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SMART HYDROGELS FOR ADVANCED DRUG DELIVERY

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ABSTRACT: Hydrogels are three-dimensional polymeric network structures having high water content. Stimuli-responsive or smart polymers are macromolecules that show a significant physiochemical change in response to small changes in their environment. These smart hydrogels with chemical and structurally responsive moieties show excellent characteristics of reacting under different environmental conditions such as temperature, pH, light, magnetic field, ionic factors, etc. These polymers have the ability to observe a change (stimulus) in their environment, respond to it immediately, and then return to their original shape/state when the stimulus is removed. Due to the high-water content of hydrogels and more similarity with biological tissues, hydrogels provide an ideal environment for cell survival, and structure which mimics the biological tissues. More water content, soft consistency and low interfacial tension with biological fluids makes them biocompatible. Due to their superior biocompatibility and low toxicity hydrogels have a significant role in the biomedical fields. In biomedical field, these super intelligent hydrogels have gained a significant interest in tissue engineering, drug delivery, diagnostics, imaging and optics. The purpose of this review is to elaborate properties of hydrogels, their classification and their biomedical applications.

INTRODUCTION: Polymers also known as macromolecules, are made up of several repeating subunits that, depending on how they are ordered and joined, can have a wide range of distinct properties [1].

Hydrogels: Three-dimensional networks made up of cross-linked hydrophilic polymers are known as hydrogels. Hydrogels can absorb vast amounts of water (or physiological fluids) that are about thousands of times their initial dry weight and form solid or semi-solid gel like structures. Physical or chemical interactions may be involved in the crosslinking of polymer chains.

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Transient crossings are typically the consequence of physical cross-linking, which can involve weak forces like ionic bonding, hydrogen bonding, or hydrophobic contacts, or chain entanglement. However, chemical cross-linking creates permanent connections by utilizing covalent bonds [2].

Left: Hydrogel in the unswollen or dry state. The polymer chains are in close proximity and may interact with each other. However, when fluid enters the hydrogel, the polymer chains undergo hydration that leads to swelling due to this hydrophobicor electrostatic interaction.

Lightgray arrows indicate pressure being exerted on the system that leads to the swelling.

Right: The hydrogel in the swollen or hydrated state where the polymer chains are fully extended and only the crosslinks prevent the material from dissolution.

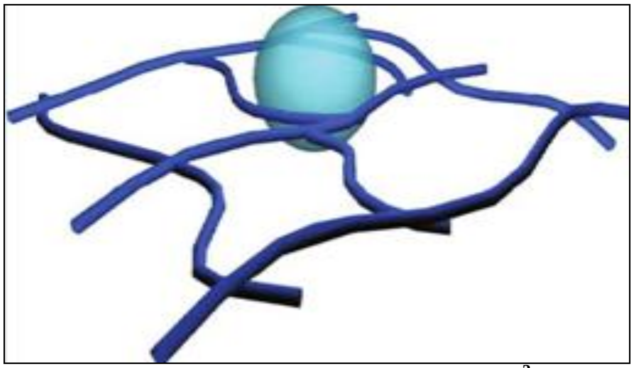

FIG. 1: HYDROGEL NETWORK [3]

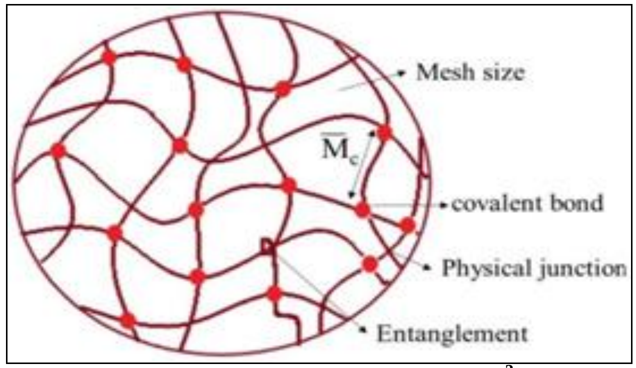

FIG. 2: STRUCTURE OF HYDROGEL [3]

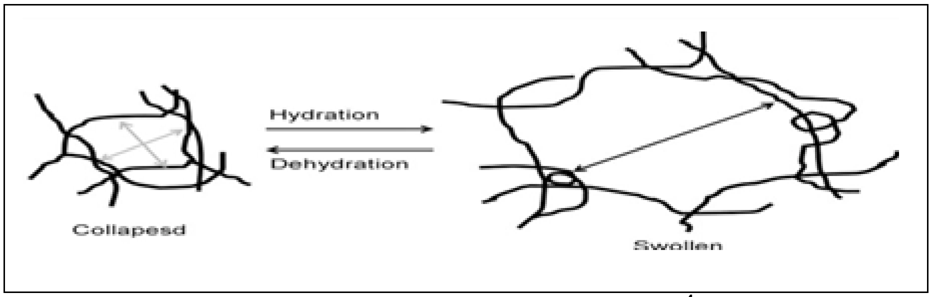

FIG. 3: SWELLING OF HYDROGEL [4]

Stimuli-responsive, Intelligent Polymers or Smart Polymers: The ability of polymers to swell and de-swell according to conditions makes them interesting for use as new intelligent materials. Polymers that change some of their properties upon the application of external stimuli are called 'smart' polymers [5]. External stimuli including pH, temperature, force, molecules, and magnetic/ electric fields can cause these polymers to alter their chemical or physical properties [1]. For instance, as the pH, ionic strength, or temperature changes, these polymers can show significant variations in their swelling behavior, sol-gel transition, network structure, permeability, or mechanical strength. Stimuli-responsive, intelligent polymers or smart polymers are one class of polymers that have recently attracted a lot of interest and study as they behave, smartly, in response to alterations in the environment.

Chemical stimuli include pH, ions, and particular molecule recognition events like glucose, whereas physical stimuli include temperature, electric and magnetic fields, and light. Certain hydrogels can also react to certain molecules, such as antigens and enzymes, which could cause a biochemical or biological reaction [6].

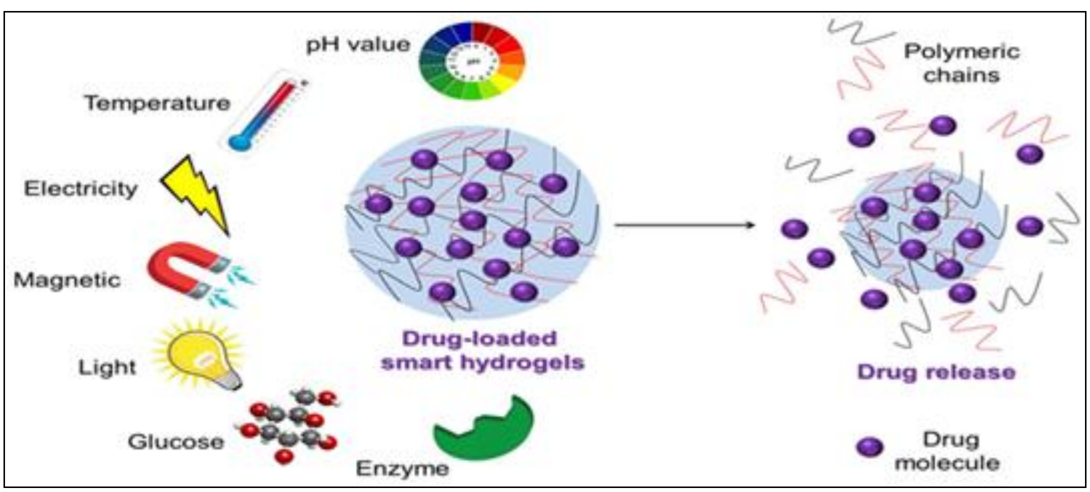

FIG. 4: VARIOUS EXTERNAL STIMULI, INCLUDING PH, TEMPERATURE, ELECTRICITY, MAGNETICS, LIGHT, AND BIOMOLECULES (INCLUDING GLUCOSE AND ENZYME), ARE CONTROLLING THE DRUG RELEASE FROM A SMART HYDROGEL [7]

Smart or stimuli-responsive hydrogels are flexible and adaptive polymers as these are able to detect changes in their surroundings and react by causing structural alterations (raising or reducing their degree of swelling) without the need for an outside driving force. The ability of these "volume-changing" phenomena to initiate medication release in response to environmental changes makes it very helpful in drug delivery applications. For the creation of self-regulated drug delivery systems with improved therapeutic efficacy, smart hydrogels become excellent candidates [4].

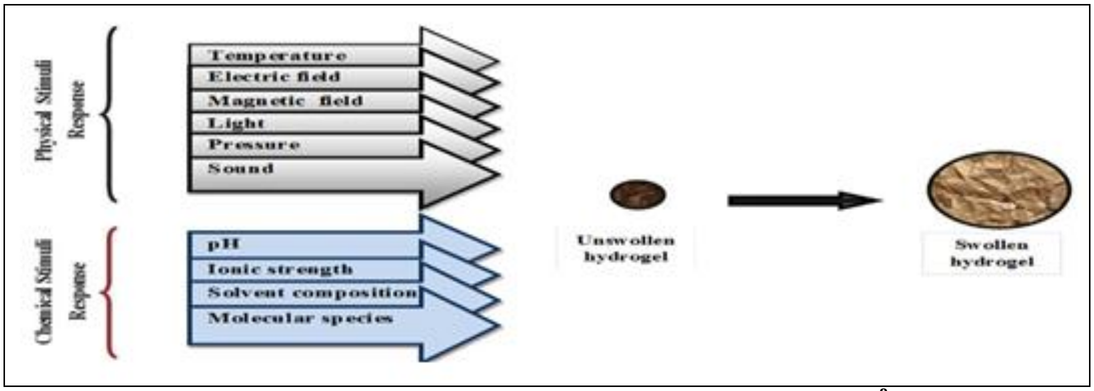

FIG. 5: STIMULI RESPONSE SWELLING HYDROGEL [8]

Classification of Smart Hydrogels: Based on the kinds of stimuli to which they respond, smart hydrogels can be categorized. Some smart hydrogels are those that react to chemical stimuli like pH, ionic factors, and chemical agents; biomolecule stimuli like glucose, antigen, enzyme, and ligand; and physical stimuli like temperature, light, pressure, magnetic, and electric fields. These hydrogels are explained below.

Physical Stimuli:

Temperature Sensitive Hydrogels: Under normal conditions, temperature of the human body is 37°C. However, under certain pathological conditions or in the presence of pyrogens, the body temperature deviates from normal. This variation in body temperature is utilized as a stimulus for the delivery of drugs from thermo-responsive delivery systems [9]. Due to changes in the surrounding fluid's temperature polymers swell or de-swell in response to that. Temperature-sensitive hydrogels are most likely stimuli-sensitive polymers that have been thoroughly studied in drug delivery research.

There are two Varieties of Reversible Gels: negatively and positively thermo-sensitive. Critical solution temperature is the measure of this type of smart hydrogels. Because of the hydrogen bonding between the polymers and the water molecules, negative thermo-sensitive hydrogels have a lower critical solution temperature below which the polymers expand in the solution, and beyond it, they contract because of the dominance of entropy. Aggregation eventually occurs when heat agitation breaks hydrogen bonds, which causes the thermo-sensitive hydrogels to shrink as the temperature rises. Hydrogels that are sensitive to positive temperature have an upper critical solution temperature, and they contract below it [10].

Positively Thermo-sensitive or UCST (Upper Critical Solution Temperature): Below this temperature, the hydrogels shrink and release solvents from the matrix because the hydrogen bonds form a complex structure, and above UCST, the hydrogel network swells as a result of the structure dissociating and the hydrogen bonds breaking [5].

Negatively Thermo-Sensitive or LCST (Lower Critical Solution Temperature): Because negative temperature hydrogels have a lower critical solution temperature (LCST), they will swell at temperatures below this critical temperature and shrink at temperatures above it. The most crucial factor for negative temperature-responsive hydrogels, LCST, can be altered by a variety of process parameters, including mixing with ionic copolymers or altering the solvent's composition [5].

Therapeutics for cancer has also focused on thermoresponsive drug delivery devices. Numerous thermosensitive polymers have been used in thermoresponsive systems. When added to the formulation in solution form, these polymers allow the solution to undergo a reversible, temperature-induced gel-sol transition when the solution is heated or cooled [11].

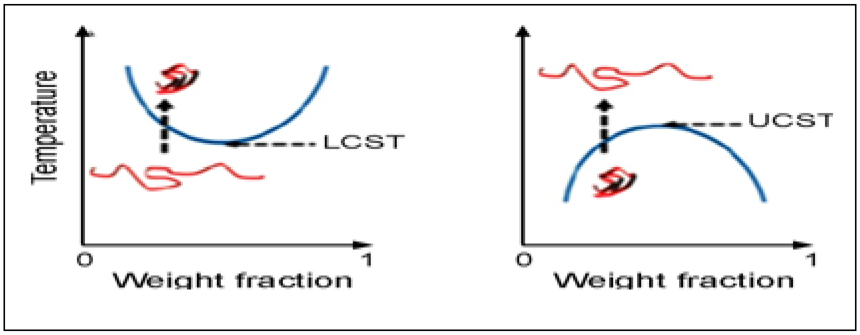

FIG. 6: SCHEMATIC SHOWING PHASE TRANSITION ASSOCIATED WITH LCST AND UCST [5]

Photo-Light Responsive Hydrogels: Hydrogels that respond to light are called light-responsive hydrogels. They consist of a photoreceptive moiety as the functional component and a polymeric network. Their physical and chemical characteristics vary as they are stimulated by light. The photochromic molecules initially absorb the optical signal and use a photoreaction that includes isomerization (cis-trans, open-close), cleavage, and dimerization to transform the photoirradiation into a chemical signal. The hydrogel's functional portion receives the latter signal, which regulates its characteristics [12]. The ability to accurately and rapidly impose a light stimulus is one of the advantages of photo-responsive hydrogels.

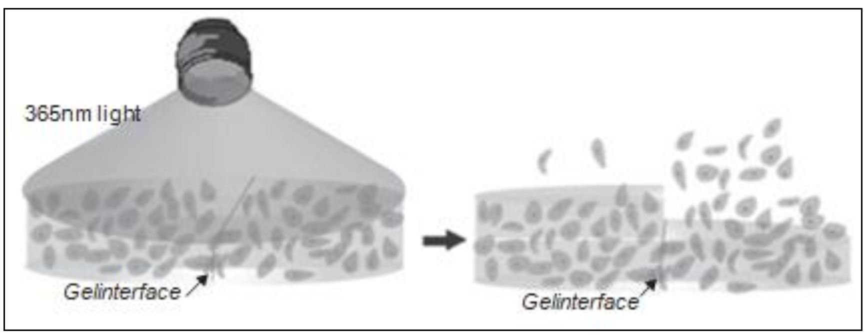

FIG. 7: PHOTOSENSITIVE RELEASE OF ENCAPSULATED RET FUSED GENE (RFG-) OR GFP-EXPRESSING HMSCS

Pressure Sensitive Hydrogels: Depending on the uncharged hydrogel theory of thermodynamic calculations, certain of the hydrogels might experience a pressure-induced volume phase shift. This theory states that hydrogels expand at high pressure and collapse at low pressure. When the temperature approaches its critical solution temperature, the poly (N-isopropyl acrylamide) hydrogels swell under static pressure. The low critical solution temperature value of temperature-sensitive gels appears to rise with pressure, which is the reason for the pressure sensitivity, which seems to be a common feature of these gels.

Electric Signal Sensitive and Magnetic Responsive Hydrogels: Small variations in electric current stimuli or external fields cause hydrogels that are responsive to electric and magnetic fields to alter their characteristics. These systems have been studied as a kind of hydrogel that may bend, swell, or shrink. These hydrogels have generally been investigated as polyelectrolyte hydrogels, which are systems with a high ionizable concentration.

Electroactive hydrogels have been created using synthetic polymers such as sulfonated polystyrene, acrylic acid/vinyl sulfonic acid, and polyvinyl alcohol. Additionally, naturally occurring polymers are frequently used to create materials that are magnetically and electrically sensitive [6]. For instance, to create these hydrogels, synthetic polymers have been combined with alginate, hyaluronic acid, and chitosan.

Ultrasound-Responsive Polymers: The term "ultrasound" refers to a wave produced by alternating current that is produced when a piezoelectric material vibrates mechanically. There are three types of waves based on frequency: low (less than 1 MHz), medium (1–5 MHz), and high (5–10 MHz). The substance may be impacted by ultrasounds in the following ways: (a) thermal, in which a rise in temperature is noted; (b) non-thermal, or cavitation, in which gas bubbles is created by ultrasonic vibrations.

Chemical Stimuli:

pH Sensitive Smart Polymers: Significant pH variations in the human body can be used to target therapeutic medicines to a particular tissue, cell compartment, or body portion. These factors make pH-sensitive polymers the best pharmaceutical systems for targeted therapeutic agent delivery. The ability to receive or release protons in response to pH variations is the primary characteristic of ionic pH-sensitive polymers. These polymers have either basic (ammonium salts) or acidic (carboxylic or sulphonic) groups in their structure. Stated differently, pH-sensitive polymers are polyelectrolytes with basic or acidic groups in their structure that can take up or release protons in reaction to variations in the surrounding environment's pH. One of the most widely used triggers for drug release among many stimuli is pH. The traditional pH-responsive carriers are predicated on the fact that the pH values of several organs, including the stomach (pH≈2) and intestinal system (pH≈7), vary significantly.

Several pH-responsive polymers, including DNA, chitosan, and poly (methacrylic acid) (PMAA), have been extensively recommended and used for local controlled drug delivery system. When pH changes after the disease's occurrence, the hydrogels can triggers disease-controlled medication release. Hydrogels undergo a gel–sol conversion when their pH changes, which is advantageous for drug encapsulation while the gel is in place and for the efficient removal of frameworks following hydrogel degradation.

Because of the numerous ionic groups in their networks, a number of natural polymers, including cellulose, hyaluronic acid, guar gum, and chitosan, have been used to create pH-responsive hydrogels [13].

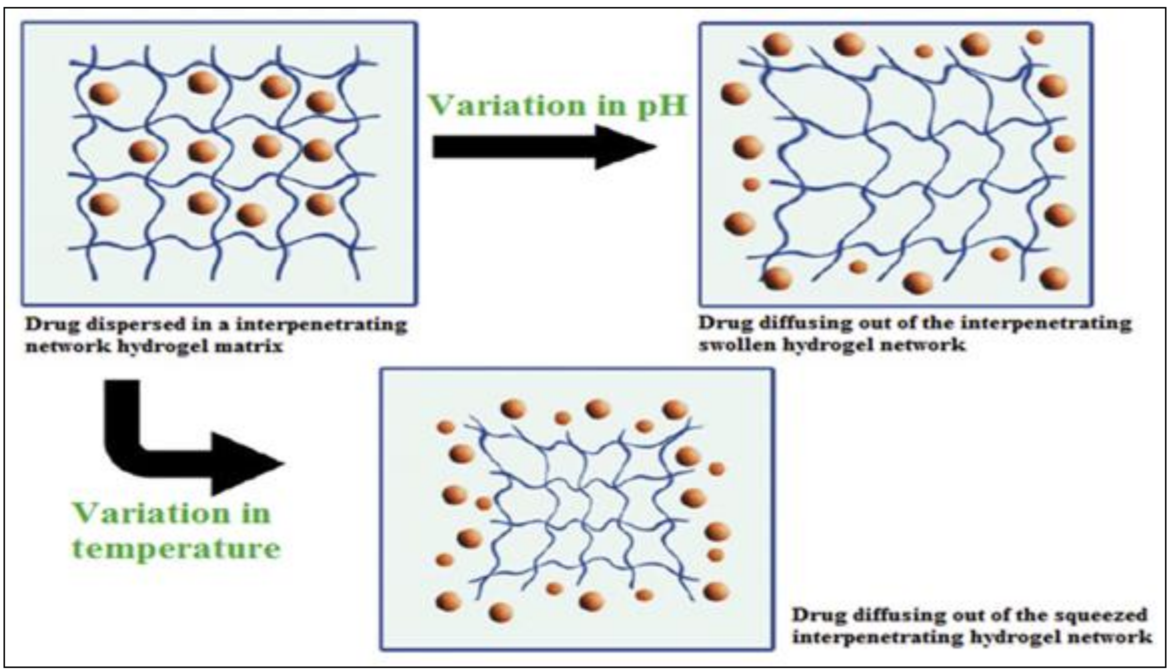

FIG. 8: A SIMPLIFIED CONCEPT OF DRUG DELIVERY BY HYDROGEL THROUGH THE CHANGE IN TEMPERATURE AND PH [14]

Glucose Responsive Hydrogels: Since, glucose-sensitive hydrogels are excellent candidates for creating insulin delivery systems that can function as an artificial pancreas to precisely distribute insulin in response to blood glucose levels. In glucose oxidase (GOD) responsive insulin delivery, the enzyme (GOD) is usually immobilized on the pH sensitive polymer with insulin. When glucose diffuses inside the gel, glucose gets enzymatically converted into gluconic acid, which leads to decrease in pH, and the polymer becomes charged due to the protonation of amino groups. The hydrogel swells, facilitating the release of insulin by the diffusion mediated process.

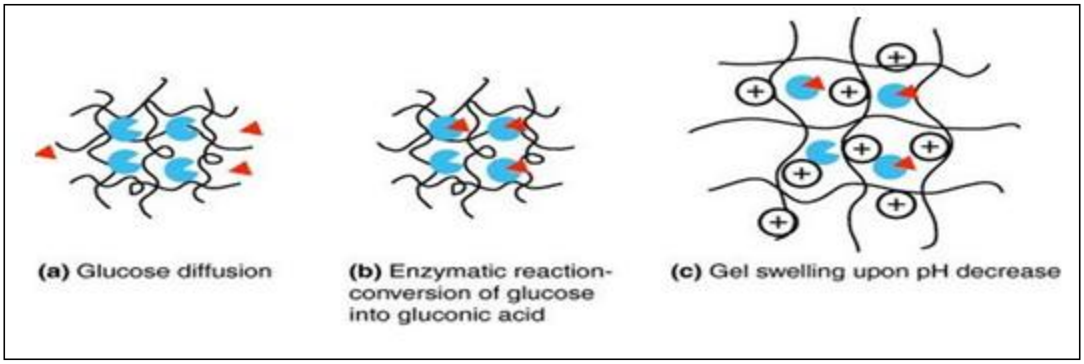

FIG. 9: SCHEMATIC REPRESENTATION OF pH-RESPONSIVE HYDROGEL WITH ENTRAPPED GOD

Application of Smart Hydrogels:

Smart Hydrogels for Drug Delivery: In practical practice, hydrogel drug delivery systems can be therapeutically useful. The absorption of various drugs for treatment can be controlled both spatially and temporally. In addition to having the drawbacks of toxicity and adverse effects, conventional drug use requires large dosages or repeated administrations to achieve a therapeutic impact. Because the mechanical and physical characteristics of the hydrogels can be adjusted. So, cross-linking a smart polymer createa gel which causes the gel to collapse and then re-swell in water when a stimulus causes it to rise or fall through its critical condition. When a drug is placed into the gel, it may explode out when the gel collapses. Hoffman and colleagues trapped cells and enzymes in smart gels, which allowed them to be turned "on" and "off" by causing the gel to inflate and collapse repeatedly.

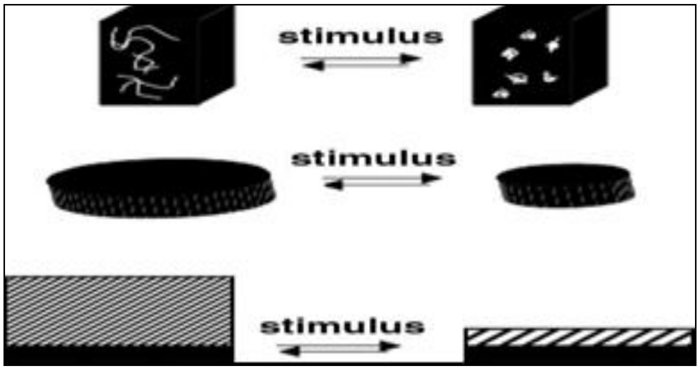

FIG. 10: COLLAPSE/EXPANSION OF A POLYMER CHAIN, A BULK HYDROGEL OR A SURFACE-IMMOBILISED HYDROGEL AS RESPONSE TO AN EXTERNAL STIMULUS

Skin Tissue Engineering: Because of their special blend of biological and physical characteristics, such as their biocompatibility and biomimetic nature, on-site cross-linking abilities, and adjustable mechanical, swelling, and degradation properties, hydrogels are regarded as appropriate and ideal materials for epidermal tissue engineering and skin regeneration.

Hydrogel scaffolds act as matrices or scaffolds that trap cells, enabling them to multiply and expand, ultimately repairing the damaged tissue.

The presence of physiologically active substances promotes migration and cell adhesion. The fundamental reason for the development of this hydrogel application in skin tissue engineering is the problems with auto-grafts and allografts, where the donor site experiences pain, repeated infections, and long-term scarring.

The availability of autologous skin is a major limiting factor in the healing of wounds, particularly burns, where tissue-engineered skin transplants have found.

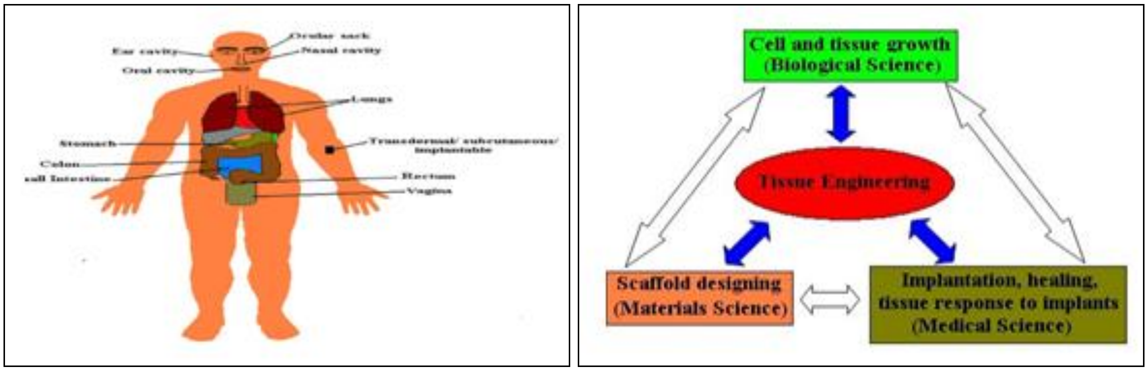

FIG. 11: MULTIDISCIPLINARY APPROACH OF TISSUE ENGINEERING

Smart Hydrogels for 3D Bio-printing: Functional 3D tissues can be bio-printed using a powerful mix of 3D printing and smart hydrogels. Hydrogel serves as a matrix in bio-printing, supporting and controlling the cells enclosed therein. Currently, hydrogel contraction and deformation caused by cellular events like migration, proliferation, and traction, as well as cellular concentration and dispersion, are evaluated using computer models. The special capacity of the smart hydrogel to respond to a stimulus will likewise affect the cells that are enclosed within it. Time is another crucial element in comprehending the dynamic cell–material interaction because hydrogels' characteristics vary over time and are thought to be crucial in predicting cell fate and tissue regeneration modeling in a quasi-static condition.

Wound Dressing: Hydrogels have capability of stimulation the regeneration of skin. It can be loaded with drug which is responsible for the treatment of wound. Hydrogel materials have been applied directly to human tissues, absorbing exudate to create a gel that successfully stops bodily fluid loss and does not stick to the wound once it has been absorbed. Hydrogels can also provide oxygen to the wound, which speeds up the development of new capillaries and epithelial cells. They can also shield the wound from bacterial invasions, which prevents bacterial growth and promotes wound healing overall.

FIG. 12: USE OF HYDROGELS IN WOUND DRESSING [15]

Diagnostics and Imaging: Hydrogels' excellent structural characteristics, high water content, fluidic transport capabilities, and bio-congeniality have made them appropriate for a range of contrast agents and imaging probes. The insertion or conjugation of various dyes, reporter molecules, or inorganic nanoparticles is made possible by the addition of multifunctional groups to the hydrogels' interior or exterior. Iron oxide and other magnetic particles can be embedded within cross-linked nanogels to improve their colloidal stability and sensitivity compared to using them as non-enclosed entities.

Optics: Soft contact lenses with HEMA or NVP and various monomers are big enough to cover the entire cornea and have the right amount of oxygen permeability to give users more convenience. When fully hydrated, PHEMA contact lenses contain about 38–40% water. For a hydrogel to be used as a biomaterial in the manufacturing of contact lenses, it needs to have certain notable physical characteristics. Luminous transmittance, refractive index, enough oxygen permeability, wettability, stability, excellent mechanical qualities, and biocompatibility are all ideal characteristics.

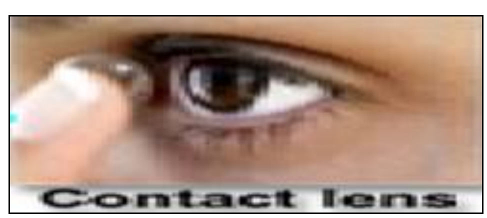

FIG. 13: USE OF HYDROGELS IN CONTACT LENS [15]

Transdermal Drug Delivery: To administer medication via the transdermal route, several hydrogel-based drug delivery devices have been developed. Formulations based on hydrogel are being investigated for transdermal iontophoresis in order to achieve improved product penetration, specifically for nicotine and hormones.

Other Hydrogels Applications:

Watering Beads for Plants: Basic hydrogel applications include coarse polyacrylamide or potassium polyacrylate matrix powders that are marketed under a variety of names, including Plant-Gel, Super Crystals, and Water-Gel Crystals. These products are used as long-term water reservoirs for plant growth in gardening, home, and occasionally commercial horticulture. Chalker-Scott of Washington State University noted in her publications on the subject that the potential risks of using the widely used watering crystals are significantly greater than the advantages of water storage and controlled release, which can also be obtained in many other ways with less of an impact on the environment, because they are made of non-renewable materials whose monomers can be toxic (such as acrylamide).

Diapers: Intriguingly, the thermodynamic affinity of hydrogel for water can be used to create super-adsorbed diapers that remain dry even after a significant amount of moisture has been adsorbent. Over the past 20 years, the development of diapers that contain hydrogel the majority of which are loaded with various sodium polyacrylate formulations has reduced the incidence of numerous dermatological diseases linked to extended contact with moist tissues.

Perfume Delivery: Patents detailing technologies for delivering volatile species began to increase in quantity in the 1990s. When it comes to turning perfumes into cyclodextrin complexes, Procter & Gamble appears to have released the most important patented inventions in the sector.

The overall objective was to create gadgets that could gradually release scents into the environment over time and swap out the traditional salt-based (sodium dodecyl benzene sulphonate) tablets for new, more useful, and, let's face it, more upscale, household cleaning products. Again, the key to the process is the ability of hydrogels to expand, which can be used in materials "wherein the release of a perfume smell is triggered by dynamic swelling force of the polymer when the polymer is wetted."

Cosmetics: Businesses can introduce novel cosmetic items based on hydrogels, including so-called "beauty masks," to the market since they can be made with a comparatively modest investment. Most often composed of hyaluronic acid (SEPHORA USA Inc.), polyvinyl pyrrolidone (Pecogel), or engineered collagen (Masqueology by SEPHORA USA Inc., BioCollagen Cosmeceuticals by NOVOSTRATA UK Ltd.), these masks promise to moisturize the skin, restore its suppleness, and encourage anti-aging effects. Pecogels work well for cosmetic applications like mascara and sunscreen cream. Furthermore, the moisturizing properties of these organic polymeric gels are combined with more sophisticated drug-delivery systems designed to release biomolecules like vitamin C or B3 in certain commercially accessible products, such as Fruit & Passion Boutiques Inc.'s Hydro Gel Face Masks.

The cosmetics industry is at the forefront of hydrogels; in fact, a pH-sensitive material P (MAA-co-EGMA) has been created for the release of cosmetic medications like as niacinamide, arbutin, and adenosine, which are well-known compounds for skin-whitening and wrinkle treatment.

Plastic Surgery: Because of their extracellular matrix-like characteristics, hydrogels were thought to be suitable materials for usage in interaction with the human body. Attempts to introduce hydrogels as new materials for plastic repair were done primarily for this reason. For many years along this path, hyaluronic acid (HA) was believed to be the solution to all problems. Macrolane is one well-known business in the industry. Beginning in 2008, Macrolane's products and procedures were especially researched to improve breast form and size and provide a more biocompatible substitute for aggressive and conventional silicone prostheses. With the exception of breasts, macrolane is now used for fillings in a variety of locations. Using a syringe, the substance is injected into the body, where it gels to restore volume. Hydrogels also show promise as bulking agents for urinary incontinence treatment. Smart injectable gels can be utilized in clinical procedures to constrict the urethral channel and lessen incontinence in patients.

Current Research on Hydrogels:

Water Purification: According to a water purification invention, it may soon be possible to produce safe, clean drinking water using only natural sunlight and low-cost gel technology. Using hybrid materials of gel polymers, engineers have created a technique that is both compact and economical. These "hydrogels," which are networks of polymer chains with high water absorbency, have both hydrophilic (attraction to water) and semiconducting (solar-adsorbing) properties. This allows for the production of safe, clean drinking water from any source, including contaminated supplies and the ocean. A new hydrogel-based solar vapor generator has been created by Texas Engineering researchers, which uses ambient solar energy to power water evaporation for efficient desalination.

The current methods of treating seawater via solar steaming are quite expensive and rely on optical devices to focus sunlight. The UT Austin team created nanostructured gels that can greatly increase the amount of water that can evaporate while using much less energy they only need naturally occurring levels of ambient sunlight to function. "Water desalination through distillation is a common method for mass production of freshwater," the team said. The hydrogels enable water vapor to be produced in direct sunlight and then piped to a condenser for freshwater delivery, but existing distillation processes, such multi-stage flash and multi-effect distillation, require substantial infrastructure and are highly energy-intensive. Even when tested on water samples from the salty Dead Sea, these hydrogels' desalinating capabilities performed flawlessly. Engineers at UT were able to considerably lower the salinity of Dead Sea water samples by using the hydrogel method to samples from one of the saltiest bodies of water on the planet.

Peptide Hydrogel Promotes Tissue Growth to Heal without Drugs: Various medications, proteins, and cells embedded in peptide hydrogel can accelerate tissue creation and healing, and found that hydrogel itself has potent therapeutic qualities. They can inject its self-assembling multi-domain peptide (MDP), which has the amino acid sequence K2(SL)6K2, into tissue to create a space for new cells to grow. Over the course of a few weeks, the body will wash it out. The rice team's research revealed some unexpected results, including the hydrogel's ability to attract nerve fibers, encourage the growth of new blood vessels, invite host cells, and trigger a transient inflammatory reaction. The peptide hydrogel's physical shape and chemical makeup influence its bioactive qualities.

Hydrogel Based Capsule May Help Patient Adhere To Medication: Ultra-log acting capsules, a novel kind of drug administration that releases medication gradually over a period of nine days while residing in the stomach. These capsules may be taken once weekly or once monthly, depending on the device, or they may be used for the duration of the treatment. Creating capsules that can stay in the gastrointestinal tract for extended periods of time rather than quickly passing through the body is a difficult challenge since many materials need to be able to survive the significant force in the stomach.

The patient could swallow hydrated hydrogel capsules, which would swell in the stomach and block passage through the pylorus. However, hydrogel, which is usually made up of a single network of crosslinking polymer chains, is quite soft and lacks the strength to withstand compressive forces.

New Stimuli Responsive Smart Hydrogels Open Door to Future Material Biology and Biomedical Applications: In the medical field, hydrogels also referred to as soft matter are essential materials for biological applications such stem cell treatment and medication administration. However, conventional hydrogels, which are composed of either synthetic polymers or biological extracts like animal collagen and are utilized in items like contact lenses and face masks, are likely to trigger allergic reactions. The intricate biological environment required for cell growth and development is too complex for them to accurately replicate. The team stitched together the photoreceptor C-terminal adenosylcobalamin binding domain (CarHC) proteins at room temperature to assemble genetically modified proteins into molecular networks to produce this new hydrogel. The only method used in the synthesis is bacterial culture, which is comparable to fermentation.

Multiamine Induced Self-Healing Poly (Acrylic Acid) Hydrogels with Shape Memory Behavior: This study reports a flexible and straightforward method for creating self-healing hydrogels with adjustable mechanical characteristics and shape memory behavior. Poly (acrylic acid) (PAAc) chains are crosslinked by ionic bonding using diethylenetriamine (DETA), a commercially available small molecule with three amino groups. The complexes of the PAAc chains with DETA create hydrophobic micro-domains in the hydrogel network. The molar ratio of PAAc to DETA can be changed to modify the mechanical properties, which are significantly improved by the collaboration of ionic bonding and hydrophobic contacts. In ambient settings, the hydrogels can self-heal quickly because of the crosslinks' physical contact. The hydrogels exhibit shape memory behavior due to crosslinking caused by the physical micro-domain's heat reactivity. It is anticipated that this innovative approach will open up new possibilities for the development of high-strength hydrogels with a variety of functions for a broad range of uses, including synthetic skin and muscle.

Newly Developed Hydrogels May Pave Way for Novel Eye Surgery Techniques: New methods of eye surgery may be made possible by recently produced elastic gel that is injected into rabbits' eyes as a liquid shoe to tern jelly-like within minutes after replacing the clear gelatinous fluid inside the eyeballs.

CONCLUSION: Smart hydrogels are an interesting class of materials that are used in diverse applications which have the ability to respond to various kinds of physical, chemicalor biochemical stimuli. Hydrogel based delivery devices can be used for oral, ocular, epidermal, subcutaneous application due to their high-water contents and soft consistency hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. Despite unique characteristics, some hydrogels are currently facing with a few challenges which need to be solved**.**

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