effective treatment involves administering erythropoietin (Epo), a low-molecular (30.4 kDa) pleiotropic glycoprotein with 165 amino acids that play a hormonal role in erythropoiesis (the maturation of erythroid progenitor cells into mature red blood cells, or RBCs) and erythrocyte differentiation. In addition to this, mounting evidence points to a broader biological function for Epo/Epo-R.

Low levels of Epo mRNA have also been found in the mouse ischemic heart, testes, lungs, human milk, enterocytes, spleen, breast gland, placenta and bone marrow macrophages, neurons and astrocytes, indicating that Epo is a multifunctional trophic factor with a variety of physiological functions, a tissue targeted regulation and numerous mechanisms of action. Additionally, it has been discovered that Epo and Epo-R are increased in the spinal cord and brain following damage, and their protective significance in ischemia animal models has been demonstrated.

EPO is a promising therapeutic option for various neurodegenerative conditions, including spinal cord injury, glaucoma, Parkinson's disease, and Alzheimer's. Epo's neuroprotective functions may be associated with antioxidation, antiapoptosis, angiogenesis and neurotrophic action. To evaluate and enhance the cell encapsulation method more than ten years ago, some research team employed Epo, alginate microcapsules and C2C12 myoblasts (immortalized myoblast cell line) as proof of concept. We used syngeneic and allogeneic mice to accomplish this by implanting Epo-secreting C2C12 myoblasts in the subcutaneous and peritoneum tissue. The microcapsules were made of alginate poly-L-lysine-alginate (APA).

Data showed that all implanted mice had high and stable hematocrit levels for more than 100 days without needing immunosuppressive procedures after the implantation of Epo-secreting cell-loaded microcapsules. It's interesting to note that this chemical seems to have additional biological benefits for the transplant. Epo's angiogenic and immunomodulatory qualities encouraged the development of a vascularized network surrounding the microcapsule graft and adequate biocompatibility, leading researchers to conclude that it might be a promising method for the long-term delivery of Epo. This proof of concept also clarified several hot-button issues. For xenogeneic or allogeneic transplantation, the effect of the implantation site and the viability of utilizing the same method.

These investigations also highlighted the importance of establishing a vascularized environment around the immobilization device to enable close contact between the encapsulated cells and the bloodstream and, consequently, enhance the graft's long-term efficiency. After the allogeneic model approach based on subcutaneous implantation of microencapsulated Epo-secreting cells was properly characterized and biomedical

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grade biomaterials were chosen as the most biocompatible polymers, a thorough morphological and mechanical evaluation of microcapsules containing Epo secreting C2C12 myoblasts was carried out. Epo-secreting murine C2C12 myoblasts were then subcutaneously implanted for 14 weeks into Fischer rats while temporarily immunosuppressed with Tacrolimus (FK-506). This was a successful xenogeneic technique.

The survival and long-term functionality of the graft and the mechanical properties of the encapsulating devices were examined in a follow-up investigation to determine whether developing 3D alginate scaffolds fitted with biological cues could help. The search for the ideal extracellular environment has fuelled the development of matrices and biomimetic scaffolds that incorporate integrin-mediated cell adhesion sequences like IKLLI, IKVAV, LRE, PDSGR, YIGSR, and the most popular arginine-glycine-aspartic acid (RGD), which is derived from fibronectin, a natural protein present in ECM trying to mimic the extra cellular conditions. Through the focal contacts, these moieties cause a series of intracellular signalling processes that tightly regulate connections between cells and their matrix.

We created RGD-enriched alginate capsules to trap Epo-releasing cells as part of a collaboration with David Mooney's research team. The capsule's mechanical properties and resistance to swelling and the value of the rupture force were improved by cell integrin-mediated binds to the RGD moieties in the alginate matrix. A more natural habitat for the contained cells was created by including these oligopeptides, which increased their survivability and long-term functionality in vivo. Cell encapsulation faces significant obstacles on the path to the clinical environment, including the potential for tracking cell-containing microcapsules, tracking cell survival, and managing therapeutic action (external control of the expression of the medicinal product).

Recently, we created alginate microcapsules that contained myoblasts and allowed cells to be transfected with the SFGNESTGL triple-fusion reporter retroviral vector. The latter includes the herpes simplex virus type 1 thymidine-kinase (HSV1-TK), firefly luciferase, and green fluorescence protein (GFP). The thymidine-kinase substrate ganciclovir, administered to mice, caused the death of microencapsulated myoblasts, inactivated the therapeutic effects, and made capsule monitoring after animal implantation easier. This device might provide non-invasive cell localization and viability control. Medication can be administered to cause cell death if therapy needs to be stopped. Other exciting challenges to overcome include enhancing microcapsule retention for posterior retrieval in the tissue where they are placed while reducing post-transplant inflammation. A hydrogel-based scaffold containing cell-loaded microcapsules may be advantageous for these components. These hydrogel-based scaffolds can be used in implantable (preformed scaffolds) or injectable (in situ formed scaffolds) forms; the main differences between the two types of hydrogels are in the production and administration processes. When cell-loaded microcapsules were enclosed in hydrogel scaffolds, pericapsular overgrowth was minimized, and hematocrit levels were maintained up to 80% for at least those two months, according to a histological study of the explanted microcapsules done two months after delivery [37].

9.2. Cell Encapsulation in disorders related to the Endocrine system (Example- Diabetes) :

Hyperglycemia caused by abnormalities in insulin secretion, action, or both characterizes diabetes as a metabolic disease. The challenges of replacing injured islets of Langerhans with cell-based treatments, such as the requisite immunosuppressive medicines and the limited and unpredictable supply of cadaveric donors, have stimulated the development of alternative therapeutic techniques. Several research teams have used cell microencapsulation technology to attain insulin levels and regulate plasma glucose to build a living cell-based replacement system or a bioartificial pancreas. Stem cells (SCs) were encapsulated in alginate-based microcapsules and transplanted into non-obese diabetic mice to show the reversal of spontaneous diabetes by newly produced functional islets cells.

A novel design for a bioartificial pancreas was created in a recent study by co-encapsulating islets with angiogenic proteins in multilayer alginate microcapsules. MSCs, stem cells like embryonic stem cells (ESCs), or induced pluripotent stem cells (IPSs), have been shown in several studies to develop into cells that produce insulin and may be effective in the treatment of diabetes. The project aims to obtain mature insulin-producing cells in vivo while avoiding their immune system's rejection and the development of teratomas. On differentiation of hESC into PP, they were immobilized into microcapsules made up of alginate beads before transplanting them into

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patients who have diabetes [44]. Cell encapsulation technology is having approach in developing microencapsulated β-cells. This technique increase the viability of cells in biological conditions [45].

9.3. Cell Encapsulation in Hypocalcaemia :

Clinical studies of encapsulated cells using alginate as biomaterial parathyroid tissue as a therapeutic agent applied for hypocalcemia. The status of this study showed allotransplantation in two patients without immunosuppression [33].

9.4. Cell Encapsulation in Cancer :

Promising methods for cancer treatment have emerged due to significant advancements in the field of anti-tumour immunotherapy. More recently, it produced the first clinical application using autologous dendritic cells that the Food and Drug Administration approved. Numerous strategies have been devised, including using entire tumour cells, pulsed dendritic cells, naked DNA expression plasmids, tumour peptides, or epitope-enhanced peptides. The application of autologous tumour cells is intriguing because they contain all the tumour-associated antigens, preventing the separation of a single epitope and enabling a more comprehensive anti-tumour immune response.

Although allogeneic tumour cells have also been extensively investigated, their survival in the receiver is limited since the host immune reaction soon eradicates them (human leukocyte antigen-dependent and innate natural killer-dependent mechanisms). Additionally, allogeneic tumour cells may lack the antigens to trigger a particular immune response to the host's tumour. Autologous or allogeneic tumour cells have been genetically modified to release various cytokines to improve the host immune response. This method was used in multiple cell-based vaccination studies in animal models, and its effects on tumour rejection were assessed for immunomodulatory properties or adjuvant effects of the cytokines.

It was discovered that the granulocyte-macrophage colony-stimulating factor (GM-CSF) had a strong stimulatory effect on the cells at the vaccination site, improving the processing and presentation of the tumour-associated antigens to CD4 and CD8 T cells. In mice that had previously received vaccination with GM-CSF-producing irradiated tumour cells, it has been demonstrated that this method can induce potent, specific, and long-lasting antitumor immunity, resulting in the rejection of small tumour burdens of melanoma cells as well as lung, colon, and renal cancer cells. Ex vivo genetically engineered tumour cells that produce GM-CSF have been used as an immunization technique for several animal tumour models, including leukaemia, melanoma, and glioma.

Additionally, preclinical and clinical trials involving patients with non-small-cell lung cancer, prostate cancer, melanoma, renal cell carcinoma, and pancreatic cancer have been carried out. These encouraging investigations have shown that GM-CSF can effectively trigger an antitumor immune response when created locally at the injection site for tumour cells, with little to no systemic harm. However, the autologous strategy imposes the need for customized genetic engineering of autologous tumour cells, resulting in unpredictably high amounts of GM-CSF release [46].

There are several methods for treating different solid tumours that involve the use of microcapsules containing cells that produce other therapeutic compounds.Some of these strategies involve encasing cells that secrete antiangiogenic proteins like endostatin, angiostatin, or the combination of endostatin, soluble neuropilin-1, and thrombospondin-2. These strategies are based on the theory that most solid tumours cannot grow past a critical size without angiogenesis because of insufficient tissue oxygenation and nutrient supply. Other research teams have used encapsulated cells that have been genetically modified to release interleukin-6 (IL-6) or tumour necrosis factor (TNF) to trigger an immune response against malignancies. As the tumour cells adapt to a particular therapy over a period of time, a combination of therapies may be necessary to attack the tumour and increase therapy success.

Encapsulated cells have also been utilized to produce antibodies or retrovirus over an extended period. Hybridoma cells that release immunostimulatory antibodies were enclosed by researchers (anti-CD137 and anti-OX40 mAb). The immunostimulatory monoclonal antibodies released by the implanted encapsulated hybridoma cells improve tumour-specific cellular immunity, as demonstrated by the microcapsules given to animals with created tumours. Several research teams are presently examining the potential benefits of MSC encapsulation in managing various cancers. In one of these studies, Goren et al. demonstrated that genetically modified MSCs secreting hemopexin-like protein (PEX) when enclosed in alginate-PLL microcapsules retain their ability to proliferate and differentiate as well as their long-term stability.

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These microcapsules were implanted in a model of human glioblastoma, with results showing an increase in tumour cell death and a decrease in tumour growth, blood vessel development, and proliferation [44].

9.5. Cell Encapsulation in Central nervous system (CNS) :

In numerous preclinical injury models and clinical settings, the successful use of cell therapy, or cellular transplantation, to the injured or deficient CNS to restore form and function has been demonstrated. Clinical grafts of embryonic nigral tissue and adrenal medullary autografts were used to replace the missing neurotransmitter dopamine in patients with Parkinson's disease (PD). One of the cornerstones of transplantation therapies in the CNS is cellular transplantation, which offers a local source of neurotransmitters and trophic factors (i.e. neurotrophins) using these so-called cellular "minipumps." To replace the destroyed neural circuitry, foetal nigral grafts have demonstrated the capacity to create functional reinnervation. However, the host striatum must receive the grafted dopamine neurons.

Fetal dopamine neurons must be isolated at an early stage of development to survive transplantation, which is a technically challenging task. Additionally, axonal bridges for the restoration of the damaged spinal circuitry and glial elements to make up for the loss in sclerotic lesions have been achieved by the use of neural grafts. This chapter is primarily concerned with using cell therapy as biologic minipumps to replace depleted levels of neurotransmitters or to deliver local neurotrophins as a neuroprotective measure. Although it is believed that cellular minipumps can supply neuroactive molecules locally in the therapeutic range, one possible drawback is dosage. As was mentioned for the tissue parenchyma pump technology, having a point source of factor reduces the diffusion distance.

9.6. Cell Encapsulation in Parkinson's disease :

Parkinsonian patients' striatal dopamine depletion is treated by implanting dopamine-secreting cells that have been enclosed in an immunoisolatory polymeric membrane which are directly into the corpus striatum. As a result, encapsulated cells' newly created dopamine can be sent right to the desired location. Dopamine diffuses into the surrounding tissue and passes through the membrane. The host tissue's reactivity to the immobilized cells in the lack of immunosuppressants, the encapsulated cells' sustained survival and functionality, and the efficiency of cell encapsulation therapy are considered as main obstacles to encapsulated cell therapy [47]. Encapsulated therapeutic cells when implanted into central nervous system, release incorporated immunomodulatory substance in a controlled manner [48].

X. CHALLENGES TO THE DEVELOPMENT OF CELL ENCAPSULATION THERAPY :

1. No reproducible results are observed in animal models. So, there is a requirement for biocompatible and reproducible materials that could fabricate immunocompatible devices using standardized technology.
2. Secretion of therapeutic products embedded in polymer matrix for a prolonged period is essential for cell encapsulation technology.
3. Survival of graft is not only influenced by the quality of biomaterials used, but also small fibrotic overgrowth is seen in capsules though purified polymers are used. The viability of cells encapsulated is polymer weight dependent.
4. Factors such as individual imperfections and microgeometry of encapsulation devices along with site of transplantation must be considered carefully.
5. Though xenogeneic cells are available widely due to the spread of animal viruses to humans, they are not used currently.[49]
6. A stepwise approach to dealing with these challenges might bring success to the field of cell encapsulation technology [1].

XI. FUTURE PERSPECTIVES OF CELL ENCAPSULATION TECHNOLOGY :

1. Cell encapsulation technology reports an ideal polymer with high resistance to osmotic swelling and good compatibility criteria.
2. Cancer is metastasized based on angiogenesis. This mechanism of cancer proliferation could be studied using cell encapsulation technology. In this aspect, endostatin and angiostatin secreting cells are used in cell encapsulation technology studies of cancer research.
3. A recent study on cell encapsulated cadherin and hybridoma cells showed positive results in inhibiting angiogenesis in vitro.
4. Using cell encapsulation technology, various cells such as cytochrome P450 enzyme, nitric

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oxide synthases and interlukin2 can be successfully applied for different treatments [49].

5. Optimized encapsulation decrease the chances of degradation and increase cell integrity in in vivo conditions [50].
6. Layer by layer cell encapsulation technology avoids damage of cells after transplantation [51].

XII. CONCLUSION :

Cell-based therapies using encapsulated producer cells can maintain high local tissue concentrations of medications with short biological half-lives by sustained release over an extended period. Such producer cells can also be genetically modified to secrete various chemicals. The systemic toxicity of the medications, the low encapsulation efficacy, and the high cost of the encapsulation production process are all drawbacks of the majority of these encapsulation techniques. Cell encapsulation offers a viable alternative for the in situ 689 delivery of biological substances, with the advantages of blood-brain barrier circumvention, long-term release of the therapeutically active chemical, and decreased adverse effects. Additionally, cell encapsulation enables the creation of customized therapies that can use patient-specific and combinatorial components based on the genetics of the malignancy. Recent evidence from the preclinical and clinical studies suggests that this strategy merits attention for the future treatment of brain tumours. Several encapsulation matrices may be taken into account.

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