Universidade de Lisboa

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An overview on polymeric hydrogels used on pharmaceutical applications

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Monografia orientada pela Professora Doutora Isabel Alexandra Caldeira Ribeiro Monge da Silva, Professora Auxiliar

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Abstract

Products referred to as "hydrogels" are a class of polymeric materials that can hold a substantial amount of water in their three-dimensional networks, without dissolving in it, due to their hydrophilic nature. The presence of ionic interaction and hydrogen bonding facilitates this insolubility in water by granting the hydrogels the required mechanical strength and physical integrity. Their high-water content gives them a physical resemblance to tissues, great biocompatibility, and the capacity to quickly encapsulate hydrophilic medicines.

Drug delivery, food additives, biomedical implants and devices, tissue engineering, regenerative therapies, as well as cellular immobility or cell encapsulation are just a few of the many uses for hydrogels.

Substantial innovation has been accomplished in the field of hydrogels during the last few decades, with hydrogels being denoted by their responsiveness to external stimuli, such as pH, temperature, electrical, light, and magnetic field. This has led to their increased adoption in pharmaceutical uses. Current research is resulting in the development of therapeutic strategies for different types of cancer, with hydrogels proving to be an important type of drug delivery system to explore in this field. Furthermore, research is being done in novel materials, with nanogels, microgels and 3D printed hydrogels increasingly being used in a wide range of applications.

In view of this, the purpose of this dissertation is to offer a contemporary assessment of hydrogels, with a special emphasis on their applications in healthcare, such as drug delivery, taking into consideration the more novel approaches in the field, namely nanogels, microgels, and 3D printed hydrogels. It will also establish key categorisation criteria and explain existing preparation techniques.

Several research papers were analysed in order to get a detailed and broad view of the field. By reviewing these, this thesis will provide a clear overview of hydrogels and their uses in the pharmaceutical field.

Keywords: Hydrogels; Classification; Drug Delivery; Stimuli-Responsive

Resumo

Os hidrogeles são uma classe de materiais poliméricos que podem reter uma quantidade substancial de água na sua estrutura tridimensional sem se dissolverem nela, devido à sua natureza hidrofílica. A presença de interação iónica e ligações de hidrogénio facilita esta insolubilidade em água, conferindo aos hidrogeles a resistência mecânica e a integridade física necessárias. O seu alto teor de água confere-lhes semelhança física com os tecidos, grande biocompatibilidade e capacidade de incorporar rapidamente fármacos hidrofílicos.

Sistemas de libertação de fármacos, aditivos alimentares, implantes e dispositivos biomédicos, engenharia de tecidos, terapias regenerativas, bem como imobilização ou encapsulamento celular são apenas alguns dos muitos usos dos hidrogeles.

Nas últimas décadas verificou-se uma inovação substancial no campo dos hidrogeles, com estes a serem caracterizados pela sua capacidade de resposta a estímulos externos, como pH, temperatura, luz, campo elétrico e magnético, o que levou ao aumento das suas aplicações no campo farmacêutico. A recente investigação nesta área tem resultado no desenvolvimento de estratégias terapêuticas para diferentes tipos de cancro, com os hidrogeles a mostrarem ser um importante tipo de sistema de libertação de fármacos a ser explorado. Além disso, novos materiais com nanogeles, microgeles e hidrogeles impressos em 3D estão a ser objeto de artigos de investigação, sendo cada vez mais usados numa ampla gama de aplicações.

Nesta perspetiva, o objetivo desta dissertação é o de oferecer uma revisão atual dos hidrogeles, com ênfase especial nas suas aplicações na área da saúde, designadamente em sistemas de libertação de fármacos, levando em consideração as abordagens mais inovadoras na área, como nanogeles, microgeles e hidrogeles impressos em 3D. Para além disso, estabelece-se critérios-chave de categorização dos hidrogeles e descreve-se as técnicas de preparação existentes.

Foram analisados vários estudos de investigação para obter uma visão detalhada e ampla do campo. Ao fazer a sua revisão, esta tese providenciará uma visão clara sobre os hidrogeles e seus usos no campo farmacêutico.

Palavras-chave: Hidrogeles; Classificação; Sistemas de libertação de fármacos; Responsivo a Estímulos

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Abbreviations

3D	Three-dimensional
3TC	Lamivudine
5-FU	5-Fluorouracil
AA	Acrylic acid
AIDS	Acquired immunodeficiency syndrome
ALG	Alginate
AUL	Absorption under load
AZT	Zidovudine
BEV	Bevacizumab
ChS	Chondroitin sulphate
CMc	Carboxymethylated curdlan
CMC	Carboxymethylated cellulose
CNS	Central nervous system
CPHs	Conducting polymer hydrogels
DNA	Deoxyribonucleic acid
EGCGs	Epigallocatechin gallates
EMA	European Medicines Agency
Europe PMC	Europe PubMed Central
FDA	Food and Drug Administration
HA	Hyaluronic acid
HA-E	EGCG conjugated hyaluronic acids
HA-T	Tyramine conjugated hyaluronic acids
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose

LBG	Locust bean gum
MDPI	Multidisciplinary Digital Publishing Institute
MDs	Maltodextrins
NCC-3TC-AZT	Nano co-crystal of Lamivudine and Zidovudine
NP	Nanoparticles
NPCs	Neural progenitor cells
O/W	Oil-in-water
PA	Polyacrylamide
PANii	Polyaniline
PBH	Protein-based hydrogels
PEG	Polyethylene glycol
PLA	Polylactide
PNIPAAm	Poly(*N*-isopropylacrylamide)
PPy	Polypyrrole
PSB	(Polysaccharide-based) natural hydrogels
PTh	Polythiophene
PVA	Poly(vinyl alcohol)
PVME	Poly(vinylmethylether)
PVP	Poly(*N*-vinylpyrrolidone)
RNA	Ribonucleic acid
SA_Ty	Tyrosinase isolated from Streptomyces avermitillis
SAPs	Superabsorbent polymers
SPHs	Superporous hydrogels
SPIE	Society of Photo-Optical Instrumentation Engineers
T2DM	Type 2 diabetic mice

TPT-SLNs-TRHS	Thermoresponsive hydrogel technology with solid lipid nanoparticles
TTH	Triggerable tough hydrogels
UV	Ultraviolet
VSNPs	Vinyl silica nanoparticles
W/O	Water-in-oil

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1 Introduction

There are numerous drug delivery systems each with their own advantages and disadvantages, ranging from the more conventional, like tablets, syrups, and ointments, to more novel approaches, like liposomes, nanoparticles and microemulsions (1). One drug delivery approach that has been gaining prevalence in the recent decades is hydrogels.

Gels are an intermediate state of matter between solid and liquid states and an important class of soft matter. These consist of a porous three-dimensional network of cross-linked polymer chains, that allows them to trap enormous volumes of solvent.

Classification of gels depends on the nature of the solvent trapped in their structure. Gels in which the space between macromolecules is filled by water are known as hydrogels (2–4).

Hydrogels are defined as polymeric systems with the capability of swelling in water and retaining a significant fraction (>20%) trapped in its structure, without dissolving in water. This insolubility in water is facilitated by the existence of ionic interaction and hydrogen bonding, providing the necessary mechanical strength, as well as physical integrity to the hydrogels (4,5). This water absorbing behaviour occurs primarily due to the existence of hydrophilic groups, such as -OH, -COOH, -CONH, -$CONH_2$ and -SO_3H, in the polymer chain (6). Due to their high-water content, hydrogels have a physical likeness to tissues, can have good biocompatibility and the capacity to efficiently encapsulate hydrophilic medicines. Furthermore, because they are usually produced in aqueous solutions, the danger of drug denaturation and aggregation when exposed to organic solvents is reduced (7).

Hydrogels have a wide range of applications, including food additives, pharmaceuticals, biomedical implants and devices, tissue engineering and regenerative medicines, as well as cellular immobility or cell encapsulation. Their uses encompass diverse fields, such as artificial muscle development, controlled drug delivery, biosensors, wound dressings, contact lenses, and super-absorbents (4).

In recent years, literature on this subject has become more prevalent, particularly in the pharmaceutical and biomedical fields. Most of the publications found are under the

scope of specific applications, in which hydrogels could be readily applied to medical treatment.

Recent reviews on hydrogels address different approaches to classification, specific preparation methods and focus on reviewing recent developments across a range of application fields, both medical and non-medical (2–4,8).

Since a great deal of new research is being done on hydrogels, in recent years, many reviews can be out of date, especially those published before 2017. In addition to this, most of the reviews are limited in scope, choosing to discuss hydrogels in very specific contexts and not necessarily focused on pharmaceutical applications.

This thesis intends to provide an up-to-date review on hydrogels focusing particularly on their applications in the medical field, such as drug delivery, and to explore the most recent approaches being developed in the field with nanogels, microgels and 3D printed hydrogels. Moreover, it will outline relevant classification criteria and explain existing preparation methods, giving examples of their use.

By doing this, this paper aims to increase accessibility on the subject of hydrogels for researchers and other medical professionals, in order to speed up their own research and ultimately improve treatment.

It will first address hydrogel classification based on different criteria, providing context and examples for each. It will then cover hydrogel structure, discussing two of the most widely used models behind the hydrogel swelling mechanism. There will be a section on hydrogel preparation technologies. Followed by one on drug delivery applications, focusing on tissue locations suitable for hydrogel-based drug delivery systems and on stimuli-responsive hydrogels, an interesting approach to specific pharmaceutical needs. It will then proceed to discuss nanogels and microgels. Finally, 3D printed hydrogels will be addressed.

2 Methodology

To carry out this work, a literature review was conducted through a search in the following databases - PubMed, Wiley Online Library, Science Direct, American Chemical Society Publications, Europe PMC, Springer Link, Research Gate, SPIE Digital Library, Multidisciplinary Digital Publishing Institute (MDPI) - which was carried out between January and October 2022. This search was made employing the following keywords “hydrogel”, “pharmaceutical application”, “classification”, “structure”, “administration routes”, “3D printing”, “preparation”, “nanogels”, “microgels” and “stimuli-responsive”, combined according to the chapter in question.

The bibliographic research carried out was based on two main inclusion and exclusion criteria. First, articles published after the year 2012 were given preference on being considered for literature review. Secondly, review articles, book chapter, mini reviews and research articles that include *in vitro, in vivo,* and human studies published in English were preferred.

3 Hydrogels Classification

The hydrogel products can be classified using a variety of criteria. Namely their origin, physical state, cross-linking type - which can be physical or chemical - but also on network electrical charge and on degradability - meaning whether hydrogels are biodegradable or non-biodegradable.

Different classifications are used depending on context, as one method might be more useful than others. For instance, in manufacturing, source and cross-linking type are more relevant as they describe the way in which hydrogels are made, whereas for administration it might be more useful to know the physical state of a hydrogel to know how to administer it to the patient.

The previously mentioned criteria will be addressed in this section.

3.1 Classification based on source

In relation to their source, hydrogels can be divided into two groups based on their natural or synthetic origins (2,9,10). Figure 1 depicts a classification of hydrogels based on their origin (6).

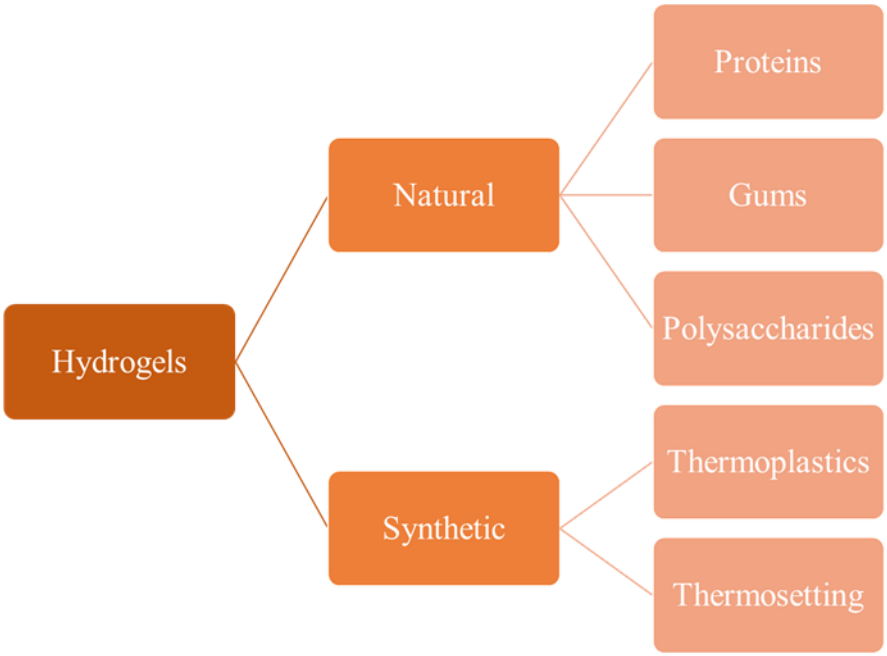

Figure 1: Classification of Hydrogels Based on Origin

Some examples of natural polymers are gelatine, alginate (ALG), chitosan, silk fibroin, collagen II, agarose, and hyaluronic acid (HA). These can be proteins, gums, or polysaccharides and are mostly biocompatible, reducing stimulation of inflammatory and immunological responses of the host tissues. On the other hand, these will generally have poor strength and toughness, not meeting clinical requirements (11).

There are also synthetic polymers which provide numerous advantages, including large water absorption capacities, as well as reasonable gel strength and cost (4,12). Synthetic polymers include polyacrylamide (PA), poly(*N*-isopropylacrylamide) (PNIPAAm), sodium polyacrylate, poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA). They can be subdivided into thermoplastics and thermosetting, often called thermoset. The two have different characteristics, which are detailed in Table 1 (13). Some examples of thermoplastics are polyolefins, polyvinyl chloride, styrenics, acrylics, as well as polycarbonate, polyesters, polyamides, polyethers, polyurethanes, polysulfones and polyimides. As thermosets there are epoxies, phenolics, alkyds, vinyl esters, unsaturated polyesters, polyurethanes and aminoplastics (13).

Table 1: Comparison of the Properties of Thermoplastics and Thermosets

Thermoplastics	Thermosets
Soft	Rigid
Clear	Opaque
High Volume	Low volume
Ease of processing	Difficult to process
Higher initial material cost	Lower initial material cost--
Lower heat resistance	Higher heat resistance
Higher temperature processing	Lower temperature processing

3.2 Classification based on physical state

Based on physical properties, hydrogels can be classified into three types: solid, semi-solid and liquid hydrogels, as can be seen in Figure 2. This is the classification used most often for biomedical applications (4).

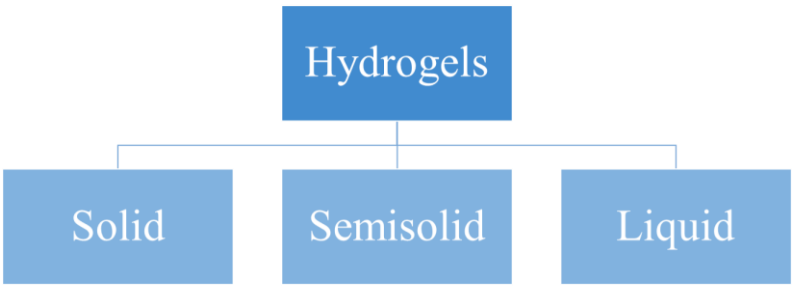

Figure 2: Classification of Hydrogels Based on Physical State

3.2.1 Solid Hydrogels

Solid hydrogels have the capacity to mimic most biological tissues in their complex tissue structure with specific physical, chemical, electrical, and biological properties, providing the essential cellular microenvironment (4,14).

Their strong cross-linked network structure and solid nature at room temperature, with the capability to swell in aqueous systems, such as biological fluids and buffer

solutions, allows them to be frequently used for the preparation of hydrogels for biomedical, environmental, and ecological applications (4).

Recently, to increase their applicability for different purposes, several researchers have introduced inorganic metals in its structure providing optical, electrical, and magnetic properties to these hydrogels making them more attractive for different fields (15). For instance, Sethi *et al.* (16) developed a multi-component, fluorescent hydrogel comprising chitosan and gelatine with maleic acid as a cross-linking agent for heavy metal detection. Sun *et al.* (17) devised a solid β-hairpin peptide hydrogel for sustained release of active chemotherapeutics, such as vincristine. The proposed hydrogel was a solid, preformed gel that, due to shear-thinning qualities, could be syringe injected and instantly regain solid gel properties (17).

3.2.2 Semisolid Hydrogels

Semisolid hydrogels are unique due to their strong adhesive interactions with interfacial forces (e.g. van der Waals, hydrogen bonds and electrostatic) and soft tissue networks. As such, these hydrogels can as well be referred to as bio-adhesive or muco-adhesive hydrogels. (4) These specific properties have proved to be highly useful for controlled drug delivery in ocular, nasal, buccal, sublingual, rectal, vaginal, and transdermal administration routes (18–21).

These hydrogels are prepared with two types of materials. One of these should possess biological nature, for example chitosan, hydroxypropyl cellulose, and plant gum; and the other should be a polymeric material of high molecular weight, such as poly(*N*-vinyl pyrrolidone) (PVP) and PVA (14,22–24). This gives the hydrogel complex a bio-adhesive nature with good wetting, absorption, and de-absorption properties (4).

An example of this type of hydrogel is a semisolid wet sol–gel silica/hydroxypropyl methyl cellulose formulation developed by Albiero *et al.* (24) for controlled release of Serpin B3 to promote wound healing, in particular diabetic wound healing.

Another example, is the cutaneous formulation of a Carbopol Ultrez®-based hydrogel containing dexamethasone-loaded nanocapsules developed by Marchiori *et al.* (25), which appears as a promising approach to treat antiproliferative-related dermatological disorders.

3.2.3 Liquid Hydrogels

Liquid hydrogels are, as the name suggests, liquid in phase at room temperature, but at a specific temperature form a soft tissue-like elastic phase with good functionality (4,26–30).

These hydrogels have an unmatched biocompatibility, function-ability, and ease of synthesis, as well as the possibility of self-adjustment of their network, such as pore sizes, according to environmental conditions (28).

Their properties ease the incorporation of drugs, cells and proteins in the hydrogels as well as permitting their use without the need of any surgical procedures, due to highly hydrophilic properties, which allow the use of injection route to target sites. Such characteristics make them attractive in regenerative medicine, cell biology and biomedical applications (4).

Injectable systems saw early success with systems that could gel in place, with liquid hydrogels being injected into tissues and subsequently solidifying. As an example, for transcorneal administration of 5-fluorouracil (5-FU), Fabiano *et al.* (31) developed a chitosan-based thermosensitive ophthalmic hydrogel that is fluid at 4°C (instillation temperature), semisolid at 35°C (eye temperature). In another instance, Kuddushi *et al.* (32) reported on a self-healable injectable hydrogel for targeted and sustained delivery of doxorubicin in the treatment of breast cancer.

3.3 Classification based on cross-linking type

Based on the nature of the cross-link junctions in their networks hydrogels can be divided into two categories: i) physical cross-linked, also referred to as self-assembled, ii) chemical cross-linked (4,8). Cross-linking is an effective method of categorising since it affects both the manufacturing process and the end product, and consequently the possible applications (33).

Chemically cross-linked hydrogels have permanent junctions, due to the existence of covalent bonds between different polymer chains, and as such, cannot be dissolved in any solvents unless the cross-link point has been cleaved (2,4,34).

In physical gels, the nature of the cross-linking process is physical, attaining transient junctions via physical processes such as hydrophobic interactions, chain

aggregation, crystallisation, polymer chain complexion, and hydrogen bonding (8,34). The design flexibility of a physically cross-linked hydrogel is considerably restricted, due to the struggle to dissociate the variables, such as: gelation time, internal network pore size, chemical functionalisation, and degradation time (4).

The preparation of hydrogels through chemical cross-linking is a highly effective method, however due to their reported toxicity, the cross-linkers should be removed before use. In contrast, in physically cross-linked gels, dissolution is prevented by physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions. Thus, an alternative to cross-linker toxicity can be to manufacture hydrogels using physically cross-linked techniques (35).

There are several physical and chemical cross-linking methods, as can be seen in Figure 3, these will be further explored in this section.

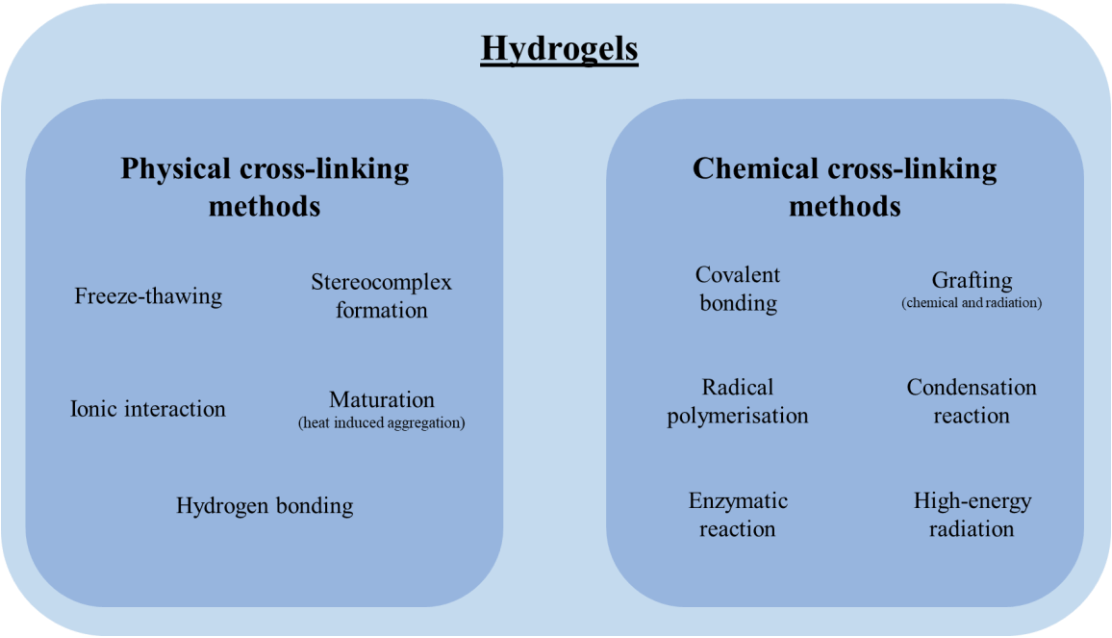

Figure 3: Methods of Cross-Linking Hydrogels

Natural and synthetic polymers were employed to create several kinds of chemical and physical hydrogels, which were then used in a variety of applications, as can be seen in Table A.1, Appendix A1.

3.3.1 Physically Cross-linked Hydrogels

There are different methods documented in the literature for manufacturing physically cross-linked hydrogels. Hydrogels created by physical cross-linking vary significantly in structure, including porous size, elasticity, and physical state; depending on the method used for obtaining them. Because of their different properties, they may be employed for a variety of purposes.

3.3.1.1 Freeze-thawing

Repetitive freeze-thaw cycles can be used to create physically cross-linked hydrogels, also referred to as cryotropic gels (36,37).

This mechanism is based on the structure forming microcrystals as a result of freezing and thawing (8). There are quite a few polysaccharides that can create cryotropic gels, and among those are HA, carboxymethylated curdlan (CMc), carboxymethylated cellulose (CMC), xanthan, β-glucan, locust bean gum (LBG), starch (amylose, amylopectin, and their blends), maltodextrins (MDs), and agarose (38).

One well-known example of the use of this technique are PVA hydrogels. When PVA aqueous solutions are kept at room temperature, a low mechanical strength gel progressively forms, but when subjected to the freeze-thawing procedure, a sturdy and extremely elastic gel is obtained. In this process the PVA molecular weight, PVA concentration in the water, freezing temperature, freezing period, and number of cycles affect the final gel's characteristics (4,8,39).

In comparison to PVA hydrogels obtained through conventional techniques, these hydrogels are more porous, spongy, rubbery, and have higher elastic characteristics thanks to hydrogen bonding (4).

3.3.1.2 Stereocomplex formation

Racemic crystal formation when mixing two enantiomers of low molecular weight with chiral centres is a well-known phenomenon. The same way, racemic crystallite formation in polymers with opposing chirality has also been noted. Such racemic crystallite production has been referred in the literature as stereocomplexes (40), which Dumas *et al.* first described in 1972 (41).

Stereocomplex crystallisation occurs in a solution during solvent evaporation or precipitation and in bulk while undergoing non-isothermal or isothermal crystallisation (42). The main benefit of this approach is how simple it is to create a hydrogel by mixing each product in water to dissolve it. (4)

The first description of polylactide's (PLA) capacity to develop stereocomplexes was provided by Ikada *et al.* (43) in 1987. This method has since been applied in the fields of biomedical applications and drug delivery (44), for example, in the development of a double cross-linked temperature/pH dual responsive hydrogel for controlled and targeted release of doxorubicin, prepared by the stereocomplexation of hydroxyethyl methacrylate (HEMA)-polylactide and chemical cross-linking of ethylene glycol dimethacrylate (45).

Another instance of the use of this method is a biodegradable dextran hydrogel, obtained through the stereocomplexation of dextran(L)-lactate and dextran(D)-lactate, for the controlled release of pharmaceutically active proteins, such as lysozyme and IgG (46).

However, because slight variations in stoichiometry can weaken or abolish the stereochemical interaction, the very narrow range of polymer compositions that can be used with this technique is a significant constraint to stereocomplexation (47).

3.3.1.3 Ionic interaction

Ionic cross-linking typically takes place between two molecules or polyelectrolytes with opposing charges (4,48). The gel formation upon the addition of counter ions is influenced by variables such as ionic strength, pH, counter ion type, and functional charge density of the solution.

A well-known case of a polymer that can be cross-linked by ionic interactions is ALG. The polysaccharide ALG contains residues of mannuronic and glucuronic acids and can be cross-linked by divalent cations like Mg^{2+}, Ca^{2+} and Ba^{2+} (8,48). An example of the use of ALG is the development of a hydrogel for sustained oral delivery of flurbiprofen, composed of ionically cross-linked beads of partially oxidised alginate with Ca^{2+} ions, that were then covalently cross-linked with adipic dihydrazide (49).

Other hydrogels in this category include the poly-[di(carboxylatophenoxy) phosphazene] (50) and the chitosan-glycerol phosphate salt mineral salt (51).

Ionic cross-linking is frequently used in *in situ* gelling systems (48).

3.3.1.4 Maturation

Heat-induced aggregation known as "maturation" produces hydrogels with precisely structured molecular dimensions (4,34).

The heat-induced gelation of gum arabic is the best illustration of this hydrogel system. This phenomenon is a result of the gum arabic's protein components aggregating as a result of thermal processing (34).

This aggregation causes a rise in molecular weight, which leads to the formation of a hydrogel with increased mechanical characteristics and the ability to bind water. (4,52,53) The process has also been applied to various gums, including gum ghatti and *Acacia kerensis*, for use in denture care (54).

3.3.1.5 Hydrogen bonding

One of the most significant non-covalent interactions that gives materials properties like self-healing, shape memory, and dynamic energy dissipation is hydrogen bonding (55).

For example, the creation of a hydrogen-bond on the CMC network by distributing CMC in 0.1 M HCl is an excellent representative of such hydrogel. In this procedure, the sodium ions in CMC got replaced by the hydrogen in the acid. This decreases the solubility of CMC and CMC molecules aggregate, with hydrogen bonds being formed (56).

In another instance, Zhong *et al.* (3) used vinyl silica nanoparticles (VSNPs) and Fe^{3+} ions to produce physical cross-linked acrylic acid (AA) hydrogels. In this case, the hydrogel's polymer chains are physically cross-linked by hydrogen bonds and ionic interactions mediated by Fe^{3+} ions, resulting in ionic nanocomposite physical hydrogels. Excellent mechanical characteristics of this hydrogel include tensile strength of 860 kPa and elongation at break of 2300%. The hydrogels also have excellent self-healing abilities, and the recovered hydrogel may be stretched around fifteen times longer than before (3). The authors suggest that this formulation might have possible uses in biomedical applications.

One other recent example of the use of this method is a hydrogen bond cross-linked hydrogel, composed of humic acid and PVP, with self-healing and adhesive properties developed as a haemostatic (57).

3.3.2 Chemically Cross-linked Hydrogels

There are various methods reported in the literature to obtain chemically cross-linked hydrogels. These produce hydrogels with different characteristics, enabling them to be used for different applications.

3.3.2.1 Covalent bonding

The solubility characteristics of water-soluble polymers are due to the existence of functional groups, primarily -OH, -COOH, and -NH_2, used in the creation of hydrogels (8). Covalent bonds can be formed between polymer chains through the interaction of functional groups with complementary reactivity, such as an amine-carboxylic acid or isocyanate-OH/NH_2 reaction, or through Schiff base formation (4,8). Moreover, cross-linkers, such as glutaraldehyde, epichlorohydrin, adipic acid dihydrazide, and polyaldehydes, are frequently employed to create cross-linked hydrogel networks from a variety of synthetic and natural polymers in chemical cross-linked hydrogels (4,58).

For example, Lü *et al.* (59) investigated the potential use of a chondroitin sulphate (ChS) based hydrogel that employed covalent cross-linking through acyl-hydrazone bonds as an injectable and self-healing hydrogel with covalent cross-linking *in vivo* for cranial bone repair.

As another example, a covalently cross-linked hydrogel, composed of PVA, ALG and poly(ethylene glycol) diacrylate, revealed to be able to deliver *Equinacea purpurea* extract in a controlled manner for an extended period of time (60). Covalently cross-linked hydrogels have also been studied for live cell encapsulation (61).

3.3.2.2 Grafting

The polymerisation of a monomer on the backbone of a pre-made polymer is used in the creation of hydrogels based on grafting. Grafting can be defined as chemical grafting or radiation grafting depending on the type of activation initiator used (4).

In chemical grafting, a chemical reagent reacts to activate the macromolecular backbones (4). Grafting of an ester-diol based polyurethane onto highly hydrophilic

chitosan to form a hydrogel via hydrophilic-hydrophobic balancing is an example of this system (62).

Radiation grafting is the name given to grafting that is started by the application of high energy radiation, such as gamma and electron beams. For example, Nisar *et al.* (63) used gamma-irradiated graft copolymerisation to synthesise extremely porous, pH-responsive, and biocompatible chitosan-based hydrogel beads utilising L-glutamic acid as the monomer. The potential use of the glutamic acid grafted chitosan hydrogel beads as a smart and biocompatible vehicle for controlled anti-cancer drug delivery systems was investigated, with the anti-cancer drug doxorubicin being loaded into the hydrogel beads (63).

3.3.2.3 Radical polymerisation

Chemically cross-linked gels can also be produced via radical polymerisation of low molecular weight monomers in the presence of a cross-linking agent. Being a very efficient technique that results in the gel forming quickly even under mild conditions, it is one of the most used procedures for producing hydrogels (4).

In hydrogels developed through this cross-linking method, swelling can be controlled by the amount of cross-linker used. Furthermore, stimuli-sensitive materials can be created by incorporating a cross-linker with specified qualities (8).

Various water-soluble (synthetic, semisynthetic, and natural) polymers have been utilised in this technique to create hydrogels (8). For example, Lee *et al.* (64) investigated molybdenum disulphide's multifunctional role in the creation of composite hydrogels. In this study, MoS_2 nanoplatelets form radical species via a redox reaction with persulfate in aqueous conditions, initiating the polymerisation of acrylic monomers and providing noncovalent cross-linking points without the need for external stimuli or extra cross-linkers, resulting in the formation *in situ* of hydrogels embedded with inorganic flakes.

3.3.2.4 Condensation reaction

Another type of cross-linking between reactive groups is created by condensation reactions between hydroxyl or amino groups and carboxyl groups (or derivatives), this method commonly utilised in polymer synthesis to produce polyesters or polyamides (65).

De Nooy *et al.* (66,67) provided an excellent illustration of these condensation processes by describing the Passerini and Ugi condensation reactions. The hydrogels produced by this Passerini condensation have ester bonds in their cross-links. A carboxylic acid and a carbonyl molecule (aldehyde or ketone) are condensed with an isocyanide to produce α-(acryloxy) amide. An amine is added to this reaction mixture in the Ugi condensation process, generating α-(acrylamino)amide (66,67).

These condensation reactions were employed for the production of polysaccharide-based hydrogels, such as a degradable poly(ethylene glycol) hydrogel suitable for the delivery of protein drugs (68) and a degradable injectable poly(aldehyde guluronate) hydrogel for bone tissue engineering (69). Another example is a novel hydrogel developed through a condensation reaction between *o*-phthalaldehyde and *N*-nucleophiles (primary amine, hydrazide and aminooxy) to be applied in hydrogel bio-adhesives for wound closure and with potential for a wide range of biomedical applications (70).

3.3.2.5 Enzymatic reaction

An approach based on an enzymatic reaction can also be used to create a hydrogel (4) and figure 4 is a schematic illustration of this enzymatic method.

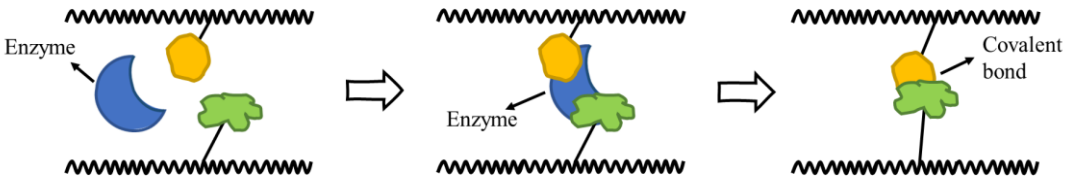

Figure 4: Schematic Illustration of the Enzymatic Method

For example, Kim *et al.* (71) described the formation of a tissue adhesive and anti-inflammatory hydrogel via high-affinity enzymatic cross-linking of polyphenolic Epigallocatechin gallates (EGCGs). A mixture of EGCG conjugated hyaluronic acids (HA-E) and tyramine conjugated hyaluronic acids (HA-T) reacted with tyrosinase isolated from *Streptomyces avermitillis* (SA_Ty) to generate a cross-linked sticky hydrogel with a fast enzyme kinetic.

This method was also used by Wei *et al.* (72) to fabricate an antioxidant supramolecular hydrogel based on feruloyl-modified peptide and glycol chitosan, via a mild laccase-mediated cross-linking reaction, for improving cutaneous wound healing.

3.3.2.6 High-energy radiation

High-energy radiation, such as gamma (γ) or electron beam radiation, can be used to polymerise unsaturated molecules. Water-soluble polymers are derivatised with vinyl groups when exposed to gamma or electron beam radiation, resulting in the formation of radicals on the polymer chains via the homolytic scission reaction (73,74). Additionally, high intensity radiation promotes the development of hydroxyl groups in water molecules, which can damage polymeric chains and result in the generation of microradicals. When these microradicals recombine on distinct chains, covalent bonds develop, resulting in a cross-linked structure. The benefit of this procedure is that it can be carried out in water under benign conditions (room temperature and physiological pH) and without the need of harmful cross-linking agents. However, irradiation of polymers such as PEG and PVA causes the creation of cross-links consisting of C-C bonds, which leads to non-biodegradable gels (75).

Other examples include the use of high energy irradiation to generate poly(viny1 methyl ether) (PVME) and PNIPAAm hydrogels (4).

3.4 Classification according to network electrical charge

On the basis of presence or absence of electrical charge located on the cross-linked chains, hydrogels may be categorised into four different groups, depicted in Figure 5 (4,76):

i. Non-ionic (neutral).
ii. Ionic (being anionic or cationic).
iii. Ampholytic containing both acidic and alkaline groups.
iv. Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

Neutral or non-ionic hydrogels have no charge on either their backbone or their side groups. These expand in aqueous medium exclusively as a result of interactions between water and polymers (76). Examples of non-ionic hydrogels include hydrogels based on the following polymers: PA (77,78), PEG (79), PVA (80), poly-hydroxyl methacrylate (81).

Ionic hydrogels comprise cationic (positive charge bearing) and anionic (negative charge bearing) hydrogels. The pH of the aqueous phase, which determines the degree of ionic chain dissociation, controls how much a hydrogel of this nature will swell. Cationic hydrogels, which contain a positive charge in their backbone, exhibit greater swelling in acidic conditions since chain dissociation is favoured at low pH values (76). Among the monomers employed in the manufacture of cationic hydrogels are aminoethyl methacrylate, vinyl pyridine, diethylaminoethyl methacrylate, and dimethylaminoethyl methacrylate (82,83).

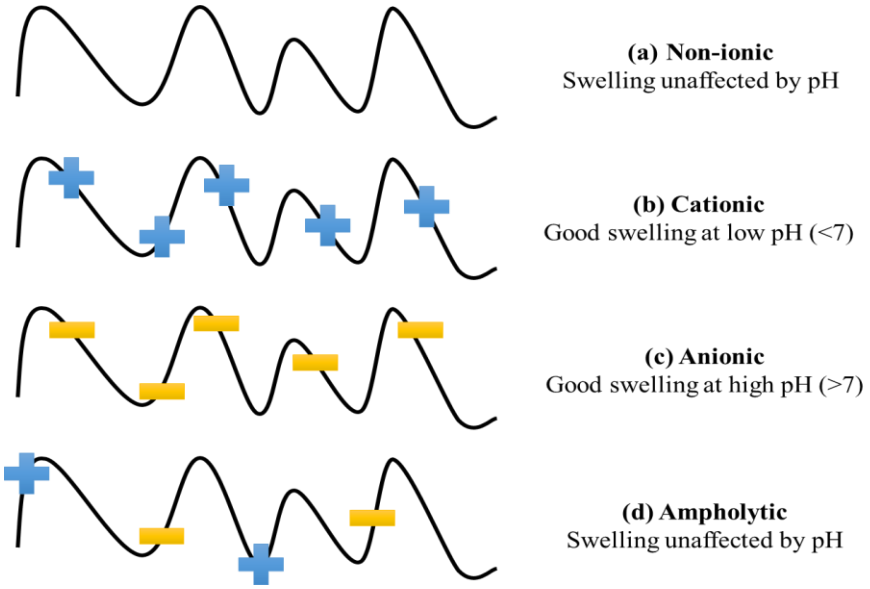

Figure 5: Diagram of Different Hydrogels Based on Presence of Electric Charge

(a) Non-ionic, (b) Cationic, (c) Anionic and (d) Ampholytic

Polymeric hydrogel chains are represented by black curved lines and the pendant moieties are represented by light coloured symbols.

Anionic hydrogels which usually contain negative ions that are bound to the polymer network (84), on the other hand, dissociate more at higher pH levels, resulting in greater swelling in neutral to basic solutions (76). Among the monomers of anionic hydrogels can be counted p-styrene sulfonic acid, methacrylic acid, itaconic acid, AA, crotonic acid and maleic acid (85), as well as xanthan gum (86).

Hydrogels which contain both negative and positive charges on the same polymer chain are named ampholytic hydrogels, as shown in Figure 5d. Each structural repeating unit in this hydrogel has both acidic and basic groups, and their charges are balanced at the isoelectric point. Just a slight change in pH can alter the overall ionic characteristics of these hydrogels. Monomers in the production of ampholytic hydrogels include *N*-

isopropylacrylamide / [[3 - (methacryloylamino) propyl] dimethyl (3 – sulfopropyl) ammonium hydroxide] (87).

In another example of ampholytic hydrogels, Baker *et al.* (88) copolymerised two monomers, [(methacrylamido)propyl]trimethylammonium chloride and sodium styrene sulfonate, with acrylamide to form an ampholytic hydrogel. The zwitterionic monomers, *N* - (3 – sulfopropyl) – *N* – methacrylamidopropyl – *N* - dimethylammonium betaine and *N*-(3-sulfopropyl)-*N*-methacroyloxyethyl-*N*,*N*-dimethylammonium betaine, were also both copolymerised with acrylamide to form this type of hydrogel. Ampholytic polyelectrolyte regenerated cellulose hydrogels were effectively created using cellulose, chitosan, and carrageenan monomers (89).

Polybetaines, which contain moieties with both cationic (quaternary ammonium group) and anionic (carboxylate, sulfonate, phosphate/phosphinate/phosphonate groups) groups in the same structural unit, are an important class of smart polymers with unique and specific properties that belong to the zwitterionic material family. Polybetaines are classified into three types based on their anionic groups: poly(carboxybetaines), poly(sulfobetaines), and poly(phosphobetaines) (90,91). Some monomers used to produce zwitterionic hydrogels are methacrylate, acrylate, methacrylamide and acrylamide (91).

3.5 Classification based on degradability

Based on their degradability, hydrogels can be considered either biodegradable or non-biodegradable (8). Biodegradable hydrogels have been used in drug delivery systems, such as thermo-sensitive hydrogels, injectable hydrogel drug delivery systems for local cancer therapy, and even for antibacterial applications, such as the biodegradable gold nanocomposite hydrogels studied in 2012 (15,27,28,30,92–94).

Non-biodegradable hydrogels have been used as polymeric hydrogel-based vitreous endo-tamponades, which can be used in the treatment of retinal detachments and tears by providing support to the retina after retina surgery (95). These have also been investigated as possible non-biodegradable scaffolds for tissue regeneration, particularly PVA hydrogels prepared by freeze-thawing procedure (96).

4 Hydrogel structure

Hydrogels possess many properties that can be determined by their structure. The ideal hydrogel material would possess all of the following functional characteristics (2):

- The maximal equilibrium swelling with the optimum absorption capacity in saline;
- Desired rate of absorption (preferred particle size and porosity) depending on the application requirement;
- Maximum level of absorption under load (AUL);
- The lowest soluble content and residual monomer;
- Lowest cost of manufacturing;
- Maximum level of stability and durability during storage and in a swelling environment;
- Greatest degree of biodegradability without producing toxic species during degradation;
- pH-neutrality after swelling in water;
- Colourlessness, odourlessness, and absolute non-toxicity;
- Photo stability;
- The hydrogel must have the ability to either maintain or return the ingested solution, depending on the application's needs, for rewetting (*e.g.*, in agricultural or hygienic applications).

Obviously, a hydrogel sample cannot fulfil all of the above-mentioned requirements at the same time. In fact, the synthetic components used to achieve the highest level of some of these qualities will result in inefficiency of the others. As a result, in practice, the manufacturing reaction variables must be tuned to obtain an optimum balance of the qualities. For instance, luminous transmittance, sufficient oxygen-permeability, wettability and permeability to water and stability are required for hydrogels used for contact lens applications (97); sanitary hydrogel products must have the maximum absorption rate, the lowest re-wetting, and the lowest residual monomer, while drug delivery systems should be porous and respond to stimuli, like pH or temperature (2).

Some of the crucial metrics for network structure characterisation studies are the volume fraction in the swelling state ($\upsilon_{2,s}$), the associated mesh size (ξ), and the

molecular weight of the polymer chain between nearby cross-link points (M_c). A measure used to describe the degree of cross-linking is the molecular weight between adjacent cross-link locations, whether they are connected by a covalent connection or through physical interaction. A parameter called the volume fraction of polymers in the swollen state determines how much fluid may be absorbed and held within the hydrogel structure. These parameters are related to each other and can be computed theoretically or determined using a variety of experimental procedures (98,99).

There are different theories behind the Hydrogel Swelling Mechanism. In the following paragraphs the two most widely used models, the equilibrium swelling theory and the rubber elasticity theory, will be discussed, as well as how the mesh size is determined.

4.1 Equilibrium Swelling Theory

The analysis of hydrogels devoid of ionic domains can be done using the Flory-Rehner equation, which describes the mixing of polymers and liquid molecules (64). Two reverse forces establish the equilibrium state of the hydrogel that has swelled in a fluid. The thermodynamic force of mixing favours swelling in one case, whereas the stored force in stretched polymer chains prevents swelling in the other (65).

Equation 1 describes how these two forces balance one another for the physical situation in terms of Gibbs free energy:

$$\Delta G_{total} = \Delta G_{elastic} + \Delta G_{mixing}$$

Equation 1

While $G_{elastic}$ represents the contribution from the elastic retractive forces generated within the gel, G_{mixing} represents the outcome of the spontaneous mixing of the fluid molecules with the polymer chains. The latter refers to a measurement of how well the polymer interacts with the fluid molecules around it. The polymer-solvent interaction parameter, χ_1, is typically used to express this compatibility. (100)

Differentiation of Equation 1 with respect to the number of solvent molecules, while keeping the temperature and pressure constant, results in Equation 2 ,where $\Delta\mu$ is the chemical potential of the penetrating solvent (98,99).

$$\mu_1 - \mu_{1,o} = \Delta\mu_{elastic} + \Delta\mu_{mixing}$$

Equation 2

The chemical potential outside the gel should be equal to the chemical potential inside the gel in the equilibrium state $\Delta\mu_1 = \Delta\mu_{1,o}$. As a result, the chemical potential shift caused by the free energy of mixing and the elastic force contained in stretched polymer chains must cancel each other out (98,99).

The previous Flory–Rehner theory was modified for a hydrogel synthesised from an aqueous phase. Due to elastic forces acting on the water the chemical potential was significantly altered, which caused the volume fraction density of the polymer chains to alter during the cross-linking process (101). Due to the thermocomplex system from the ionic domain of the polymer chains, which brings an additional modifying element into the Gibbs free energy, the presence of ionic moieties in hydrogel makes the mathematical model significantly more complex (98,99).

4.2 Rubber Swelling Theory

From a mechanical standpoint, hydrogels are similar to natural rubbers considering that they deform elastically in response to applied stress (98,99). Both Treloar (102) and Flory *et al.* (103) described the structure of the hydrogels using their elastic properties. The original elasticity theory, however, does not apply to hydrogels synthesised in solvent (98,99).

Peppas *et al.* described the theory of rubber elasticity in Equation 3, the only form of hydrogel structure analysis, with hydrogels produced in solvent.

$$\tau = \frac{\rho RT}{\bar{M}_c}\left(1 - \frac{2\bar{M}_c}{\bar{M}_n}\right)\left(\alpha - \frac{1}{\alpha^2}\right)\left(\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right)^{1/3}$$

Equation 3

In this equation τ represents the applied stress to the polymer sample, ρ represents the polymer density, R represents the universal gas constant, T represents the absolute experimental temperature, $\bar{M}_c$ represents the molecular weight between cross-links, $\bar{M}_n$ represents the molecular weight of the polymer chains prepared under identical conditions, but in the absence of the cross-linking agent; α represents is the elongation ratio of the polymer chains in any direction, $\upsilon_{2,s}$ represents the polymer volume fraction

in the swollen state and $\upsilon_{2,r}$ represents the polymer volume fraction in the relaxed state (98,99).

4.3 Mesh Size Calculation

The key mechanism of drug release from hydrogel matrices is diffusion, which occurs through the space available between macromolecular chains, commonly referred to as a pore. Hydrogels can be categorised according to the size of these pores, as macro-porous, micro-porous or non-porous (99). The correlation length, ξ, defined as the linear distance between two consecutive cross-links, is a structural metric that is frequently used to describe the size of pores and can be calculated through Equation 4.

$$\xi = \alpha(\bar{r}_0^2)^{1/2}$$

Equation 4

Where α is the elongation ratio of the polymer chains in any direction and $(\bar{r}_0^2)^{1/2}$ is the root-mean-square, unperturbed, end-to-end distance of the polymer chains between two neighbouring cross-links (104). The elongation ratio, α, can be determined using the volume fraction of the swollen polymer, $\upsilon_{2,s}$, as follows in Equation 5:

$$\alpha = (\upsilon_{2,s})^{-1/3}$$

Equation 5

The unperturbed end-to-end distance of the polymer chain between two neighbouring cross-links can be calculated by Equation 6:

$$(\bar{r}_0^2)^{1/2} = l(C_n N)^{1/2}$$

Equation 6

Where l is the length of the bond along the polymer backbone (1.54 Å for vinyl polymers), C_n is the Flory characteristic ratio, and N, the number of links per chain, can be calculated by Equation 7:

$$N = \frac{2\bar{M}_c}{M_r}$$

Equation 7

Where M_r is the molecular weight of the repeat unit. Finally, combining all the equations above, the correlated distance of the polymer chains between two adjacent cross-linking points can be evaluated by Equation 8:

$$\xi = \left(v_{2,s}\right)^{-\frac{1}{3}} \left(\frac{2C_n \bar{M}_c}{M_r}\right)^{1/2} l$$

Equation 8

In combination with diffusion studies of model drugs and proteins, a detailed theoretical characterisation of the network structure of the polymer carrier in terms of the correlation length, ξ, provides an important insight into the complex structure of polymer networks and aids in the design of drug delivery carriers (99).

5 Hydrogel Preparation Technologies

Polymeric hydrogels are typically produced using one of two well-established methods: polymerisation of hydrophilic monomers or modification or functionalisation of existing polymers, those being natural or synthetic (2,8).

Simply, a hydrogel is a hydrophilic polymeric network that has been cross-linked in some manner to create an elastic structure. As a result, any approach that can be used to manufacture a cross-linked polymer can also be utilised to build a hydrogel.

Water-soluble natural or synthetic polymers are typically cross-linked to form hydrogels through a variety of methods, including chemically linking polymer chains, using ionising radiation to generate main-chain free radicals that can recombine as cross-link joints, and physically interacting via electrostatics, entanglements, and crystallite interactions.

Hydrogels can be formed using any of the polymerisation processes available, including bulk, solution, and suspension polymerisations. Table 2 provides some examples of different types of hydrogels, demonstrating how different methods of synthesis and cross-linking affect their shape and potential applications.

Monomers, initiators, and cross-linkers are the three primary components of hydrogels, which can be diluted in water or other solvent to adjust the heat of polymerisation. However, one disadvantage is the presence of impurities left over from the preparation process, which include unreacted monomers, initiators, cross-linkers, and side products, as can be seen represented in Figure 6 (2,8).

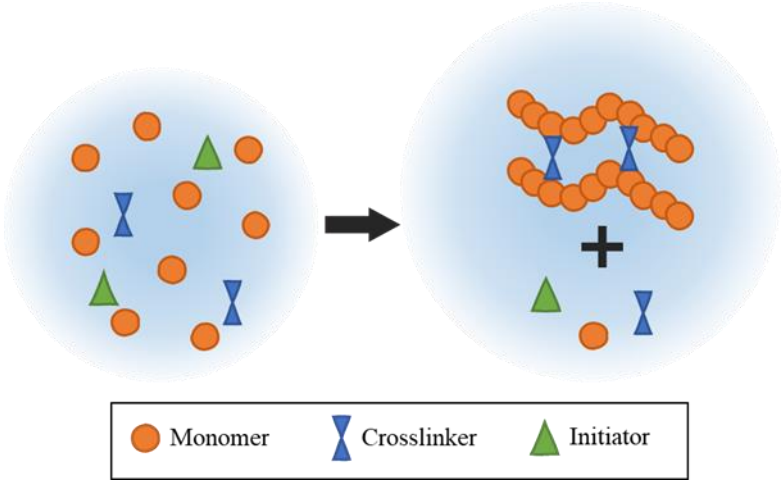

Figure 6: Schematic Diagram of Hydrogel Preparation

Table 2: Hydrogel Types and respective Methods of Synthesis

Hydrogel type	Monomers used	Method of synthesis/cross-linking	Shape	Applications	Reference
SAPs hydrogel-superabsorbent polymers	Acrylamide, acrylic acid, salts of acrylic acid including sodium, and potassium acrylates	Bulk, solution, inverse-suspension	Films, membranes, particles	Drug delivery, targeted drug delivery, nano/controlled drug delivery	(2,4)
SPHs - superporous hydrogel	Acrylamide, acrylic acid, salts of acrylic acidincluding sodium, and sulfopropyl acrylates, 2-hydroxyethyl methacrylate	Mostly aqueous solution	Any shape including particles, sheet, film, rod	Where size-independent high and very fast swelling is required. Uses for drug delivery that involve intestinal peroral protein and peptide administration and stomach retention	(2,105)
TTH - triggerable tough hydrogels	PA, ALG	Mostly aqueous solution	Highly stretchable and flexible in sheet or film	Gastric resident dosage forms	(106)
CPHs - conducting polymer	Polyaniline (PANii), polypyrrole (PPy) and polythiophene (PTh)	Irradiation, aqueous solution, grafting	Powder, Sheet	Implantable electrochemical biosensors, electro-stimulated drug release, biological adhesions, tissue engineering, bio-active electrode coating	(4,6)
PSB (Polysaccharide-based) natural hydrogels	ALG, chitosan, gelatine, carrageenan, gellan gum, guar gum, pectin, cellulose, agarose, and xanthan gum, etc.	Bulk, freeze-thaw	Any shape including film, powders, sheets, and bulk	Bioactive coatings, controlled drug release, blood purification, regenerative medicine for cell delivery	(4,38,42)
PBH - protein-based hydrogels	proteins (i.e., silk, collagen, actin and myosin, gelatine, fibrinogen, elastin, keratin), natural/synthetic polysaccharides (i.e., chitin, cellulose, dextran, amylose, and glycosaminoglycan's) or polynucleotides (i.e., DNA, RNA)	Grafting, aqueous solution	Bilayer (similar with extracellular matrix), rod, ring, films	Cell encapsulation, articular cartilage repairs, advanced engineering of elastic tissues (skin, lung, vessels)	(4,107)
Synthetic polymers hydrogels	PVP, poly(electrolyte complexes), poly(hydroxyalkyl methacrylates), poly(acrylate), PA, poly(meth-acrylamide), poly(*N*-vinyl-2-pyrolidone), and PVA	Irradiation, aqueous solution, suspension, bulk, freeze-thaw	Any shape including film, powders, sheets, and bulk	Dressings, contact lenses, tissue engineering, drug delivery, artificial tears, cell encapsulation, artificial organs, coating materials and sensor systems	(4,11,42)

Gels can be formed using any of the polymerization processes available, including bulk, solution, and suspension polymerization, as well as grafting and irradiation polymerization, which will be discussed in this section.

5.1 Bulk polymerisation

Bulk hydrogels can be made from one or more monomers. Because of the large range of monomers available, it is possible to create hydrogels with the appropriate physical properties for a given application. In most hydrogel formulations, a minimal amount of cross-linking agent is included. Typically, radiation, ultraviolet, or chemical catalysts are used to start the polymerisation reaction. The type of monomers and solvents employed influence the choice of an appropriate initiator. The hydrogels polymerised can be put together in a range of shapes and sizes, including films and membranes, rods, particles, and emulsions (2).

Bulk polymerisation is the most basic approach, requiring solely monomer and monomer-soluble initiators. The high concentration of monomer causes a high rate of polymerisation and degree of polymerisation. The viscosity of the reaction, on the other hand, increases significantly during the conversion that creates heat during polymerisation. Controlling the reaction at low conversions can help to avoid these issues. Bulk polymerisation has the advantage of producing high molecular weight polymers with high purity (108).

For instance, 2-hydroxyethyl methacrylate hydrogels were developed by Seidel and Malmonge (109) through this method, which creates a homogenous hydrogel, resulting in a glassy, transparent, and extremely rigid polymer matrix. The glassy matrix swells when immersed in water, becoming soft and flexible. A hydrogel with these characteristics can be used in contact lenses (2).

5.2 Solution Polymerisation/Cross-linking

In these type of reactions, ionic or neutral monomers are combined with the multifunctional cross-linking agent with the polymerisation being thermally initiated by UV-irradiation or a redox initiator system. The inclusion of solvent as a heat sink is the primary advantage of solution polymerisation versus bulk polymerisation. To eliminate the monomers, oligomers, cross-linking agent, initiator, soluble and extractable polymer, and other contaminants, the hydrogels must be washed with

distilled water. When the amount of water used during polymerisation exceeds the water content corresponding to the equilibrium swelling, phase separation occurs, and a heterogeneous hydrogel is created (2,108). Common solvents used for solution polymerisation of hydrogels include water, ethanol, water-ethanol mixtures, and benzyl alcohol. The synthesis solvent can then be eliminated once the gel is formed by swelling the hydrogels in water (2).

As an example, solution polymerisation was used in the preparation of a chitosan and poly(D,L-lactide)-PEG-poly(D,L-lactide)-based hydrogel dressings for wound treatment in clinical settings (110). In another instance, this technique was also utilised in the development of a pH-sensitive hydrogel, consisting of hydroxypropyl-β-cyclodextrin grafted poly(methacrylic acid), for site-specific delivery of the antineoplastic drug cytarabine in the colonic region (111).

This preparative method is typically challenging to handle due to a rubbery or solid reaction product, mono/polydispersity, the absence of sufficient reaction control and an increase in the sol content, mainly caused by uncontrolled thermal and hydrolytic cleavage. However, because it is a faster procedure, less expensive, and has appropriate swelling qualities, this method is usually chosen for laboratory and industrial scale, (Figure 7) (8).

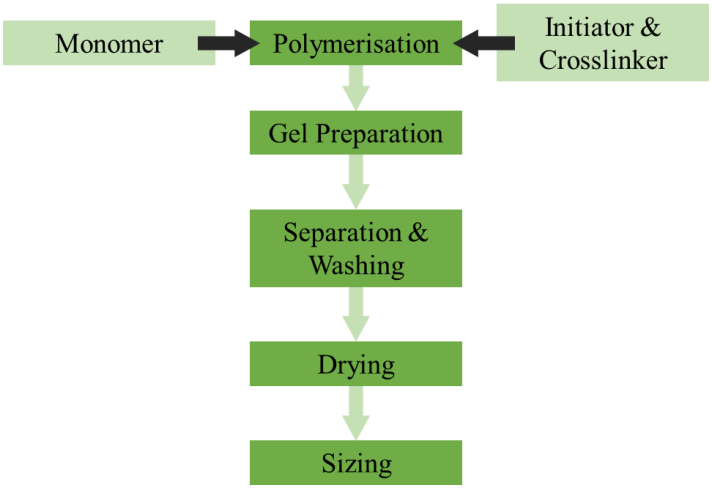

Figure 7: Block Diagram of Solution Polymerisation

5.3 Suspension Polymerisation

This method comprises a water-in-oil (W/O) process instead of the more common oil-in-water (O/W), thus being referred to as inverse-suspension polymerisation. The

monomers and initiator are dispersed as a homogeneous mixture in the hydrocarbon phase using this approach. The resin particle size and form are primarily determined by the viscosity of the monomer solution, agitation speed, rotor design, and dispersant type (108). This method's main advantage is that the products obtained are in the form of powder or microspheres (beads), thus grinding is not required (2).

This method is a more adaptable system with a high swelling capacity and quick absorption kinetics (112). Each particle includes all of the reactive species when the initiator dissolves in the dispersed (aqueous) phase. As a result, each acts as an isolated micro-batch polymerisation reactor that can be easily removed using centrifugation or filtration. As a result, the inverse-suspension method has additional advantages over the solution method, such as control of reaction heat elimination, regulation of mono/polydispersity, and particle size modification. Li *et al.* (112) developed a novel N-succinylchitosan-graft-polyacrylamide/attapulgite composite hydrogel prepared through this method.

The suspension polymerisation method (Figure 8) is very similar to the solution polymerisation technique, but with higher yield, a small distribution size, smoothness, sphericity, clarity, and less creation of unwanted fine particles (8).

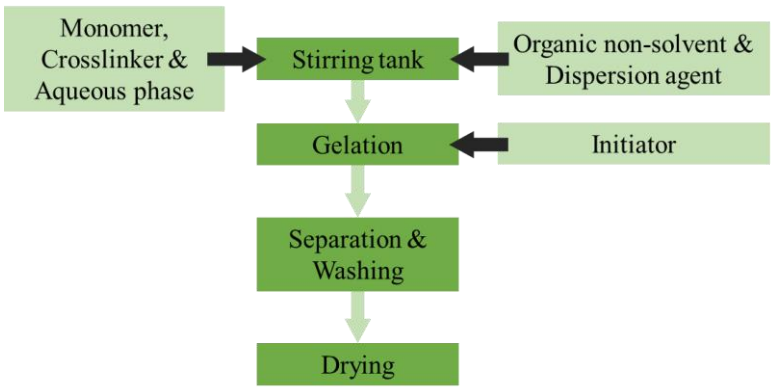

Figure 8: Block Diagram of Suspension Polymerisation

5.4 Grafting to a support

In general, hydrogels produced by bulk polymerisation have a fragile structure. A hydrogel's mechanical characteristics can be improved by grafting it onto a stronger support surface. This process involves generating free radicals on a stronger support surface and then directly polymerising monomers onto it, resulting in a chain of monomers covalently bonded to the support (2). Through grafting procedures, a variety

of polymeric supports have been employed to synthesise hydrogels, for example, a hydrogel was prepared by grafting acrylamide-co-sodium methacrylate onto chitosan (113).

5.5 Polymerisation by irradiation

Ionising high energy radiation, such as gamma rays and electron beams, has been utilised as an initiator to prepare unsaturated chemical hydrogels. Irradiating an aqueous polymer solution causes radicals to develop on the polymer chains. Furthermore, radiolysis of water molecules produces hydroxyl radicals, which attack polymer chains, culminating in the creation of macro-radicals (2).

Recombination of macro-radicals on distinct chains results in the production of covalent bonds, causing the formation of a cross-linked structure. Polymers cross-linked by radiation include PVA (73,74), poly(ethylene glycol), and poly(acrylic acid). The creation of reasonably pure and initiator-free hydrogels is the primary advantage of radiation initiation over chemical initiation (2).

6 Application of hydrogels in drug delivery

The off-target effects of systemically administered drugs are a well know major obstacle in designing therapies with simultaneously the desired efficacy and acceptable toxicity. As such, developing strategies to enable site-specific drug delivery, thereby decreasing the concerns previously mentioned, has become an ever more important field of study. That has led to the development of several targeting strategies modulating drug delivery in both preclinical and clinical settings, including hydrogels, which have drawn interest as excellent candidates for controlled release devices, as well as bio-adhesive devices or even targetable devices of therapeutic agents (4,5,8,92,99,114).

Hydrogel delivery systems can maximise the therapeutic benefits of drug delivery through more accurate targeting and controlled release (7). This section will elaborate on two approaches to achieve this in hydrogel formulations developed for pharmaceutical applications, focusing firstly on the different administration routes available for these drug delivery systems, followed by more complex hydrogel formulations with stimuli-responsive hydrogels, allowing activation only under particular conditions.

6.1 Administration Routes

Hydrogel-based drug delivery systems can be applicable for several tissue locations, such as oral, ocular, rectal, nasal, and subcutaneous tissue. Figure 9 illustrates a variety of sites available for the application of hydrogels in drug delivery (92,99)

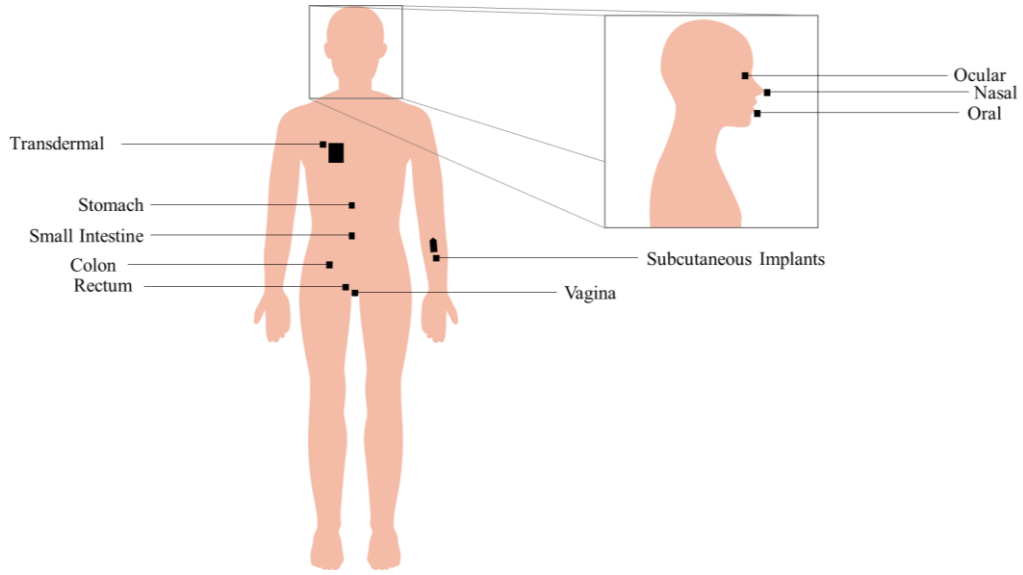

Figure 9: Tissue Locations Suitable for Hydrogel-Based Drug Delivery Systems

Examples of hydrogel-based drug delivery systems that use each administration route can be found in Table A.2, in the Appendix.

6.1.1 Peroral drug delivery

Oral medicine administration is possibly both the most inexpensive and the one which provides maximal patient compliance. Oral delivery can be used to target the mouth, stomach, small intestine, and colon. The hydrogels' bio-adhesive properties might aid in medication delivery to the mouth cavity or particular locations of the gastro-intestinal (GI) tract (92,99).

The key factor in the local treatment of oral cavity infections is retaining the delivery system at the site of infection for an extended length of time. As such hydrogels with mucoadhesive properties are preferred for this delivery method. Due to their mucoadhesive properties, these hydrogels are an important approach to locally treat illnesses such as fungal and viral infections, periodontal diseases, and oral cavity cancers (92,99). An interesting use of this is the sustained release of lidocaine through a mucoadhesive hydrogel (21), which could be used as a local anaesthetic during dental procedures.

Because of the ease of administration of medications for compliance therapy and its vast surface area for systemic absorption, the GI tract is undeniably the most preferred route of drug delivery. It is, nevertheless, the most complicated method, requiring various techniques to administer medications for successful therapy (99). GI tract hydrogel-based delivery systems range from gastroretentive systems, that could be used for extended drug delivery of an antibiotic such as clarithromycin (115), to pH-responsive hydrogels, that will not swell and release its contents in the stomach, but only in the intestine and colon responding to the pH levels, being able to provide for the administration of peptides and proteins, such as insulin and growth hormone (116,117).

6.1.2 Rectal drug delivery

Many types of drugs have been delivered via the rectal route, although patient satisfaction varies due to discomfort caused by administered dosage forms. Its principal applications have been for local treatment of rectum-related illnesses such as haemorrhoids. Furthermore, it is widely known that drugs taken from the lower region of the rectum enter straight into the systemic circulation. As a result, the rectal route is an effective method of administration for medicines that undergo extensive first-pass metabolism. This method of administration has been used in sustained release of morphine through a hydrogel suppository (118), as well as in paediatric procedural sedation with pentobarbital (119). One issue commonly associated with this route is that, in conventional methods, the release of the drugs is done in an irregular manner, and the suppositories might be unable to be adequately kept at a specific spot in the rectum and can migrate upwards to the colon. This will result in variations in the bioavailability of certain drugs (99).

6.1.3 Ocular drug delivery

Many physiological restrictions in ocular drug administration impede successful drug transport to the eye due to its defensive systems, such as effective tear drainage, blinking, and limited corneal permeability. Thus, conventional eye drops containing a drug solution are swiftly eliminated from the eye, and the pharmaceuticals delivered have limited absorption, resulting in low ocular bioavailability. Hydrogels'

mucoadhesive and elastic properties help in providing a prolonged ocular residence time of drugs (120,121).

6.1.4 Nasal drug delivery

The combination of a rich vasculature and a highly permeable structure inside the nasal membranes allows for rapid drug absorption, which should enable a faster beginning of action than peroral administration. Besides this, intranasal administration also avoids first-pass elimination (122).

As a direct delivery of drugs to the central nervous system, intranasal administration offers a non-invasive alternative to typical invasive intracerebroventricular injection, effectively bypassing the blood brain barrier (123). As seen in Zaki *et al.* (122), with the intranasal administration of the antiemetic drug metoclopramide hydrochloride in an *in situ* gelling mucoadhesive hydrogel, consisting of poloxamer 407 and PEG.

6.1.5 Topical drug delivery

This delivery method is one that has already been thoroughly tested, and it is mostly focused on antibacterial wound dressings (124,125), providing the necessary environment to cicatrisation while fighting infection . For example, silver nanoparticle-loaded gelatine hydrogel pads were developed as antibacterial wound dressings (124). Another topical antimicrobial delivery system was developed by Gao *et al.* (125) consisting of an acrylamide hydrogel containing nanoparticle stabilised liposomes.

6.1.6 Transdermal drug delivery

In recent years, transdermal administration has been studied as a feasible route for systemic drug administration (126–128). Some of the benefits of this route are the constant rate at which drugs can be delivered, quick termination of treatment by simply removing the device, and the ability to circumvent hepatic first-pass metabolism. Furthermore, due to their high-water content, swelling hydrogels might give a better sensation for the skin than traditional ointments and patches (99).

For example, Arafa and Ayoub (126) developed a pregabalin in niosomal hydrogel, consisting of hydroxypropyl methylcellulose (HPMC) and Carbopol 934, for controlled transdermal drug delivery system. In another instance, a Pluronic® F127-reduced

graphene oxide laden hydrogel was developed for transdermal delivery of buprenorphine to treat osteoarthritis (128).

6.1.7 Vaginal drug delivery

The vaginal method has traditionally been used to treat local genital disorders such as infections, vaginitis, and labour induction/prevention. As a result, a wide range of pharmacologically active chemicals, such as antibiotics (129), antifungals, antiprotozoals, antivirals (130), labour inducers, spermicidal agents, and sexual hormones, have been developed for vaginal administration (131).

6.1.8 Injectable hydrogels

An injectable hydrogel is primarily predicated on the premise that the hydrogel may be injected as liquid into the human body, where it will later solidify *in situ*. As a result, these have piqued the interest of researchers in medication delivery, tissue engineering, and dermal fillers (132). The most frequent injection administration routes used are intravenous (IV) injections, intramuscular (IM) injections, subcutaneous (SC) injections and intradermal (ID) injections.

A self-assembled tacrolimus nanoparticles cross-linking thermosensitive hydrogel, consisting of Pluronic® F127 and HA, was developed for subcutaneous injection for local rheumatoid arthritis therapy (133). Another example of this administration route is the development of a self-assembling doxorubicin silk hydrogel for the focal treatment of primary breast cancer (134).

NovaBone Putty® is an injectable hydrogel currently found on the market. It is a synthetic bone grafting material made of bioactive glass 45S5 microparticles (both osteoconductive and osteoinductive bioceramic materials) that comes in pre-filled syringes for convenient administration to bone defect locations (135). Another formulation that is commercialised is Juvéderm®, a hyaluronic acid gel to be used as dermal filler for the correction of facial wrinkles and folds (136,137).

6.1.9 Hydrogel implants

Implantable drug delivery systems allow a medicine to be released for a long-lasting period of time, typically months or years. Since all implants remain in contact with

tissues for extended periods of time, it is critical for all materials composing the system to be biocompatible (138).

An example is Dextenza®, a biodegradable dexamethasone ophthalmic insert for intracanalicular use indicated for the treatment of ocular inflammation and pain following ophthalmic surgery and the treatment of ocular itchiness associated with allergic conjunctivitis. It releases the drug for up to 30 days and it is slowly reabsorbed throughout the course of the treatment, clearing the nasolacrimal duct (139).

6.2 Stimuli-Responsive Hydrogels

Stimuli-responsive hydrogels react to environmental stimuli and undergo unanticipated changes in their growth processes, network structure, mechanical strength, and permeability, earning them the moniker "environmentally sensitive, smart hydrogels" (65). Stimuli can be physical, such as light, pressure, temperature, electric fields, magnetic fields; chemical, such as pH; and even biochemical, involving responses to ligands, enzymes, antigens, or other agents (8). Figure 10 (65) depicts their reversible behaviour in the face of external stimuli.

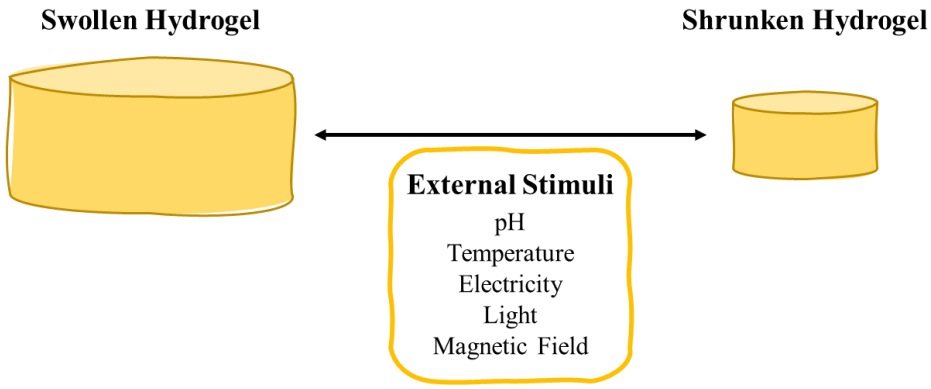

Figure 10: Smart Hydrogels Subjected to an External Stimuli

Unlike conventional hydrogels, these give more efficient and beneficial qualities to the system and improve the application level. Stimuli-responsive hydrogels are appealing biomaterials for pharmaceutical, medical, and biotechnological applications (8,65). Table A.3, in the Appendix, summarises articles about smart hydrogels grouped by their stimuli-responsiveness.

6.2.1 pH-Responsive Hydrogels

A polymer is called pH-responsive if it contains pendant acidic (carboxylic or sulphonic groups) or basic (ammonium salts) moieties capable of giving or receiving protons in response to a pH shift in the environment (65). The swelling process that occurs in aqueous solution is caused by the association, dissociation and binding of different ions to polymer chains (98).

These have potential uses in drug delivery, sensing, 3D cell culture, antimicrobial, wastewater treatment, and tissue engineering (140–143). One interesting application of pH-responsive hydrogels is the hydrogel made from dibenzaldehyde-functionalised polymer and polyaspartylhydrazide with incorporated black phosphorus nanosheets for intravenous delivery of doxorubicin to tumour sites where pH levels decrease below the physiological range (144).

6.2.2 Temperature-Responsive Hydrogels

Temperature-sensitive hydrogels are distinguished by their capacity to expand or shrink in response to changes in the surrounding fluid's temperature. These can be characterised as either positive temperature sensitive systems, with the hydrogel swelling with temperature increase, or negative temperature sensitive systems, with the hydrogel shrinking instead. One of the most significant kind of hydrogels are thermally reversible hydrogels, which are aqueous solutions that undergo sol-gel transitions in response to specific stimuli (8,65).

This type of hydrogel can be used in drug delivery, tissue engineering, imaging, and even in wound dressing and sensors (145–147). A temperature-responsive chitosan-based hydrogel was developed for transcorneal administration of 5-FU (31).

6.2.3 Photo-Responsive Hydrogels

Photo-responsive polymers are unique polymers that react to light and dark conditions, causing changes in their structure and conformation (148). These are created by incorporating a photo-responsive functional group (chromophore) into the polymer chain, and the reaction can be reversible or irreversible depending on the chromophore utilised. The most extensively researched photo-responsive polymers are those containing azobenzenes and spiropyran as the chromophore (65). Patnaik *et al.* (149) developed an azobenzene-modified dextran as a nanogel system

for controlled release of aspirin. Photo-responsive hydrogels can be employed in microfluidic devices, drug delivery, soft robotics, and actuators (150–152).

6.2.4 Electro-Responsive Hydrogels

In general, electric stimulus-responsive hydrogels are polyelectrolytes with cations (for example, chitosan) or anions (for example, polyacrylic acid) on their structure (153). These are a class of smart polymers that present a response, such as swelling or deswelling, to an external electric field (65). Interesting research is being developed on electro-responsive hydrogels, with these being applied to different administration routes, such as transdermal (154), injectable (155), and implantable (156) drug delivery devices being developed in recent years.

6.2.5 Magnetic-Responsive Hydrogels

As opposed to other stimuli-responsive hydrogels whose stimuli-responsive features are derived from the hydrogel networks themselves, magnetic-responsive hydrogels are always created by incorporating magnetic-responsive additives in the hydrogel networks. The insertion of magnetic inclusions makes the naturally non-responsive hydrogels sensitive to external magnetic stimuli, allowing them to magnetically deform, move, and change in a distant and adjustable manner under the manipulation of magnetic fields (157). For example, F_3O_4 nanoparticles were incorporated into a cellulose-based hydrogel to achieve remotely controlled drug release of 5-FU from the hydrogel beads under an external magnetic field (158).

Other smart hydrogels have also been studied in a variety of applications, including glucose-responsive hydrogels as possible insulin carriers (159,160).

While the hydrogels discussed previously have always been responsive to one single stimulus, that is not the case for all the stimuli-responsive hydrogels. For example, an injectable temperature/glucose hydrogel prepared with N-isopropylacrylamide, 3-acrylamidophenylboronic acid, and ALG was developed for controlled release of insulin (160). This system proved to be a safe carrier for insulin delivery with good biocompatibility and good sol-gel transition reversibility in response to changes between normoglycaemic and hyperglycaemic levels.

7 Recent Advances in Hydrogels

Nanoparticles and hydrogels are both commonly studied for controlled drug release. Drug molecules enclosed inside the hydrogel network are released by diffusion, swelling, and chemically mediated processes (161).

While hydrogels have tissue-like characteristics, they may also suffer from burst release and rapid drug molecule diffusion out of the polymer matrix. Nanoparticles (NP), on the other hand, influence release kinetics through their customised polymer structure, particle size, and production conditions (162). By combining the two platforms, NP-gels form matrices with exceptional versatility in adjusting drug release kinetics for varied delivery applications, which is difficult for each platform to do so alone (94). For example, a biodegradable gold nanocomposite hydrogel was developed by Jayaramudu *et al.* (15) , by using acrylamide and wheat protein isolate. This hydrogel was found to have excellent antibacterial properties and activity against *S. pyogenes* and *E. coli*. As such, it has the potential to be applied to wound and burn dressings.

In other wound dressing applications, free-radical polymerisation was used to create thermoresponsive hydrogels comprising PNIPAAm and cellulose nanocrystals in the absence of any additional cross-linkers (145). Metronidazole, an antibiotic and antiprotozoal often used for skin infections, was utilised as a target drug to examine drug-loading and hydrogel release features. At 37ºC, the hydrogels demonstrated a burst drug release followed by a slow and sustained release. These findings indicate that this is a viable material for wound dressing.

Another area of interest is targeted drug delivery of antineoplastic drugs. Topotecan, a chemotherapeutic medication, was loaded into solid lipid nanoparticles and then mixed into poloxamer 407 and poloxamer 188 solutions to construct a thermoresponsive hydrogel system for colorectal administration, as per Xing *et al.* (142). The thermoresponsive hydrogel technology with solid lipid nanoparticles (TPT-SLNs-TRHS) allowed for the regulated release of topotecan while preventing toxicity to local tissues. TPT-SLNs-TRHS antitumor effectiveness was tested in xenograft nude mice, which revealed that the system's antitumor activity remained stationary for 28 days.

In another study, Huang *et al.* (163) studied doxorubicin encapsulated into poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone) - PEG - poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone) nanoparticles that form an injectable, thermosensitive, and nanoparticle self-aggregated hydrogel for peritumoral chemotherapy. *In vivo* data demonstrated that a single peritumoral injection was more efficacious than several intravenous doses of the free drug and of the drug-free nanoparticles in a mouse model. This suggested that this hydrogel could maintain release, reducing injection frequency and systemic toxicity.

Researchers are studying how to apply hydrogels to administer medications for infectious illnesses. Lamivudine (3TC) and zidovudine (AZT) are two drugs used to treat HIV and prevent AIDS progression. To obtain good AIDS therapy, patients must take these two chemicals on a regular basis. Excessive dosing can diminish adherence, which can lead to treatment failure. As such, Witika *et al.* (164) embedded the nano co-crystal 3TC and AZT medication in Pluronic® F127 thermoresponsive hydrogel (NCC-3TC-AZT). According to the *in vitro* release data, the release time of 3TC and AZT from the NCC-3TC-AZT-THSs is more than 168 hours. Cell toxicity findings revealed that this hydrogel has no effect on cell viability when compared to AZT and 3TC treatment alone.

The integration of microtechnology with hydrogels is another promising area for developing enhanced drug delivery systems. Combination approaches might be based on spherical or fibre-like hydrogel microparticles or microparticles integrated inside macroscopic hydrogels via various approaches (165).

Yang *et al.* (166) investigated the use of polysaccharide-based hydrogel microparticles for oral insulin administration in streptozotocin-induced type 2 diabetic mice (T2DM). Long-term therapy with these microparticles dramatically reduced the symptoms of polyuria, polydipsia, polyphagia, and weight loss in diabetic mice. In addition, oral treatment with insulin hydrogel microparticles reduced fasting blood glucose levels, improved insulin resistance, and increased insulin sensitivity in T2DM. This study concluded that insulin polysaccharides-based hydrogel microparticles may exhibit promising anti-diabetic activity and the potential to be a drug candidate for T2DM. Further study would be necessary to check if these findings are applicable to drug delivery for humans.

In addition to drug delivery applications, hydrogel microparticles show promise in biomedical applications ranging from cell and drug delivery, to the creation of scaffolds for tissue healing and bioinks for 3D printing (167).

The examples given show just how versatile these type of systems can be, not only for drug delivery, but also in other applications such as biomedical.

8 3D Printing Hydrogels

Three-dimensional (3D) printing was initially presented in 1986 as stereolithography, in which laminae of a fluid substance respond to ultraviolet light and are subsequently printed in layers to form solid 3D objects (168). This technology has gradually evolved to produce structures and gadgets for a wide range of industrial uses. It allows for the manufacture of complicated geometries with great precision and cheap cost (114). These are some of the reasons why 3D printing is widely regarded as the next global industrial and manufacturing revolution, with several applications in industries such as aerospace, automotive, robotics, energy, education, food, chemical, pharmaceutical, and biomedical (10).

In fact, 3D printing has evolved quickly in the field of medication administration and personalised medicine in the recent decade, since it can tailor dose forms to each individual's age, weight, organ function, and illness severity. Nonetheless, 3D printing technology has several shortcomings as compared to conventional pharmaceutical formulation manufacturing processes, particularly in commercial large-scale production (169).

To provide context, the most well-established processes for 3D printing hydrogels are laser-based, extrusion-based, and inkjet printing (10). Khaled *et al.* (170) used three-dimensional (3D) extrusion-based printing to develop multi-active tablets with distinct controlled release profiles for three drugs: captopril, glipizide, and nifedipine. This combination of medications has the potential to be used to treat diabetics with hypertension (170). This compartmentalisation approach was also used to build the polypill, which was developed by the same research group. This package comprises five compartmentalised medicines, each with two separately regulated and well-defined release profiles. This technology provides this adaptability, which is especially advantageous for patients who are taking many drugs (171).

In a separate study, a hydrogel formulation consisting of Pluronic® F127 and alginate was developed for local drug delivery of therapeutic gold nanoparticles to cervical cancer. The 3D printed hydrogel allows for greater geometrical adaptation to the patient's anatomy, improving local delivery therapy (172).

This technology can also be applied to manufacturing formulations for paediatric use, as can be seen in Tagami *et al.* (173) where a gummy drug formulation composed of gelatine and an HPMC-based hydrogel was designed to deliver lamotrigine, an antiepileptic drug. This study shows that 3D printing is an effective method for preparing gummy drug formulations with various shapes in different colours, and that the methodology may improve drug adherence of paediatric patients in future clinical settings.

On applications other than drug delivery it is worth mentioning important studies done in the biomedical field. In a recent study, the investigators created and employed innovative self-healable pre-cross-linked hydrogel microparticles comprising chitosan methacrylate and PVA hybrid hydrogels as bioinks for extrusion-based 3D printing of scaffolds with remarkable fidelity and biocompatibility. These aid in the proliferation of bone marrow-derived mesenchymal stem cells and the production of cell spheroids, both of which are critical for tissue engineering (174).

Current technologies for bioprinting functional tissue still lack acceptable biofabrication techniques for creating complex 3D micro-architectures required for directing cell development and encouraging tissue maturation. Because of the complexity of the central nervous system's (CNS) structure, 3D printing of its structures has yet to be achieved. Koffler *et al.* (175) describe the use of a microscale continuous projection printing technology to generate a complex CNS structure for regenerative medicine applications in the spinal cord. And while the study was done on 3D biomimetic hydrogel scaffolds tailored to the dimensions of the rodent spinal cord, the researchers believe that this process can be scalable to human spinal cord dimensions and lesion geometries. The capacity of the 3D-printed scaffolds loaded with neural progenitor cells (NPCs) to facilitate axon regeneration and generate new 'neural relays' across locations of total spinal cord injury was examined and the results showed that injured host axons regenerate into 3D biomimetic scaffolds and synapse onto NPCs implanted into the device, and that implanted NPCs extend axons out of the scaffold and into the host spinal cord below the injury, restoring synaptic transmission and

significantly improving functional outcomes. These findings indicate that, through precision medicine, 3D biomimetic scaffolds can improve CNS regeneration (175).

9 Conclusion

Polymeric hydrogels have a variety of fundamental features that allow them to display unique properties, leading them to be used in a wide range of fields. Their uses range from tissue engineering, including skin, cartilage, and bone regeneration; to pharmaceutical applications with the development of new drug delivery methods. It is also important to note significant agricultural, industrial, and environmental applications.

This thesis has given an insight into hydrogels and how they are used and will increasingly be used in medicine. It has covered drug delivery, such as an injectable and thermoresponsive self-assembled nanocomposite hydrogel for long-term anticancer drug delivery, with doxorubicin (176) and a mucoadhesive hydrogel providing sustained release of lidocaine (21). Nanogels, microgels, and 3D printed hydrogels are all new and emerging areas of research that have been addressed, as well as various existing preparation methods. A large part of this paper was dedicated to hydrogel classification in order to provide a more comprehensive overview than those already existent.

This paper can be used as a broad introduction to hydrogels for researchers and medical professionals looking to implement them in treatment.

In further research, more emphasis should be put into addressing the unique requirements of complex and advanced drug delivery systems. The key objective for the future decades will be to meet the usage needs while reducing the complexity of the hydrogel formulation. Foremost, the most urgently required strategy will be to find a cost-effective technique to increase the efficacy of the hydrogel system.

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Appendix

A. Tables

Table A.1: Various Types of Chemically and Physically Cross-linked Hydrogels

Cross-linking		Polymers	Applications	References
Physically Cross-linked	Freeze-Thawing	PVA	Transport And Release of Drugs, Proteins and Peptides	(177)
		PVA	Whole cell immobilisation	(178)
	Stereocomplex Formation	Poly(lactic acid) (PLA)	Drug Delivery	(42,179,180)
	Ionic Interaction	1-methyl-3-hexadecylimidazolium salicylate	Drug Delivery	(32)
		Chitosan	Antigen Delivery	(181)
	Maturation	Gum Ghatti	Denture Care	(54)
	H-Bonding	Polyvinylpyrrolidone (PVP)	Haemostasis and Wound Healing	(182)
		Poly(methyl vinyl ether-alt-maleic anhydride), poly(vinyl alcohol) (PVA), and tannic acid (TA)	Biocompatible Drug Carriers	(183)
Chemically Cross-linked	Covalent Bonding	Chondroitin Sulphate	Cranial Bone Repair	(59)
	Chemical Grafting	Chitosan	Drug Delivery	(62)
	Radiation Grafting	Chitosan	Drug Delivery	(63)
	Radical Polymerisation	N,N'-methylene bis(acrylamide)	Drug Delivery	(64,184,185)
	Condensation Reaction	N-isopropylacrylamide, AA	Drug Delivery	(186)
	Enzymatic Reaction	Feruloyl-modified peptide and glycol chitosan	Cutaneous Wound Healing	(72)

		Mixture of EGCG conjugated hyaluronic acids (HA-E) and tyramine conjugated hyaluronic acids (HA-T)	Anti-Inflammatory Hydrogel	(71)
	High-Energy Radiation	PA/Copper-ALG	Biomedical	(187)

Table A.2: Hydrogel-Based Drug Delivery Systems by Administration Site

Administration Site	Polymer	Application	References
Oral Cavity	Pluronic® F127 + Polyethylene oxide	Thermo-responsive oral mucoadhesive hydrogel for the administration of the anti-cancer drug paclitaxel	(188)
	PVA/ALG microspheres loaded carbopol hydrogel	Mucoadhesive hydrogel providing controlled release of tramadol	(189)
	Catechol-chitosan	Mucoadhesive hydrogel providing sustained release of lidocaine	(21)
GI tract	Chitosan+ ALG	pH-responsive hydrogel for administration of Polyethylenimine (PEI)/siRNA complexes combined with poly-lactide (PLA) and coated with polyvinyl alcohol (PVA) as an anti-inflammatory option in diseases such as inflammatory bowel disease	(190)
	Starch+ pectin	Probiotic colon delivery	(191)
	Montmorillonite + Chitosan + AA + acrylamide + PVP	Gastroretentive system for extended drug delivery of Clarithromycin	(115)
	Methacrylic acid + N-vinyl pyrrolidone + poly(ethylene glycol) monomethylether monomethacrylate	pH-responsive hydrogel for oral administration of peptides and proteins such as insulin and porcine growth hormone	(117)
	Hydroxyehtylacryl chitosan + sodium alginate	pH-responsive hydrogel for site-specific oral drug delivery in the intestine and colon	(116)
Rectal	PEG 4000 + 1,2,6 hexane triol + dicyclohexylmethane 4,4' diisocyanate	Monolithic sustained-release morphine hydrogel suppository	(118)
	Starch	Rectal administration of Morphine Hydrogel	(192)
	Hydroxypropylcellulose (Klugel GF 300mPa)	Pentobarbital hydrogel for rectal administration in paediatric procedural sedation	(119)

	PEG	Hydrogel rectal spacers for prostate brachytherapy	(193)
Ocular	Deacylated gellan gum + kappa carragenan	Ion-sensitive hydrogel with increased residence time on the corneal surface	(120)
	Betaxolol hydrochloride + P407 + P188 + polycarbophil	Thermosensitive in situ gelling and mucoadhesive ophthalmic drug delivery system	(163)
	Poly-2-hydroxyethyl methacrylate (p-HEMA)	Sustained-release p-HEMA gels loaded with dimyristoyl phosphatidylcholine (DMPC) liposomes during a period of about 8 days	(194)
	Propoxylated glyceryl triacylate and silicone	Glaucoma therapy by extended release of timolol from propoxylated glyceryl triacylate nanoparticle-laden silicone hydrogel contact lenses	(195)
	Poly(2-hydroxyethyl methacrylate) (HEMA/PVP) Silicone (TRIS/NVP/HEMA)	Use of a cationic surfactant cetalkonium chloride for controlling the release of drugs, such as Diclofenac, Ketorolac and Levofloxacin, from hydrogels for contact lenses	(196)
	Poly-hydroxy ethyl methacrylate (p-HEMA)	Brij 98 (surfactant) loaded p-HEMA hydrogel for extended release of Cyclosporine A	(197)
	Chitosan hydrochloride	Thermosensitive ophthalmic hydrogel with chitosan nanoparticles with 5-FU	(31)
Topical	Gelatine	Silver nanoparticle-loaded gelatine hydrogel pads as antibacterial wound dressings	(124)
	Acrylamide	Hydrogel Containing Nanoparticle Stabilised Liposomes for Topical Antimicrobial Delivery	(125)
Transdermal	HPMC + Carbopol 934	Pregabalin in niosomal hydrogel for controlled transdermal drug delivery system	(126)

	Pluronic® F127-reduced graphene oxide	Reduced graphene oxide laden hydrogel for transdermal delivery of buprenorphine to treat osteoarthritis	(128)
	Gantrez® S-97 (copolymer of methylvinylether and maleic acid) + PEG PVA + PVP	Hydrogel-forming microneedle arrays to transdermally deliver tuberculosis drugs, namely rifampicin, isoniazid, pyrazinamide and ethambutol	(127)
Vaginal	Hydroxyethylcellulose + PEG 400	Mucoadhesive cellulosic derivative sponges as drug delivery system for vaginal application	(198)
	Pluronic® F127 + chitosan	Topically applied thermosensitive and mucoadhesive hydrogel containing metronidazole for the treatment of Trichomonas vaginalis infections	(129)
	Pluronic® + HPMC	Thermosensitive and mucoadhesive pluronic®/HPMC hydrogel containing the mini CD4 M48U1 as a promising efficient barrier against HIV	(130)
Nasal	Poloxamer 407 + PEG	Intranasal administration of the antiemetic drug, metoclopramide hydrochloride in an *in situ* gelling mucoadhesive hydrogel	(122)
	Chitosan + hydroxyl propyl methyl cellulose	Intranasal mucoadhesive temperature-mediated *in situ* gel containing ropinirole	(123)
	Gellan gum + carbopol 934P	Intranasal mucoadhesive *in situ* gel of metoclopramide hydrochloride	(199)
Injectable	Polyvinyl caprolactam–polyvinyl acetate–PEG (Soluplus®)	Self-assembled tacrolimus nanoparticles cross-linking thermosensitive hydrogels for subcutaneous injection for local rheumatoid arthritis therapy	(133)
	Pluronic® F127 + HA	Injectable and Thermoresponsive Self-Assembled Nanocomposite Hydrogel for Long-Term Anticancer Drug Delivery, with Doxorubicin	(176)

	Silk	Self-Assembling Doxorubicin Silk Hydrogels for the Focal Treatment of Primary Breast Cancer	(134)
	Collagen	Small molecules combined with collagen hydrogel direct neurogenesis and migration of neural stem cells after spinal cord injury	(200)
	Agarose	Sustained local delivery agarose hydrogel with embedded methylprednisole encapsulated in biodegradable PLGA based nanoparticles	(201)
	Pluronic® F127	Thermosensitive injectable smart hydrogels for controlled drug delivery system	(146)
	HA + methylcellulose	Intrathecal delivery of a polymeric hydrogel with drug-loaded poly(lactide-co-glycolide) nanoparticles after spinal cord injury	(202)
Implant	PEG – gelatine methacrylate	Biomimetic 3D-printed scaffolds with neural stem cells for spinal cord injury repair	(175)

Table A.3: Smart Hydrogel Usage by Stimuli-Responsiveness

Stimuli	Polymer	Application	Reference
pH-responsive	Dibenzaldehyde-functionalized polymer (DF-PEG) and polyaspartylhydrazide with incorporated black phosphorus nanosheets	IV delivery of Doxorubicin to tumour sites	(144)
	Poly(itaconicacid-co-N-vinylpyrrolidone)	Oral delivery of high isoelectric point-exhibiting therapeutic proteins (calcitonin)	(203)
	Salecan + 2-acrylamido-2-methyl-1-propanesulfonic acid	Controlled insulin delivery, oral drug delivery system	(204)
	Carboxymethyl cellulose/2-hydroxyethyl acrylate	Transdermal delivery of naringenin	(140)
Thermo-responsive	Poloxamer 407 and Poloxamer 188	Nasal delivery of phenylephrine hydrochloride	(19)
	Pluronic®- HPMC	Vaginal microbicide hydrogel, containing peptide mini CD4 M48U1	(130)
	Chitosan	Transcorneal administration of 5-FU	(31)
	Hexamethylene diisocyanate + Pluronic® F127 + HA	Injectable and thermoresponsive self-assembled nanocomposite hydrogel for long-term delivery of doxorubicin	(176)
	Pluronic® F127 + Polyethylene Oxide	Sol-Gel Composites of Paclitaxel/Dimethyl-β-Cyclodextrin for buccal delivery	(188)
Photo-responsive	α-cyclodextrin and poly(ethylene glycol)-modified dendrimer encapsulated platinum nanoparticles	Near Infrared Light-responsive and Injectable hydrogel for delivery of bortezomib	(151)
	Azobenzene-modified dextran	Nanogel system for controlled release of aspirin	(149)
Electro-responsive	2-dimethylamino ethyl methacrylate (DMAEMA), sodium 4-vinylbenzene sulfonate, styrene , and acrylate-poly(ethylene glycol)-N-hydroxysuccinimidylester	Injectable delivery of the antiepileptic drug phenytoin sodium	(155)
	Poly(ethyleneimine) +1-vinylimidazole + PVA + AA	Transdermal delivery of indomethacin	(154)
	PA + PPy	Controlled release of the drug risperidone through implantable hydrogel	(156)

Magnetic-responsive	Cellulose with F_3O_4 nanoparticles	Remotely controlled drug release of 5-FU from hydrogel beads under external magnetic field	(158)
	Starch + Co-doped zinc ferrite nanoparticles	Magnetic controlled release of prednisolone	(205)
	Chitosan with Iron (III) and (II) added as magnetite precursor	Magnetic controlled release Doxorubicin and Rifampicin	(206)