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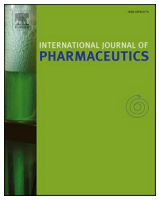

Review

Fundamental advances in hydrogels for the development of the next generation of smart delivery systems as biopharmaceuticals

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ABSTRACT

Recent advances in developing and applying therapeutic peptides for anticancer, antimicrobial and immunomodulatory remedies have opened a new era in therapeutics. This development has resulted in the engineering of new biologics as part of a concerted effort by the pharmaceutical industry. Many alternative routes of administration and delivery vehicles, targeting better patient compliance and optimal therapeutic bioavailability, have emerged. However, the design of drug delivery systems to protect a range of unstable macromolecules, including peptides and proteins, from high temperatures, acidic environments, and enzymatic degradation remains a priority. Herein, we give chronological insights in the development of controlled-release drug delivery systems that occurred in the last 70 years or so. Subsequently, we summarise the key physicochemical characteristics of hydrogels contributing to the development of protective delivery systems concerning drug-targeted delivery in the chronospatial domain for biopharmaceuticals. Furthermore, we shed some light on promising hydrogels that can be utilised for systemic bioactive administration.

1. Drug delivery systems

Drugs, i.e., pharmaceutical active ingredients (API) or therapeutic agents, are interchangeable terms describing the active ingredients enclosed by medicines. Formulation of drugs into medicines in different administrative forms blended with other constituents known as excipients. These excipients play a crucial role in the mechanisms of delivery; the protection of the drugs from incompatible environments such as stomach acidity; the dissolution rate; the solubility of drugs; the absorption throughout an epithelial transmembrane; the bioavailability of different active ingredients; and the patient's compliance, e.g., masking malodour and unpalatable taste (Aulton et al., 2013; Van der Merwe et al., 2020).

However, the rules and criteria that govern the incorporation process of drugs and excipients into safe and effective medicines are profoundly convoluted. The complexity of the biological living system and the diversified nature of drugs attributed to a complex and wide range of physicochemical and biological barriers affect the delivery of effective and safe medicine. Drugs can vary from small chemical molecules and peptides to large proteins. Furthermore, conventional chemical molecules are assorted into weak acids and weak bases, ionised and unionised, and polymorphic and amorphous compounds. For example, the moieties of antimicrobial peptides (AMPs) are often blended into ionic, cationic, and unionised molecules. These physicochemical and biological characteristics influence the behaviour of the molecules in the multifunctional physiological living systems. It impacts the dissolution rate, solubility, stability, transepithelial permeability, therapeutic effect, and clearance of these drugs, which should be considered throughout the drug discovery process (Aulton et al., 2013). Such ceaseless challenges limit the number of marketed drugs despite the pharmaceutical industry's intensified global research and development. Approximately-one out of ten thousand preclinically tested products makes their way through the final processes of the marketplace (Gassmann et al., 2018).

As in the case of AMPs, whereby the molecule is significantly more complex and incredibly sensitive compared to conventional APIs, Just over the past three decades, more than 200 remedial proteins and 100 therapeutic peptides have been introduced to the pharmaceutical market across various clinical indications including cancer, autoimmune, endocrinological, and neurological conditions, and very few for infectious diseases (Muheem et al., 2016). Hence, the lack of a comprehensive delivery system that amalgamates optimal drug bioavailability and patient compliance has hindered the clinical translation of hundreds of potential therapeutic AMPs alongside other bioactive molecules into medicines. Poor luminal permeability, high cytosolic metabolism,

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gastric degradation, and the first hepatic clearance of these proteins and peptides lead to low bioavailability. Therefore, the parenteral administration route is still considered the methodology of choice for bioactive molecules requiring frequent injections that reduce patient compliance (Gupta et al., 2013; Muheem et al., 2016).

The orally controlled-release drug delivery system is the most constructive formulation option in increasing patient compliance, reducing cost, and the number of administered doses of particular medicine (Wang et al., 2019). This idea has been the subject of many research investigation projects. Consequently, a small number of peptides, mainly hormone-based biopeptides, have been introduced to the market in an oral dosage form, primarily as an enteric-coated tablet, to overcome the limitations of gastric degradation. For example, Leuprolide for the treatment of endometriosis has been encapsulated by "Enteris Biopharma" in an enteric-coated polymer that applies a barrier against dissolution in the gastric environment, but it does not possess the required timely release characteristics (Iqbal et al., 2011). Another example, an oral lyophilized formulation of "Desmopressin," which is used to treat nocturnal enuresis, has been developed by the manufacturer (Ferring Pharmaceuticals) after deregistering the nasal form by the FDA (De Guchtenaere et al., 2011). According to the manufacturer, Desmopressin is a small peptide consisting of 9 amino acids that can evade the gastric degradation process by utilizing freeze-drying technology (De Guchtenaere et al., 2011). This technology might not apply to larger peptides with different amino acid sequences easily exposed to degradable enzymes due to larger surface area. Hence, there is not yet a helpful vehicle for AMPs to offer slow-release patterns for better patient compliance and higher medication efficacy. Nevertheless, Yao et al. (2014) managed to form an aqueous-phase synthesis of HPMC/PAA hybrid nanogel. In doing so, the team encapsulated insulin into nanogels and showed the ability of the ingested new formula to maintain healthy levels of blood sugar readings in diabetic mice.

To overcome these physicochemical and biological impediments that alter and, in some cases, abolish the drug activity in vivo, scientists have been focusing for the last few decades, across multiple disciplines, on different technologies to advance and customise controlled drug delivery systems (CDDS). These technologies target the long-lasting and protection aspects of the active ingredient; the releasing kinetics and bioavailability; the localization; the affinity; the pharmacodynamics; and the therapeutic effect of the drug (Bajracharya et al., 2019; Choonara et al., 2014; Siew, 2018; Tibbitt et al., 2016).

1.1. The chronological conceptualisation of CDDS and the emergence of the polymeric model

In the past, pharmaceutical scientists formulated drugs via basic formulations of medicines that guaranteed complete and instantaneous release of the active ingredients upon their contact with the physiological fluid. Generally, the result should significantly increment drug bioavailability beyond the therapeutic levels in such scenarios. Consequently, a plethora of patient toxicity incidences, severe drug adverse reactions, and short half-lives of drugs was reported (Siepmann et al., 2012; Szycher, 1986; Yun et al., 2015). Hence, in the early 1950s, pharmaceutical scientists introduced the concept of prolonged drug release from medicine to control unwanted adverse reactions (Yun et al., 2015). This fundamental concept swiftly inspired scientists from different backgrounds to join forces and be part of a versatile and rewarding scientific enterprise. Therefore, the collaboration between multidisciplinary scientists, including chemists, physicists, pharmaceutical scientists, and biological and medical experts, resolved the physiochemical and biological challenges that hamper drug development (Peppas, 2013).

In 1952, Smith Klein Beecham was the first pharmaceutical organisation to implement the concept of a sustained drug delivery system which showed maintenance of the experimental drug's therapeutic level over 12 h (Yun et al., 2015). The technology that was employed then was the "spansule." They experimented with belladonna alkaloids (atropine), a nonselective muscarinic receptor antagonist (anticholinergic). Atropine is used in gastroenterological procedures to reduce mucosal secretions and heart rate. The average duration of action of atropine sulphate is between 3 and 4 h which can be enhanced by one more hour with the aid of mucic acid (atropine mucate or hyperduric atropine) (Mushin et al., 1953).

In contrast, utilizing the "spansule" technology, the atropine effectiveness was prolonged for up to 12 h (Thomson, 1955). This technique involves distributing the required dose to many identical small pellets coated unequally with digested wax. Consequently, the prolonged effect of the drug was attained through sequential dissolution rates of the coated pellets depending on the thickness of the wax (Thomson, 1955).

Soon after, the concept of controlled drug release started gaining significant momentum. The idea gained recognition following the work of Takeru Higuchi 1961, a pioneer scientist in this field. Higuchi introduced the controlled drug vehicle's physicochemical principles as the foundation of the mathematical model that describes the continuous drug transport from a saturated concentration through a layer possessing the dissolved drug. Then, he was the first to forward the idea that a cumulative fraction of drug release into a medium from a saturated vehicle is proportional to the square root of time (Siepmann and Peppas, 2011b). After that, this theory was developed further when Higuchi introduced the porosity of the vehicle as one of the critical factors that dictate the diffusion coefficient (Higuchi, 1963). Further developments have pursued this to the mathematical model. Biophysicists have targeted the relationship between the drug release, the diffusion (biodegradability), and the swellability of the matrix (Paul and McSpadden, 1976; Peppas et al., 1980).

Alongside the pioneering developments of mathematical modelling of the drug diffusion and release kinetics, there was another venture in progress concerning the fabrication of the controlled drug delivery vehicle. In 1964, Folkman et al. from Harvard Medical School researched, elucidating a prolonged drug therapy methodology based on a controlled drug delivery vehicle made of silicon rubber polymer to deliver small molecules (Folkman and Long, 1964). Ten years later, this methodology was developed further to function as a sustained-release vehicle for various applications, including implants for large proteins assigned for angiogenesis research and five-year contraceptive implants (Folkman, 1990; Wathoni et al., 2018).

Towards the end of the second decade of this historical era of the pharmaceutical world, a prominent group of researchers joined a newly established commercial company producing controlled drug delivery systems, providing an example of how scientists can change venture capitalists' minds. According to Peppas, a remarkable landmark in the pharmaceutical industry was originated by Dr Alejandro Zaffaroni in 1967 when he established ALZA corporation, which immediately attracted an impressive number of chemical and pharmaceutical researchers (Peppas, 2013). Nowadays, ALZA is a world-leading developer and manufacturer of various controlled drug delivery systems, including patches, implants, and oral forms that make drug administration more efficient and effective (Lähteenmäki and Jukarainen, 2000; McCoy and Hoskins, 2007). ALZA develops different systems under its drug portfolio and other worldwide pharmaceutical companies (McCoy and Hoskins, 2007). For example, the osmotic drug delivery system was one of the first controlled drug delivery technologies that have been developed. Moreover, it was one of the most promising systems *(prior to the discovery of responsive hydrogels and the stimulated release of the drug at the target site)* for controlled drug delivery, primarily because of the zero-order kinetics, which is independent of the initial drug concentration (Gupta et al., 2010; Keraliya et al., 2012).

Osmotic drug delivery systems have been developed for both oral administration and implants. The mechanism of action relied on an inner core carrying the drug alongside a swellable polymeric system. This reservoir is coated with a semipermeable membrane which permits the solvent to percolate into the polymer and increase its volume

pushing the drug solution out of the reservoir through an orifice (Keraliya et al., 2012). A broad range of osmotic drug delivery systems has been developed after introducing osmotic technology. In 1955, Australian scientists Rose and Nelson developed the so-called Rose-Nelson system to deliver drugs to cattle and sheep guts (Rose and Nelson, 1955). Rose-Nelson system was subjected to different modifications introduced by Higuchi and Leeper, described in a US patent (Higuchi, 1973) and was developed, in a later stage, by ALZA corporation Higuchi-Leeper system. The osmotic technology has been modified further to produce the Alzet and Osment systems; the elementary osmotic system; the push–pull system; and the controlled porosity osmotic system (L-OROS), followed by the sandwiched osmotic tablet (Keraliya et al., 2012; Ranade, 1990).

The transdermal drug delivery system (TDDS) was another central area explored successfully by ALZA researchers and others during the infanthood of the controlled drug release systems (McCoy and Hoskins, 2007). TDDS delivers a steady amount of therapeutically effective drugs across a patient's skin. Moreover, the transdermal delivery methodology allows a constant flow of drugs with short biological half-lives, eliminates the bolus injections' undesirable side effects, and prevents the first-pass hepatic metabolism of the drug (Hanumanaik et al., 2012; Ranade, 1990). The main components of patches are the polymer matrix, the drug, and the permeation enhancer. The polymers used for TDDS can be natural, e.g., cellulose derivatives and gelatine, synthetic elastomers, e.g., silicon rubber, and synthetic polymers, e.g., polyvinyl alcohol. Furthermore, the mechanism of the drug delivery system is based on diffusion out of the polymeric system through a membrane to the skin and entering the bloodstream, driven by a gradient in concentration (Hanumanaik et al., 2012; Pongjanyakul et al., 2003).

Based on the above, pharmaceutical scientists have revolutionized the conception of the drug delivery system and drug discovery throughout the early years (between the early fifties and the late seventies). Consequently, comprehensive novel technologies started taking control of the industry expeditiously. These early inventions have smoothed the way for further advanced and more intelligent scientific approaches and materials, such as hydrocolloids, to be introduced to the pharmaceutical field in the years ahead (Yun et al., 2014).

1.2. Hydrogels' role in controlled drug delivery systems

Hydrogels are hydrocolloids dispersed in an aqueous medium or physiological fluid (Ishwarya S and Nisha, 2022). They are hydrophilic, three-dimensional crosslinked networks of single or multiple monomers produced by chemical or physical reactions (Ahmed, 2015; Rosiak and Yoshii, 1999). Moreover, the hydrogel can swell and retain large amounts of fluids in response to various stimuli while maintaining its structural integrity and flexibility (Fig. 1) (Akhtar et al., 2016; Caló and Khutoryanskiy, 2015; Feng et al., 2022). Hence, hydrogel's structural cohesion results from water absorption enhanced by the hydrophilic functional groups attached to the polymeric backbone.

However, the immunity against degradation of such structure rises from the crosslinking between network chains (Akhtar et al., 2016; Caló and Khutoryanskiy, 2015). The degree of crosslinking of hydrogel determines the durability of the system. This durability can be ranked between weak and robust in terms of physical toughness. Moreover, it can be predicted throughout the rheological behaviour of the polymer system during its stable phase (Lauren et al., 1980). Hydrogels can be categorised based on their physical characteristics giving rise to distinct shapes, including slabs or macroscopic gels, microgels, nanogels, coatings, and films. As a result, they can commonly be used as responsive carriers for different agents used in a wide range of medical and clinical applications, including biosensors, tissue engineering, and cells and drug delivery devices which have become a significant area of research interest (Choonara et al., 2014; Ganji and Vasheghani-Farahani, 2013; John, 2022; Lee et al., 2013; Peppas et al., 2006; Tibbitt et al., 2016; Wang et al., 2019; Zhang et al., 2016a).

Nevertheless, biopolymer-based nanomaterials, including self-assembled peptides, exhibit unique properties as smart hydrogels-based CDDs. Self-assembly is a spontaneous association of individual molecules into a complex functional structure through noncovalent physical interactions (Yadav et al., 2020). Peptides can demonstrate self-assembly beyond the cellular structure integrity (Misra et al.). This phenomenon has been utilised in designing nano-blocks made of short peptides or amino acids for advanced CDDs. Research has been invigorated by the diversified physicochemical properties of peptides and their biocompatibility and biodegradability (Nassar et al., 2022). Dipeptides and tripeptides have been identified to carry motifs with all the required information to support the formation of sophisticated self-assembled nanostructures with unique functional characteristics encompassing mechanical rigidity, semi-conductivity, piezoelectricity, and visible luminescence (Gazit, 2015). Furthermore, manipulating the self-assembled characteristics is readily attainable through an assortment of attached amino acids or by grafting different functional groups to the main chain of the polymer (Caruso et al., 2014; Misra et al.).

In recent years, hydrogels have been widely used in the development of controlled drug delivery vehicles due to their high compatibility, biodegradability, low cost, and simple production, in addition to their ability to protect sensitive drugs from harsh environments. Furthermore, researchers utilize responsive hydrogels for controlled drug delivery systems with the vision of improving patient compliance, eliminating adverse reactions, and releasing the active agent locally at the target site (Akulo et al., 2022; Allen and Cullis, 2004; Alvarez-Lorenzo and Concheiro, 2014; Bhattarai et al., 2010; Gassmann et al., 2018; Hu et al., 2018).

Indeed, hydrogel's geometry (shape and size), chemical characteristics (hydrophilicity/lipophilicity), and cross-linking degree are critical

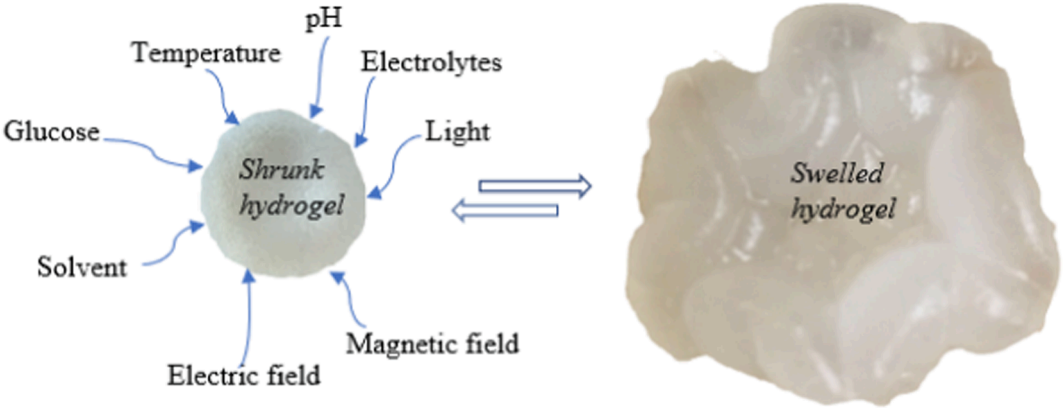

Fig. 1. Schematic illustration of the hydrogel swelling in response to different stimuli.

for its mechanical properties. These mechanical characteristics, alongside the pH and the temperature of the solvent, are critical for swellability and erosion (biodegradability) as the main parameters controlling the releasing and transporting kinetics of the drug (Caccavo et al., 2015; Kelly et al., 2019; Krese et al., 2016; Lamoudi et al., 2016; Langer, 1983; Li et al., 2005; Siepmann and Peppas, 2012). The particle size of the drug's molecule alongside the mesh size (porosity) of the hydrogel enables the loading of drugs into the gel matrix and the subsequent controlled drug release over a prolonged time from different forms, including oral, topical, and injectable hydrogels (Caraballo, 2010; Ghori et al., 2018; Korsmeyer et al., 1983; Song et al., 2018; Zhang et al., 2017).

Thus, diffusion and drug release modelling from a hydrogel is a complex physical–mathematical procedure due to the complexity of the involved parameters attributed to the drug, the hydrogel, and the solvent. The overall drug release from hydrogel is a cascade of different mechanisms of the following processes (Zhang et al., 2017):

i. The hydrocolloid absorbs percolated water/gastrointestinal fluid (plasticiser) in the glassy phase, reducing the glass transition temperature (T_g). Subsequently, the hydrocolloid experiences a transition from the glassy to the rubbery phase and an increment in volume and diffusion coefficient.
ii. Swelling hydrogel leads to significant changes in the polymer geometry, the drug/excipients concentrations, and the porosity of the polymer.
iii. Dissolution of the active ingredient and release into the surrounding medium is facilitated by the swelling and diffusion mechanisms of the hydrogel driven by the concentration gradient.

2. The T_g concept and its application in drug design

The concept of the state of the matter was fostered over the last millennium. It refers to the capacity of the matter to perform a translatory motion as a function of its molecular assembly. Based on this conceptual definition, there are apparent discontinuities in the three states of matter (gaseous, liquid, and solid) determined based on the motion timeline over a practical observation (Kasapis, 2008).

Nevertheless, cooling viscous liquids fast can avoid the crystalline solid form leading to the amorphous solid or glassy (vitreous) state (Debenedetti and Stillinger, 2001). Throughout this fast cooling/thermodynamic process, the substance reaches a glass transition temperature (T_g), where the molecules of a system enter a dynamic arrest due to time insufficiency to relocate into the minor energy state during the rearrangement and the binding process with neighbouring atoms/molecules (Jadhav et al., 2009). Consequently, a reversible T_g-dependent amorphous solid (glassy state) is created where below T_g the molecules are only vibrating, and above T_g, they gain translational and rotational motions within a viscous liquid after undergoing a solid-rubbery (supercooled liquid) state. This unique, glassy phenomenon with distinctive characteristics from the liquid and crystalline forms is regarded as the "fourth state of matter" (Debenedetti and Stillinger, 2001).

Nowadays, scientists across different specialties realise the importance and the capacity of the glassy state on the dynamics and the longevity of commercialised products and even on the conservation of certain lifeforms as it is the preserving factor for microorganisms that existed for centuries under complete dehydration conditions (Crowe et al., 1998; Sahoo et al., 2021). The glass phenomenon is an exclusive characteristic of amorphous substances. It plays a significant role in the stability of commercialised products across different fields. It determines the safety zone for food products before various chemical reactions and enzymatic activities lead to product collapse (Kasapis and Sablani, 2005). Pharmaceutically, the glassy state plays a vital role as a stabilizer and solubilizer and, subsequently, it controls the bioavailability and the safety profile of the API; moreover, it has a profound influence on the mechanism and the kinetics of the drug delivery system (Jadhav et al., 2009; Leyva-Porras et al., 2019).

Pharmaceutical scientists formulate immiscible pharmaceutical products in different polymorphic packs and amorphous forms aiming for optimal dissolution, solubility rate, and bioavailability. The structure of an amorphous material is characterized by lacking a long-range order of its molecules, leading to random aggregation of highly energetic molecules compared to a more symmetrical and stable crystallized form. The high activation energy in the amorphous state can become the thermodynamical driving force behind the dissolution and bioavailability of the drug (Gupta et al., 2004). However, this excess energy in the glassy state becomes the driving force behind potential crystallization processes (Ueda et al., 2014, Miyazaki et al., 2007). This process of hindering the crystalline form of drugs to increase solubility goes in parallel with monitoring the behaviour of the pharmaceutical product in the vicinity of the T_g as a function of shelf life (Martïnez et al., 2016).

One of the critical issues during the development of a new medicine is to establish the balance between the required degree of the drug solubility alongside the excipients for the necessary therapeutic window and the stability of the active ingredients over a reasonable shelf-life span (Sakurai et al., 2012). This balance is utterly attainable via a fundamental rationalization of the T_g as the phase time/temperature-dependent transitional point from the glassy to the rubbery state (Rahman et al., 2007). This process is influenced by temperature, pressure, and humidity, leading to changes in the amorphous substances' molecular dynamics and relaxation time (Kasapis, 2006; Rahman, 2010). To be specific, T_g is the quality control marker for the physical and chemical stability of the active pharmaceutical ingredient as a function of storage conditions (Baird and Taylor, 2012).

Manipulating the T_g of the API and improving the stability of highly amorphous APIs can be achieved, also, throughout the development of solubilizing and stabilizing carriers named solid dispersions. In 1961 Sekiguchi and Obi were the first to come up with this concept when they introduced the polyethylene glycol 6000 (PEG 6000) and poloxamer 407 as hydrophilic carriers in an attempt to commercialise the ursolic acid, which possesses a shallow rate of solubility and bioavailability with unique pharmacological applications (Eloy and Marchetti, 2014). Nowadays, polymeric carrier matrices can be utilised as solid dispersion platforms for various APIs ranked between amorphous and crystalline to manipulate medicine properties such as solubility, absorption, and physical/chemical stability (Baghel et al., 2016). They contribute new physicochemical characteristics of the API based on different physical or chemical interactions (hydrogen bonding, van der Waals forces, electrostatic, ionic, or hydrophobic interactions) between the cargo and the matrix, leading to optimised stability of the system mainly for amorphous substances (Paudel et al., 2013). Thus the three-dimensional structure of polymeric systems provides physical restrictions on the molecular mobility of the API leading to a reduction in chemical potential that hinders the instability and decomposition of the substance (Cui, 2007). Moreover, loading a highly durable polymeric system (high T_g) with an API with lower T_g leads to a complex with an intermediate T_g for both components, which results in an anti-plasticization effect on the API by increasing the viscosity reducing the dissolution rate (Baghel et al., 2016).

In addition to the regulatory effect of T_g on the dissolution, solubility, and stability of the amorphous API, the diffusion/release of the API to the surrounding physiological medium is another significant aspect of drug discovery. Thus, API diffusion from a solid dispersion system like a hydrogel is a function of the transitional degree of the matrix from the glass-solid to the rubbery-solid conditions. The generated chemical-potential forces this transition between the two states due to changes in temperature and/or pressure which continues until an equilibrium is achieved (Aulton et al., 2013; Cook and Dickerson, 1995). The relaxation process of the hydrogel matrix in the vicinity of the T_g leads to an expansion of the available free space. Subsequently, the molecular

dynamics of the active ingredient trapped inside the hydrogel mobilise, leading to a significant increment in the rotational Brownian motion resulting in a higher diffusion rate to the neighbouring phase through the polymeric membranes (Eloi et al., 2013; Kini and Patel, 2017; Martïnez et al., 2016; Paul, 2010).

In the following section, the focus will be centred on the mechanism of controlled drugs released from the hydrogel matrix. It will articulate the significance of the ***phase transition*** phenomenon existing in solid amorphous systems in contrast to the melting process in crystal materials and the "degree of fragility" (viscosity) in the vicinity of the T_g on the controlled release of drug delivery mechanisms. Moreover, we will shed some light on the ***"free volume"*** concept, which has been utilised as one of the most traditional theories of the glass transition in the vicinity of T_g.

2.1. Phase transition and the free volume concept

The phase transition is forked between two different main categories, which include: (i) the first-order (ii) and the second-order transition based on the demonstration that the matter either absorbs or releases the latent heat during the thermal process (Breaux et al., 2005; Leyva-Porras et al., 2019). Generally, during the first order, there is an absorption of the latent heat leading to a discontinuity in thermodynamic parameters, including volume (V), enthalpy (H), and entropy (S), owing to the matter transitions including crystallization, melting, condensation, and evaporation (Fig. 2. A) (Baird and Taylor, 2012).

However, in the second-order transitions, the thermodynamic parameters (V, H, S) keep showing continuity with a positive change in the slop of the increased temperature (Fig. 2B) (Baird and Taylor, 2012). In recent years, studying this phenomenon of transformation between the glassy and the rubbery states and vice versa in the vicinity of the T_g was contemplated from different angles.

Scientists have employed thermodynamic and kinetic concepts to explain the glassy state as one of the solid material's most complex physical dilemmas (Kaushal et al., 2004). As mentioned earlier, T_g is linked to thermodynamic parameters, which suggests that the glass transition phenomenon is a second-order transition. The T_g is the temperature at which the system falls out of equilibrium leading to a decrease in heat capacity as the derivative of enthalpy (Angell, 1995b). This reduction in the heat capacity of the stable crystal (lowest energy level, i.e., entropy ≈ 0) below the heat capacity of the liquid can lead to an entropy crisis (negative entropy) where the consumption of the entropy upon supercooling will lead to dissipation at the temperature of the stable crystal (Debenedetti and Stillinger, 2001). Hence, the entropy of the supercooled liquid will become less than the entropy of the stable crystal, i.e., negative entropy. Thermodynamically this is unfeasible; thus, the liquid forms a unique, glassy state at the Kauzman temperature of the stable crystal, exhibiting a second-order transition (Gibbs and DiMarzio, 1958).

Kinetically, the elucidation of the glassy state and the transitional phase can be clarified by exploring the free volume theory. Over the past few decades, the free volume notion was developed based on definitions established by material scientists, including Doolittle, Cohen and Turnbull, and Simha and Boyer (Cohen and Turnbull, 1959; White and Lipson, 2016). Subsequently, the free volume principle has gained considerable publicity as a medium to explain the dynamic and mechanical characteristics such as viscosity, transition temperature, strength, toughness, and relaxation processes of the polymeric matrix (White and Lipson, 2016) which, in turn, determine the type and order of the API release (Karavelidis et al., 2011). The concept of free volume refers to the space required for the string-like movements of polymeric segments and the occupied space by the van der Waals radii of polymeric contours affected by the thermal vibration of the individual residue (Kasapis, 2008). The free volume is the occupied volume of the equilibrium liquid at 0 K subtracted from the total volume (Vrentas et al., 1989). Quantifying this free volume is unobtainable either in a melt or glassy matrix; nevertheless, an estimate of the fractional free volume is achievable (White and Lipson, 2016) shown in Fig. 3.

Assumptions:

- u_o is the occupied volume (constant fraction of the total volume below T_g, so it has been drawn in parallel to the total specific volume (u) below T_g, with the difference being a small constant fraction of u.
- The expansion of u_o above the T_g has inflated beyond the steadiness of the initial trend leading to an increment to a new volume termed u_f (free volume).
- u_{fg} is a small fraction of the "constant" free volume at and below T_g.
- The free volume expansion component (u_T) increased with temperature T and is proportional to the difference between the expansivity below T_g (α_G) and above T_g (α_L).

Hence, the free volume component increases with temperature (u_T) according to the relation: $u_T = (\alpha_L - \alpha_G)(T - T_g)$

since: $u_f = u_{fg} + u_T$, and

$u_f = u_{fg} + (\alpha_L - \alpha_G)(T - T_g)$

Note: The difference ($\Delta\alpha$) between α_L and α_G is written as α_f *thermal expansion coefficient of the free volume,* which undergoes a discontinuity due to a significant increase in the total volume at T_g, which was depicted by a sudden and sharp change in slope (Fig. 3).

Throughout the analysis of the free volume development during the transitional phase in the vicinity of T_g, for more than 50 different polymeric systems, it was shown that synthetic polymers must have a minimum of free volume in order to be preserved in the melt state (White and Lipson, 2016). In glass transition, the free volume theory

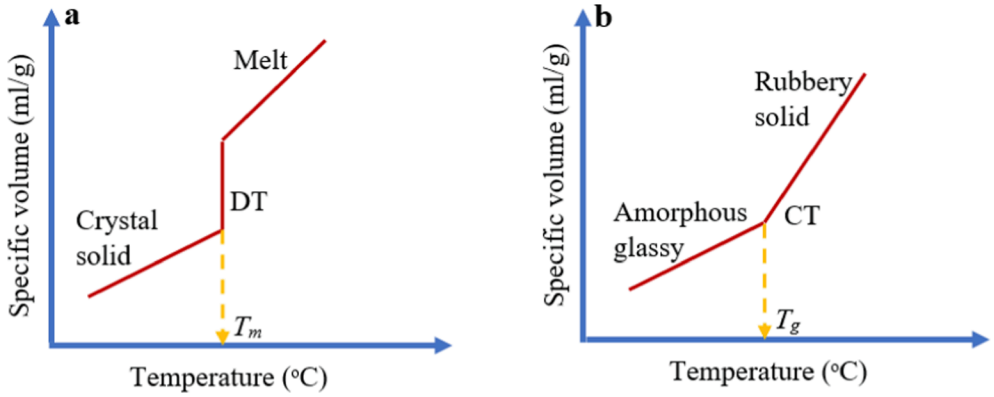

Fig. 2. Schematic representation of (A) Melting transition of a crystalline solid-state showing an abrupt sharp increase in the specific volume as a discontinuous transition (DT) that takes the event as reaching the melting temperature (T_m) in the surrounding vicinity (B) Glass transition of an amorphous solid state showing a continuous change in the slop without an abrupt change in the specific volume at T_g.

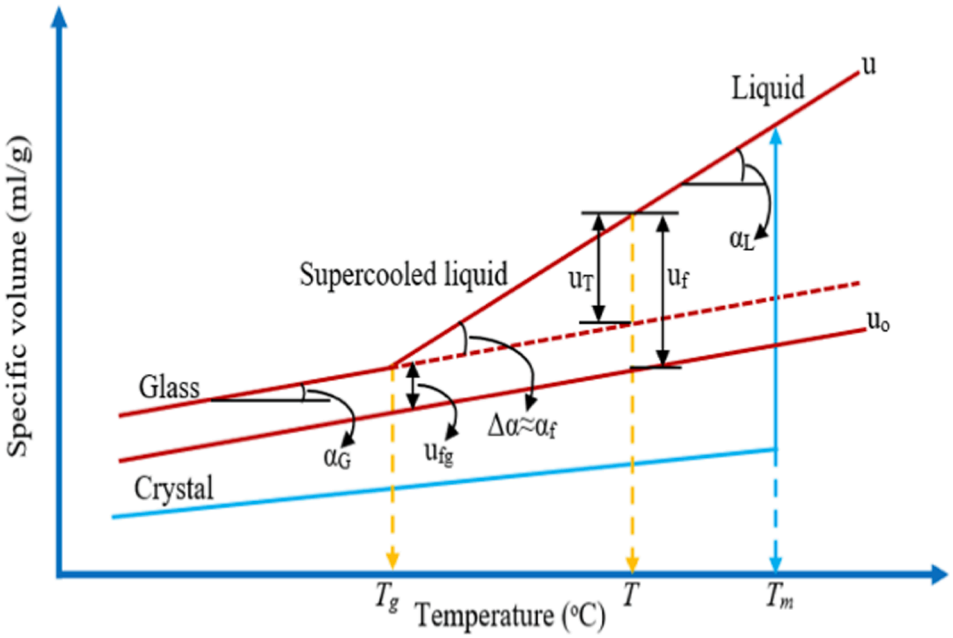

Fig. 3. Illustrating the geometrical calculations of the total free volume (u_f) as a function of temperature in the amorphous matrix (red) compared to the crystallin matrix (blue).

predicts the proportion of the free volume to be around 3 % of the total volume, which undergoes a significant expansion up to about 30 % in the melt, allowing fluids to move freely (Kasapis, 2008). This model presumes that molecular diffusion throughout the system is exclusive to a minimal free volume above the critical volume reached the specific T_g of the matrix, followed by translational motion and diffusion of the trapped molecules (Kaushal et al., 2004).

Thus, the kinetic explication of the glass transition phenomenon is based on the structural relaxation time required by the molecule to diffuse from the centre of its vibrational space to another centre across the intermolecular distance (Kaushal et al., 2004). This structural relaxation time of the matrix has been demonstrated to be inversely affected by the constituents' molecular weight, including the cargo and intrinsic viscosity (Angell, 1995a; Omelczuk and McGinity, 1992). Hence, the performance of solid dispersions is directly related to the intrinsic viscosity that has a noticeable relevance to drug dissolution and solubility (Kaushal et al., 2004). These constituent characteristics determine the T_g threshold, which directly affects the relaxation time and the free volume and, consequently, the diffusion and release kinetics of the cargo to the surrounding vicinity (Angell, 1995a; Angell, 1995b; Kaushal et al., 2004; Omelczuk and McGinity, 1992; Roussenova et al., 2014). Thus, free volume is a quantitative measure of the physical changes due to the mechanical relaxation of the matrix that governs the controlled drug release via the *Tg* threshold in amorphous hydrogels.

2.2. Methodologies used to estimate T_g

Unlike the energetically stable crystalline solid-state, the glass transition component has a relative kinetic element on the fundamental parameters (V, S, H). Moreover, T_g can vary depending on numerous reasons, such as manipulating the matrix's constituents (Baird and Taylor, 2012). As noted above, optimal solubility and stability of an active ingredient and diffusivity of the controlled delivery vehicle, alongside the reasonable physicochemical longevity, are controlled by the T_g value of the integrated substances. Thus, rationalising the glass phenomenon concerning T_g is critical for every pharmaceutical product's success and sustainable reproducibility.

Traditionally, thermal analysis methodology, differential scanning calorimetry (DSC), has been utilised to determine T_g. This technology is based on demarcating the physical behaviour of the pure individual excipients of the hydrogel (Kasapis, 2006). However, to rationalise the molecular dynamics in the rubber-to-glass transition of an integral synthetic hydrogel, small deformation mechanical analysis has been developed as a technique of choice based on the new concept of the "network T_g" (Kasapis, 2006). The network T_g is a combined analysis based on the Williams-Landel-Ferry model (WLF)/free volume theory with the modified Arrhenius equation. However, the empirical DSC T_g is required alongside the network T_g for comprehensive studies of biopolymers. The synergy of the two methodologies in identifying and characterizing the different structural transformations observed in pharmaceutical polymeric material and active substances will be discussed next.

2.3. Determination of T_g using MDSC

Physical characteristics of a material, such as heat capacity, thermal stability, percentage of crystallinity, physical aging (molecular relaxation), and T_g, can be analysed using conventional DSC systems. The DSC generates a heat flux from a heating block unit, which is transferred through a sensor of a thermal cell (during the heating of the sample over a specified heating ramp at a constant rate, for example, three °C per minute), registering the temperature difference between the sample-filled pan and the reference empty pan (Watson et al., 1964).

The difference between the sample's temperature vs the reference is plotted as an increment or reduction in the heat flow. This heat flow indicates an exothermic or endothermic reaction, respectively. Typically, the sample undergoes an absorption process (endothermic thermal process) during the transition from the glass-solid to glass-rubbery state as a function of T_g during a heating ramp, followed by another appearance of an endothermic plot correlating with the melting point if crystallisation has occurred (Fig. 4).

Twenty-five years ago, an advanced resolution measurement of the DSC system termed the modulated differential scanning calorimetry (MDSC) was introduced to the market. The MDSC technique separates, mathematically, the total heat flow chart into two distinguished signals, including (i) the reversing signal, which identifies reversible events that depend on the heat capacity, i.e., T_g, and (ii) the non-reversing signal that relates to non-reversible events which depend on kinetics (time-

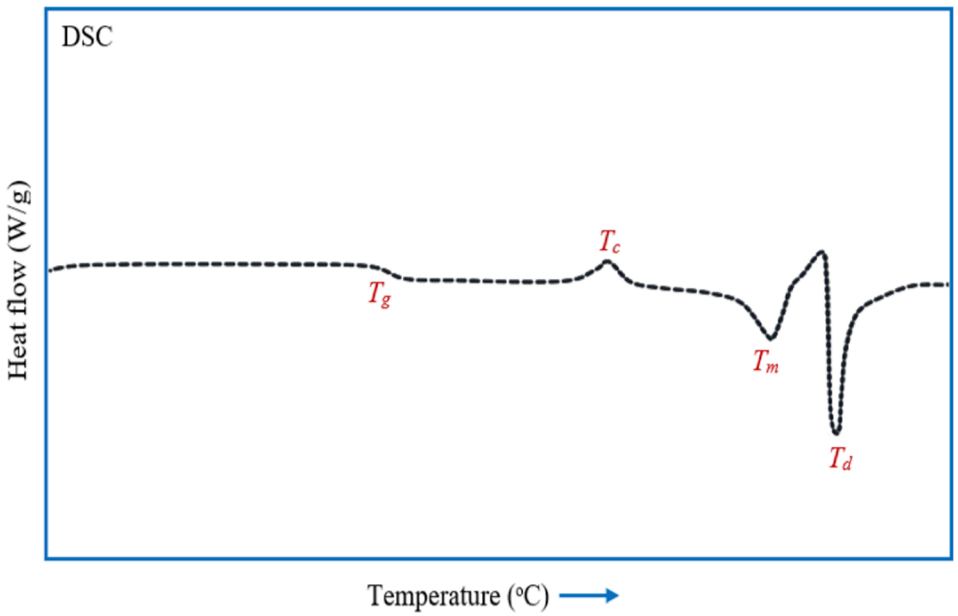

Fig. 4. Differential scanning calorimetry thermogram representing thermal transition signals in a semicrystalline substance (Leyva-Porras et al., 2019).

dependent) such as crystallization, decomposition, evaporation or chemical reaction of curing of the polymeric crosslinking system (Fig. 5) (Kasapis, 2005; Leyva-Porras et al., 2019).

That is to say, by employing a sinusoidally modulated heating rate, MDSC provides a higher degree of accuracy by separating the overlapping events in monitoring related signals in a given heating ramp.

2.4. Determination of T_g using mechanical measurements

Unlike the DSC approach, which determines the calorimetric T_g based on the temperature-induced thermodynamic changes methodology, the rheological or network T_g technique has been developed in an attempt to appreciate the fundamental value of the critical point where a distinct change in the molecular dynamics processes (mechanical deformation) of the matrix as a function of shear strain is observed (Kasapis, 2004; Kasapis and Mitchell, 2001). Hence, the network T_g ought to be located at the merging zone (section III, Fig. 6) between the glassy state (section IV, Fig. 6) where the predicted free volume is about 3 % and the rubbery region, which accommodates an expanded free volume of up to 30 % after the relaxation effect (Kasapis, 2006).

Within this frame of reference, the rheological approach is based on the concept of molecular free volume where the storage module (G') dominates over the loss module (G'') in the glass transition region (Fig. 6) and fits with the WLF equation (Lomellini, 1992):

$$log\alpha_T = log[G'(T)/G'(T_o)] = -\frac{(B/2.303f_o)(T-T_o)}{(f_o/\alpha_f)+T-T_o} \quad (1)$$

$$C_1^o = \frac{B}{2.303f_o} and C_2^o = \frac{f_o}{\alpha_f} \quad (2)$$

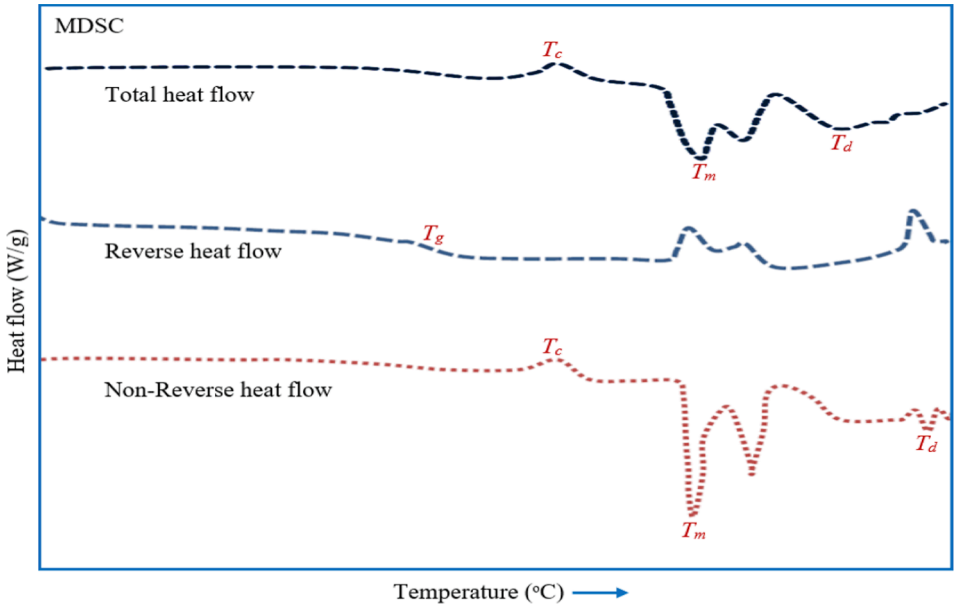

Fig. 5. Modulated DSC thermograms of the total heat flow, reversible and non-reversible events used to identify different transition temperatures of inulin, including T_g, T_c, T_m, and T_d adapted from (Leyva-Porras et al., 2019).

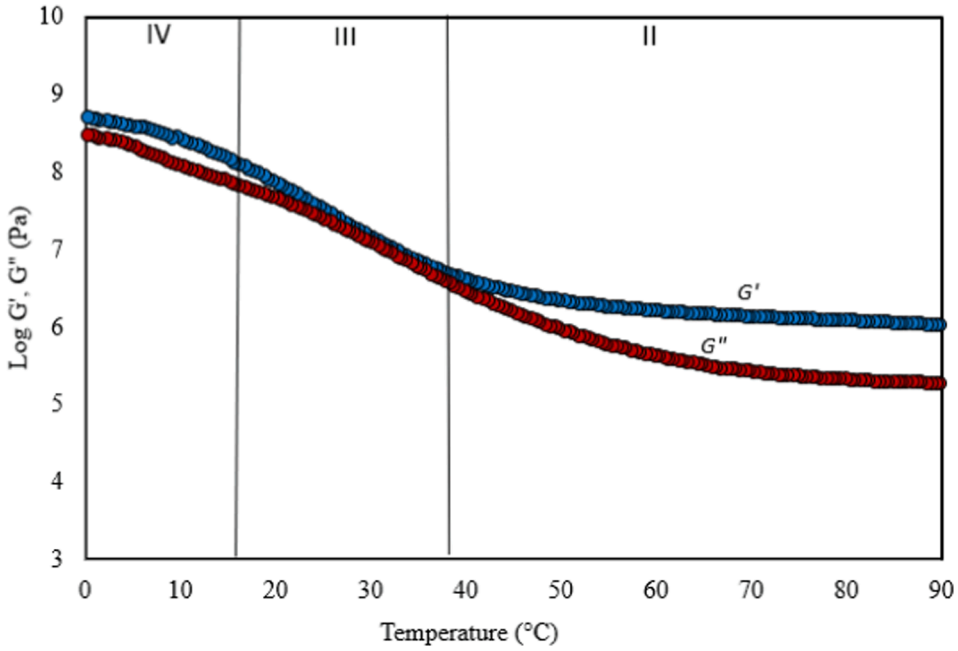

Fig. 6. Thermal profiles of *G', G"* of the HPMC-AAc hydrogel (Nassar et al., 2021).

where C°_1 and C°_2 are the WLF constants, f_o is the fractional free volume at T_o, α_f is the thermal expansion coefficient (deg^{-1}), and B is usually set to one. Applying this approach to the data yields a good fit for the higher range of temperatures, hence arguing that free volume is the overriding mechanism within the glass transition region of the matrix.

In contrast, progress in viscoelasticity within the glassy state follows the modified Arrhenius equation for a set of two temperatures shown below:

$$log_{a_T} = \frac{E_\alpha}{2.303R}\left(\frac{1}{T} - \frac{1}{T_0}\right) \quad (3)$$

where the reaction rate is proportional to exp(*Ea/RT*), E_a is the activation energy of a residual diffusion process, and R is the universal gas constant.

Based on this, results should show a discontinuity in the progress of viscoelasticity that follows the exponential Arrhenius relationship according to the predictions of the reaction rate theory below T_g. In contrast, the non-exponential WLF equation is more appropriate at higher temperatures according to the free-volume effects (Fig. 7) (Kasapis, 2008; Kasapis and Mitchell, 2001).

Note: In order to obtain the reduction factor (α_T), a variation of frequency of *G'* and *G"* should be taken for a range of temperatures that cover the glass transition region. Then, real G'_p and imaginary G''_p parts of the complex shear modulus for the hydrogel reduced to an arbitrary temperature chosen from that range (within the glass transition region) should be plotted logarithmically against reduced frequency (ωa_T) producing the so-called "master curve" of viscoelasticity. The logarithm of the reduction factor, α_T, for the hydrogel can be plotted against temperature from the data of the master curve, as it appears in Fig. 7. (Nassar et al., 2021). It should be remembered that the mechanical T_g is frequency-dependent, whereas there is an effect of the scan rate on the calorimetric T_g, which also requires reporting the onset, intermediate

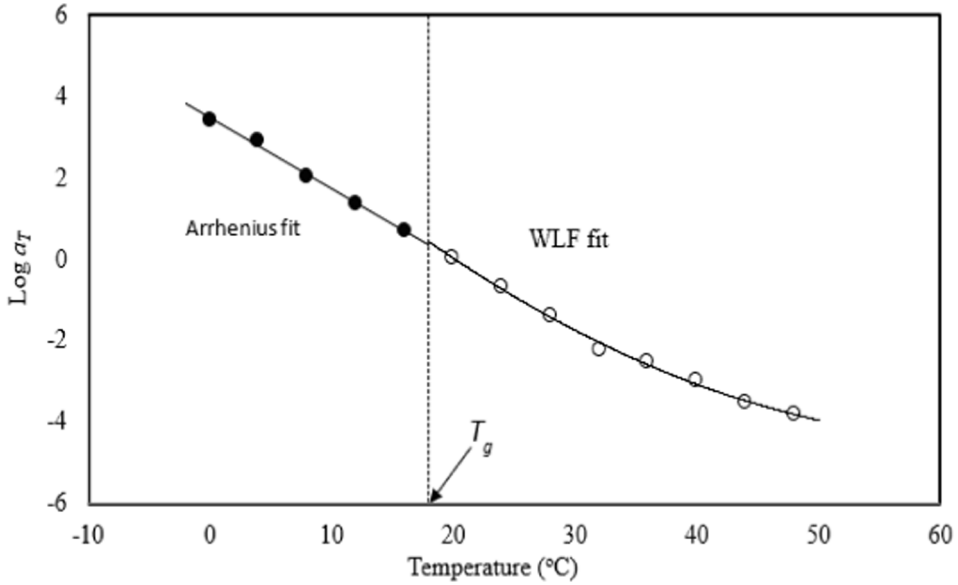

Fig. 7. The logarithm of the reduction factor, α_T, for the HPMC-AAc hydrogel plotted against temperature from the data of the master curve (Nassar et al., 2021).

and final values of the sigmoidal thermogram for its empirical estimation.

3. Theoretical modelling of relaxation and diffusion kinetics

Over the past few decades, a plethora of scientific data on drug diffusion allowed mathematical modelling of controlled drug delivery systems. Consequently, the ability to grasp drug diffusion and release mechanisms from controlled drug delivery systems became attainable (Kelly et al., 2019). A satisfactory mathematical model should demonstrate the effect of the polymer matrix with specific compositions and design parameters on drug release profiles (Siepmann et al., 2000). The significant advantages of these models are: (i) the elucidation of the underlying principle behind the mass transport mechanisms of the drug and (ii) the prediction of the effect of the polymeric vehicle's physiochemical characteristics and design on the drug release kinetics (Siepmann & Peppas, 2012). Moreover, such mathematical models can reduce the number of required research experiments, which, in turn, decreases the required time and cost for the development of the dosage form and increases the commercial viability of the final product (Li et al., 2005; Pareek *et al.*,2017).

The mathematical depiction of the entire drug release process is somewhat tricky because of the number of physical characteristics that must be considered. These include geometry (shape and size); the composition of the matrix (Siepmann & Peppas, 2012); the percolation process of aqueous solution into the hydrogel matrix; the swelling process of the matrix; the diffusion out of the matrix; the viscosity of the medium; ionic strength of the solution; and the amount of the polymer in the matrix (Krese et al., 2016; Klančar *et al.,* 2017). Other parameters include the axial and radial direction of the drug transport in a 3-dimensional system, the solute concentration; the moving boundaries and changing matrix dimensions due to the erosion process; the porosity; and the composition of the matrix (Lamoudi et al., 2016). Mathematical modelling aims to simplify the release process and gain insight into the mechanisms involved. Thus, the mathematical model focuses mainly on a few dominant driving forces (Adrover et al., 2018; Fu and Kao, 2010).

Many mathematical models have been developed to apply an algorithm that predicts the drug-release profile produced from a particular formulation. Hence, more comprehensive models must be applied when more accurate and detailed information is required. In 1855 Adolf Fick derived Fick's second law of diffusion, which describes the change in the rate of accumulation of drug concentration at any given point, which was applied to one-dimensional thin film analysis under perfect sink conditions, as follows (Siepmann and Peppas, 2012; Siepmann and Siepmann, 2013):

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial X^2} \tag{4}$$

where

- C is the solute concentration
- t is time
- D is the diffusion coefficient in dimensions of [length^2 time^{-1}] and is assumed to be constant at equilibrium
- X is the distance

Equation (4) can be integrated to plot the released relative solute mass vs square root of time:

$$\frac{M_t}{M\alpha} = f(\sqrt{t}) \tag{5}$$

where

- M_t is the quantity of solute released at any time
- M_∞ is the initial solute loading of the polymer

Fick's second law bounced back into the picture in 1961 when Higuchi presented his new empirical equation that describes the diffusion rate of an active ingredient from a matrix, in equation (6), under a "pseudo-steady-state assumption" (Higuchi, 1961; Siepmann and Peppas, 2012). Lapidus & Lordi found this equation to be highly applicable to hypromellose-based hydrogels and modified it to describe the release of soluble drugs from a matrix system (Li et al., 2005):

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \tag{6}$$

For $c_{0>}c_s$where

- M_t is the cumulative amount of released drug at time t
- A is the surface area in contact with the release medium
- D is the diffusive drug coefficient
- C_0 is the initial drug concentration
- C_s is the solubility of the drug in the polymer

At an infinite time where the absolute cumulative amount of drug that is released is equal to the amount of drug bound to the system at time 0 (t_0), equation (6) can be presented as:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \tag{7}$$

where

- M_∞ is the total cumulative amount of drug diffused at an infinite time
- K is a constant that reflects the designed variables of the system

Hence, equation (7) introduced the constant K that refers to the system's designed variables compared to Fick's second law.

Applying equation (7) at time zero where M_∞ equal $M\alpha$ in equation (5) (Fick's second law) demonstrates that the fractional released drug is proportional to the square root of time. Also, the drug diffusion rate is proportional to the reciprocal of the square root of time (Siepmann and Peppas, 2011a, 2012).

Researchers figured out that the original equation can only be applied to "ideal" control release systems because it was derived under a pseudo-steady state, and its reliability is dependent upon the following assumptions (Zhang et al., 2017):

i. The initial drug concentration is much higher than the drug solubility
ii. Drug diffusion is one-dimensional, making edge effects negligible
iii. The suspended drug micro- or nanoparticles are much smaller than the thickness of the system
iv. Swelling or dissolution of the polymer carrier can be neglected
v. The drug diffusion coefficient is constant
vi. Perfect sink conditions prevail and are maintained

In 2017 Zhang *et al.* used the Higuchi model to explain the release of acetaminophen from a 3-dimensional printed HPMC matrix as an example of a highly swellable hydrophilic hydrocolloid. It was pointed out that this model was not applicable in such a case because of the significant swellability of the matrix and the multidimensional diffusion.

The process of drug diffusion through a polymer is very complex and specific to the characteristics of several components in the system. The polymer is one of the main components of this complexity which is an active participant in the dissolution and the diffusion process unless in high porosity where the diffusion is uncontrollable or in crystalline states (Paul, 2010). Furthermore, natural, hydrophilic, hydrocolloid structures (e.g., HPMC) consist of micro and macro compartments that swell significantly when exposed to water and make diffusion considerably time-dependent (De Kee et al., 2005; Siepmann et al., 1999b). The active ingredient and other excipients' characteristics must be

considered alongside the physicochemical characterization of the hydrocolloid to apply a realistic diffusion mathematical model. For example, by having a look at the HPMC as a hydro colloidal vehicle, it has been found that the active ingredient and the HPMC diffusion coefficients depend heavily on the water content of the HPMC and the water solubility (concentration) of the different excipients (Gao and Fagerness, 1995; Siepmann et al., 1999b). The abovementioned considerations make comprehensive explanations of diffusion phenomena challenging to document. However, a relatively simple model called the power law (Korsmeyer-Peppas equation) was proposed in 1983 by Korsmeyer *et al.* to portray the entire release curve of the drug (Korsmeyer et al., 1983):

$$\frac{M_t}{M_\infty} = Kt^n \tag{8}$$

where

- M_t is the drug released at time t
- M_∞ is the total cumulative amount of drug diffused at an infinite time
- K is the kinetic constant that incorporates structural and geometric characteristics
- n is an exponent characterizing the diffusional mechanism

As can be seen, n is a critical guide for the cargo release mechanism through the polymer (Ritger and Peppas, 1987b). It is related to the geometrical shape of the system and, consequently, the release mechanism of the active ingredient (Kosmidis et al., 2003). In 1987 Ritger *et al.* showed that the power-law equation is applied to the release of cargo from different geometrical shapes of polymer systems, including slabs, spheres, cylinders, and tablets, regardless of the release mechanism (Ritger and Peppas, 1987a). They showed that the values for diffusion from slabs, cylinders, and spheres are 0.50, 0.45, and 0.43, respectively.

Thus, the actual releasing mechanism behaviour of the cargo from a hydrocolloid polymer has been simplified under the power-law equation. In this regard, n has two distinctive values; $n = 0.5$ and $n = 1$. Fick's second law occurs when n equals 0.5, and the release mechanism will follow a linear relationship with time (First Order - Diffusion Dependent Release). However, at the value of $n = 1$, the drug release will be constant and time-independent (Zero Order – Swelling Dependent Release) in the so-called anomalous or case-II (Non-Fickian) diffusion (Kosmidis et al., 2003; Ritger and Peppas, 1987a, b; Siepmann and Peppas, 2012).

The mechanism of drug release from matrices containing swellable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or polymer chain relaxational controlled, while most systems exhibit a combination of these mechanisms (Lamoudi et al., 2016). In 1989 Peppas and Sahlin developed another exciting model to investigate the mechanism of drug release from a matrix considering both diffusion and polymer chain relaxational mechanisms (equation (9)):

$$\frac{M_t}{M_\infty} = K_1 t^m + K_2 t^{2m} \tag{9}$$

where the first term on the right-hand side is the Fickian contribution, and the second term is the case-II or relaxational contribution (Peppas and Sahlin, 1989). Coefficient m is the Fickian diffusion exponent for a device, regardless of geometrical shape, exhibiting controlled release. K_1 and K_2 correspond to the release rate of diffusion and polymer relaxation, respectively. The value of m is calculated using the sample ratio, $2a/l$, where a is the diameter and l is the thickness.

So far, this review has aimed to highlight some key impediments researchers tackle by employing hydrocolloids as a controlled drug delivery system. However, this discussion's scope is to present the readers with a possible solution to overcome these hurdles without compromising the intention of utilizing the polymer and its unique physicochemical characteristics as a pharmaceutical carrier; these aspects will be discussed below.

4. Mesh size

The mesh size (pore size) is a numerical conception of a polymeric perforation, which refers to the distance between adjacent chains (Fig. 8) (Tsuji et al., 2018).

Based on the rubber elasticity theory, the mesh size is a quantifiable structural characteristic obtained from the stress–strain measurement of the viscoelastic polymer in the rubbery phase (Nishi et al., 2012). Mesh size inversely correlates with cross-linking density between the interactive polymer segments (Thakur et al., 2011). Whitehead *et al.* have demonstrated a notable reduction in the mesh size of the genipin-crosslinked gelatine polymeric system as a function of the increased concentration of the crosslinker genipin (Whitehead et al., 2019).

These results have been confirmed via electron microscopy that images link the reduction in the size of the hydrogel's pores and the increased concentration of genipin (Teimouri et al., 2019). Microstructural changes firmly dictate the kinetic release of the entrapped bioactive, which becomes the rate determinant factor of the water molecule infusion release mechanism (Teimouri et al., 2019; Whitehead et al., 2019). Mesh size can be influenced by the chemical characteristics of the biopolymer, the temperature, and the pH of the environment of the network (Peppas et al., 2006), which further control the diffusivity of the bioactive compound. Hence, mesh size portrays a geometric barrier that impacts the diffusion coefficient from controlled-release systems that exhibit diffusion and swelling in chemically controlled crosslinking (Peppas and Lustig, 1985).

Quantitative measurement of the mesh size is one of the crucial aspects that must be considered throughout the evaluation process of hydrogel design for different medical and pharmaceutical applications. The indicative distance between adjacent polymer segments can be performed using different experimental methodologies based on the deformation of the polymeric network. The discussion below focuses on a couple of theoretical analyses that can predict the mesh size based on the response to different thermodynamic deformational mechanisms, i.e., the swelling mechanism and the rheological behaviour of the elastic modulus (Ben Ammar et al., 2017).

4.1. The swelling model

Thermodynamic compatibility between the polymeric system and the solvent contributes to the development of the swelling forces due to the arising strain, which balances the counteracting retractive forces at the equilibrium point (Marmorat et al., 2016; N. A. Peppas et al., 2000). The rubbery and neutral polymeric network's mesh size (ξ) can be

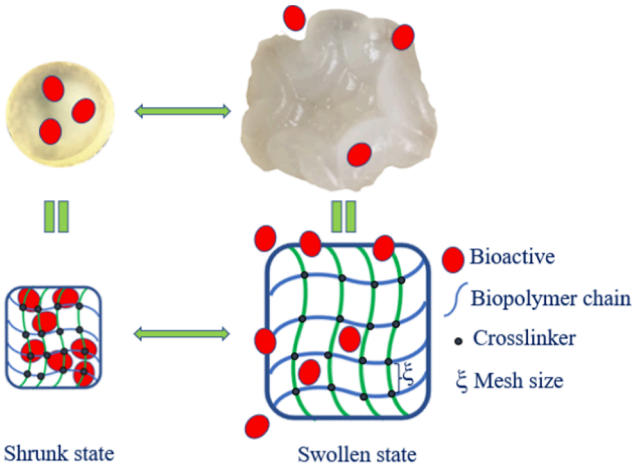

Fig. 8. Schematic illustration of the mesh size in a crosslinked polymer matrix.

obtained at equilibrium through the swelling process. These calculations are based on different elements, including the equilibrium polymer volume fraction in the swollen state ($v_{2,s}$), and the number average molecular weight between crosslinks ($\overline{M}_c$) (N. A. Peppas et al., 2000). The former describes the absorbable amount of water by the hydrocolloid. According to equation (10), this is the ratio of the hydrocolloid volume (V_p) to the swollen hydrogel (V_{gel}), and it is reciprocal to the volumetric swelling ratio (Q) (N. A. Peppas et al., 2000):

$$v_{2,s} = V_p/V_{gel} = Q^{-1} \tag{10}$$

The latter is the true representative of the crosslinking degree that relates to the theoretical degree of crosslinking, X (N. A. Peppas et al., 2000):

$$\overline{M}_c = M_0/2X \tag{11}$$

where M_0 represents the molecular weight of the repeating segment of the polymer.

This swelling model was established from a theoretical statistical framework based on entropy reduction associated with conformational deformation throughout the swelling process (Flory and Rehner, 1943). Moreover, the approach concerns the distortion process (elongation) of a newly formed chain which is the distance between two crosslinks rather than the original chain of the monomer (Flory and Rehner, 1943).

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\left(\frac{\overline{v}}{V_1}\right)\left[\ln\left(1 - v_{2,s}\right) + v_{2,s} + X_1 v_{2,s}^2\right]}{\left(v_{2,s}\right)^{\frac{1}{3}} - \left(\frac{v_{2,s}}{2}\right)} \tag{12}$$

Based on equation (12), $\overline{M}_c$ can be expressed as a function of the $v_{2,s}$, the molecular weight of the polymer chain ($\overline{M}_n$), the specific volume of the polymer ($\overline{v}$), the molar volume of water (V_1), and the polymer-water interaction parameter (X_1) (Canal and Peppas, 1989; N. A. Peppas et al., 2000). X_1, or the Flory-Huggins parameter, is an experimental, numerical factor derived from the enthalpy and entropy characteristics of the hydrogel (Safronov et al., 2015). It represents the degree of compatibility between the plasticizer and the hydrogel. This compatibility level depends on the gel's ionisation degree (Langer et al., 2020) and is employed as an adjusting factor for the gel's swellability degree. Hydrophilic gels have a low value (between zero and 0.3) due to the high ionization levels and compatibility between plasticizers and hydrogel. Values between 0.3 and 0,55 indicate moderate miscibility due to lower ionization levels generally found in hydrophobic gels (Akalp et al., 2015; Langer et al., 2020; Safronov et al., 2015).

In order to implement the Flory-Rhener analysis, it is required to obtain some of the parameters experimentally (Whitehead et al., 2019). Swelling measurements are utilized to obtain the polymer volume fraction in the swollen state. Hence, using the weight swelling ratio, q_w, and the volume swelling ratio, q_v, we can calculate $v_{2,s}$, as follows:

$$q_w = \frac{m_s}{m_0} \tag{13}$$

$$q_v = 1 + \frac{(q_w - 1) \times p_2}{p_1} \tag{14}$$

$$v_{2,s} = \frac{1}{q_v} \tag{15}$$

where m_s is the mass of the saturated gel at equilibrium, m_0 is the mass of the dry gel, p_1 is the density of the percolating solvent, and p_2 is the density of the polymeric network.

The polymer volume fraction ($v_{2,s}$) can be utilized to determine the molecular weight between crosslinks ($\overline{M}_c$), allowing calculation of the mesh size (Marmorat et al., 2016):

$$\xi = v^{-1/3} l_0 \sqrt{2\overline{M}_c C_n / M_r} \tag{16}$$

where l_0 is the length of the bond along the polymer backbone, C_n is the characteristic ratio of the polymer, which can be calculated in equation (17), and M_r is the molecular weight of the repeating unit.

$$C_n\ C_\infty = \frac{2l_{per}}{l_s} - 1 \tag{17}$$

where l_{per} is the persistence length of the crosslinked molecule, and l_s is the linear segment assuming $l_s = l_0$ (Ma et al., 2013; Marmorat et al., 2016).

4.2. The rheology model

Rheological studies explore the flow of the material (liquid, semi-solid, and solid) by measuring its multiplex viscoelastic behaviour in response to an applied force. The applied force (shear stress), such as rotation over a slight angle at a wide range of different temperatures, can lead to changes in the plastic flow of the solid hydrogel. Hence, the changes in the molecular dynamics of the material are manifested by the generation of two distinctive moduli, including *G' and G''. The G'* is the store (elastic) module which measures the stored deformation energy by the material during its resistance to stress (the energy that compensates the deformation after removing the stress load). However, *G"* or the loss (viscous) module, measures the deformation energy used by the material to change the structure via overcoming the resistance of the material to stretching and allowing some molecules to start slipping over (Aulton et al., 2013; Karvinen et al., 2019).

Based on the rubber elasticity theory estimating the mesh size as a macrostructural feature of the hydrogel is attainable provided that the crosslinks are firmly bound to the backbone facilitating a uniform deformation of the network (Welzel et al., 2011, Akagi et al., 2013). Hence, rheological experiments demonstrate hydrogels' elastic behaviour, which is profoundly related to the network structure (Welzel et al., 2011). It has been found that the average mesh size can be calculated from the storage modulus using the following equation:

$$\xi = \left(\frac{G' N_A}{RT}\right)^{-1/3} \tag{18}$$

where G' is the storage module, N_A the Avogadro constant (6.022×10^{23}), R is the molar gas constant (8.314 J/K mol), and T is the temperature (Karvinen et al., 2019; Welzel et al., 2011).

5. Rationalising the design of the hydrogel-based CDDS for biopharmaceuticals

Based on the above mentioned, it is pivotal to appreciate the physiochemical principles concerning the intra/interactions within these systems influencing the carrier's relaxation and diffusion kinetics and its responsiveness to various stimuli such as pH and temperature, the compatibility between the biologic and the carrier, and the chronospatial delivery mechanism offered by the carrier at different physiological compartments (Kulkarni et al., 2013; Orgul et al., 2017).

The primary principles in polymer science that can form the conceptual basis of the pharmaceutical trajectory in delivering biologics are the glass transition temperature (T_g) and the directly related feature termed "free volume" of the glassy polymeric-solvent system (Jadhav et al., 2009; Kasapis, 2005; Kasapis, 2006; Kasapis and Sablani, 2005; Panyoyai et al., 2016; van der Put, 2010). The complementarity between the free volume and the T_g can be concluded from the free volume theory, which hypothesizes that the effective diffusion coefficient of micro-constituent transport would increase upon reaching the T_g threshold due to the matrix's relaxation process and subsequent enlargement of the free volume within the polymer (Paramita and Kasapis, 2018; van der Put, 2010).

In the biopolymeric system, the rapid cooling process results in a

higher molecular density of the matrix (small free volume) throughout the glass transition region (Paramita and Kasapis, 2018). Besides, molecules of such a system continue to undergo a transformation or the so-called "physical aging "or "annealing." contributing to a more glassy state with greater negative enthalpy and entropy associated with higher density (Zografi and Newman, 2017). Specifically, rapid cooling below the melting point (T_m) leads to a supercooled liquid that retains the equilibrium properties of the system until it reaches the T_g at which the system falls out of equilibrium (Zografi and Newman, 2017). Thus, it becomes abundantly viscous, slowing down molecular diffusion. Thermodynamically, the system undergoes an entropy loss as temperature decreases, presumably due to an increment in the domain size of clustered molecules in certain regions leading to a reduction of the likely conformational changes and subsequently the claimed entropy by the matrix, especially as it approaches the T_g (Lu and Wong, 2005; Zografi and Newman, 2017). In other words, the dramatic reduction in viscosity leads to structural rearrangement that limits translational mobility and results in physicochemical stability. Regarding the encapsulated cargo, minimal free volume below the T_g minimises the random Brownian motion, leading to a lower probability of collision between the molecules in a little free space. This depressed emptiness prevents the unfolding of the peptide and consequent aggregation (Bansal et al., 2021).

The free volume is a quantitative measure of mechanical property that indicates the changes in the perforated space due to the mechanical relaxation of the matrix, which controls drug release in amorphous hydrogels (Kasapis, 2004; Zografi and Newman, 2017). Moreover, these polymeric perforations are further controlled by the distance between adjacent chains (mesh size), a quantifiable structural characteristic of the crosslinked polymer obtained from the stress–strain measurement of viscoelastic polymer in the saturated-swelled rubbery phase (Whitehead et al., 2019).

The network relaxation and biologic diffusion framework are the subsequent centrepieces of hydrogel design and functionality assessment. The diffusion of the entrapped therapeutic cargo within a hydrophobic polymer is a complex process governed by different parameters associated with the polymer chain network, described as a mesh with free space between the polymer chains (Peppas et al., 2006; Siepmann and Peppas, 2000; Teimouri et al., 2019; Whitehead et al., 2019; Zhang et al., 2017). The transportation during the releasing process of the entrapped cargo primarily occurs in the water-filled free volume regions, wherein it can be restricted due to the influx of solvent in highly porous hydrophobic polymers and by the mobility of the polymer chains reducing the free space (Kamaly et al., 2016; Phillip and Schreiber, 2013; Roosen-Runge et al., 2011). Thus, most of the theoretical models utilised in pharmaceutical drug diffusion are based on the structure and morphology of the hydrogel, backed up by the free volume concept for the diffusion system; nevertheless, considering other structural properties, namely the mesh size as an opening gate between the polymer chains (Ben Ammar et al., 2017; Şen et al., 2007; Teimouri et al., 2019).

Prominent research in modelling diffusion of active ingredients based on the free volume theory; the swelling ratio of the hydrogel; the size of the solute; the solute diffusion coefficient; the mesh size; and other structural characteristics of the hydrogel form the basis of the mathematical modelling of the biologic diffusion mobility. Modelling of the swelling and diffusion kinetics can be performed by utilising various theoretical applications such as Fickian diffusion theory (Siepmann et al., 1999a; Siepmann et al., 2000; Siepmann and Peppas, 2012).

Various conventional methodologies commonly utilised in pharmaceutical and polymer science to assess different aspects, such as the total solid content; swelling behaviour, crosslinking degree, and mesh size, can also be employed in such research. Such work allows innovating of a responsive, efficient, and compatible chronospatial controlled-drug delivery system protecting the bioactive therapeutic, enhancing its bioavailability, reducing adverse reactions, and boosting the patients' compliance (Yun et al., 2014; Yun et al., 2015).

6. Different types of hydrogel-based CDDS

Hydrogels can be designed in various sizes and shapes as sophisticated structures and responsive, biodegradable, and compatible biomaterials. The principles that govern the hydrogel's geometry and conformation are the basis of the drug's administration and intended delivery site. There are three different main sizes that hydrogels can be constructed, including macroscopic (mm - cm), microgel (less than 5 μm), and nanogel (10–100 nm) (Li and Mooney, 2016). The upcoming discussion will review the characteristics of these three different categories and their clinical applications.

6.1. Macroscopic hydrogels

The dimensional order of the macroscopic hydrogels is estimated between millimetres and centimetres. Accordingly, they are designed in various forms, including skin patches, wound dressings, subcutaneous implants (e.g., contraceptives), systemic implants (e.g., regenerative medicine), pulmonary arousals, and oral tablets and capsules. These different forms intend to provide a sufficient amount of drug release over a prolonged time to exert the required therapeutic effect with minimal adverse reactions (Gassmann et al., 2018).

The delivery site of the released drug from macroscopic hydrogels (e.g., hormone replacement therapy transdermal patches) is generally distanced from the action site. Hence, the drug will engage in an additional transporting journey from the releasing point to the execution site of the pharmacological action. This process might jeopardise the drug's integrity and functionality due to different physicochemical and biological barriers looming along the way (e.g., enzymatic metabolism). Moreover, the bioavailability assessment of the drug is still measured in the blood serum rather than the target site. Thus, the amount of drug loaded into a conventional macroscopic hydrogel usually exceeds the required therapeutic level, hoping for the necessary amount of drug to be delivered (Alvarez-Lorenzo and Concheiro, 2014).

The research field of hydrogels has progressed considerably since the eighties, which reflected the second phase of CDDS development. Hydrogels started mimicking living tissues by responding to external stimuli such as pH and temperature, protecting drugs from severe environmental conditions. On-off feedback response and self-healing mechanisms are characteristics that define the new generation of macroscopic hydrogels. These can be utilised in highly specialised areas of medicine-controlled delivery systems, including stem cell delivery and tissue engineering (Kopeček and Yang, 2007; Kost and Langer, 2012; Li and Mooney, 2016; Zhao et al., 2015).

Self-healing hydrogels are a smart macroscopic hydro colloidal systems that can deliver therapeutics/biomaterials after they undergo structural recovery at the delivery site without external factors (Taylor and In Het Panhuis, 2016). The self-healing hydrogel's structural and rheological characteristics govern the self-recovery process's extent and velocity. Moreover, the self-healing process depends on the constituents and the dynamic inter/intramolecular physicochemical bonding amongst the interactive molecules of the polymer (Lopez-Perez et al., 2017; Taylor and In Het Panhuis, 2016). Nevertheless, such advanced delivery systems reflect rather complex preparations that self-assemble into solid-like systems compared to solutions. In preparing subcutaneous formulations, scientists must consider multiple factors, including the primary indication, targeted site, immunogenicity, compatibility, the inclusion of biopharmaceutics, patient compliance, etc. Add to that, appropriate formulations and manufacturing processes must be developed using the quality by design principle (QbD) in relation to a control strategy, as discussed recently (Lou et al., 2022). An example of self-healing hydrogel has been presented in demonstrating the re-joining of cleaved surfaces in polyvinyl alcohol-borax-based hydrogels (Ge et al., 2019). A cut/heal process of a fabricated multifunctional hydrogel

with antioxidant and antibacterial properties was achieved owing to the dynamic bonding between the hydroxyl group of polyvinyl alcohol and the borate ester. This type of hydrogel provides a unique opportunity in regenerative medicine.

Traditional hydrocolloid architecture and structure are based on permanent network construction and irreversible chemical or physical bonding. This principle has been overruled by self-healing hydrogels that imitate the biological tissue's behaviour that continuously exists in homeostatic equilibrium between erosion and reconstruction. This enzymatic breakdown of proteins, cell organelles, and cells in the living biological tissue is a vital process followed by rebuilding the tissue via the releasing/regenerating of new cells (Badadani, 2012; de Cabo and Mattson, 2019). Such a transitional and reversible enzymatic process is crucial for hydrocolloid systems to control the release of the delivered cells to the implant site. The hydrogel releases cells during the breaking down phase and supports the awaiting ones through the self-recovery phase in an *in-vivo* pulsatile manner (Lopez-Perez et al., 2017).

Skin wound healing and management is another convoluted clinical specialty that requires involved and advanced approaches for acute and prophylactic treatment and care. The healing process of a skin wound is an array of different biological processes, including infection, inflammation, cell proliferation, and extracellular matrix remodelling (Dimatteo et al., 2018; Lindholm and Searle, 2016; Pratsinis and Kletsas, 2016; Sussman, 2000). Thus, to promote the healing process, it is required to provide the wound bed with different remedial agents (e.g., germicides and anti-inflammatories cytokines) and cell proliferation promoters (e.g., growth factors) in addition to exudate absorbents and cushioning to reduce pressure on the damaged tissue. To subdue these challenges, scientists endeavoured for a long time to develop multifunctional wound dressings, including foams and hydrogels, that offer more than one required function at a time (Fukuyama et al., 2016; Qu et al., 2018; Resmi et al., 2017; Saghazadeh et al., 2018; Sussman, 2014; Weller and Sussman, 2006). They developed a dynamic covalent self-healing injectable hydrogel with a successively controlled drug delivery of different drugs based on their chronological need throughout the wound healing process (Chen et al., 2019). The self-healing injectable hydrogel served as a platform for the antibacterial agent chlorhexidine acetate (CHA) released immediately after the injection into the wound bed, followed by an essential fibroblast growth factor (bFGF) which was released during the cell proliferation phase in a sustained release manner. Moreover, the hydrogel has a self-recovery property against damage that might occur due to shear stress (pressure on the wound area). The self-healing gel was constructed through a dynamic interaction between gelatine, adipic acid di-hydrazide, and oxidized dextran.

6.2. Microgels

Microgels are colloidal hydrogels with a diameter scaled between tens of nanometres up to five micrometres. Pharmaceutically, microgels are considered a promising family of controlled drug delivery systems. Microgel is a suspended hydrogel that can be injected locally at the target site of the active ingredient (Wang et al., 2019; Zayed et al., 2017). Their design in terms of size, porosity, crosslinking, ionicity, durability, and biocompatibility is well-regulated and can be manipulated via monomer selection and polymer ratio in composites (Ahmed, 2015; Ahmed et al., 2013; Gao et al., 2014; Yang et al., 2014). Microgels have demonstrated notable success in medicinal and biological applications, including controlled delivery systems and biosensors (Ma, 2014; Ma and Shi, 2014; Wang et al., 2019).

Microgel particles have significantly influenced the surface tension of liquids, arguably due to their amphiphilic nature. They have exerted a surfactant-like effect at the interface of liquids (emulsion stabilizer at the liquid–liquid interface) (Li and Ngai, 2013). Reduction in surface tension of an aqueous solution beyond the critical micelle concentration (CMC) leads to hydrodynamic micelle formation, which can carry and protect the dispersed drug inside the hydrophobic core (Aulton et al., 2013). This micellar system will then be available upon stimulation for drug release (Ma and Shi, 2014; Yang et al., 2014).

Microgel, as a functional micellar system, has unique physicochemical characteristics that combine the micelle surface's softness and the structural sustainability of the crosslinked network. This micellar structure shrinks and reduces in size upon receiving an external (local/remote) stimulus due to interfacial polarity changes, and consequently, the hydrogel expels its content in the surrounding environment (Fig. 9) (Li and Ngai, 2013; Ma and Shi, 2014).

For instance, a designed microgel of poly (4-vinylphenylboronic acid) cross-linked with N,*N*-methylenebis (acrylamide) has shown shrinkage upon contact with glucose which might be due to either the polarization of phenylboronic acid or the ability of the internal glucose to form glucose − bis(boronate) complexes (Zhou et al., 2014). Either way, the outcome was shrinkage of a potential microgel carrying an antidiabetic drug to reduce the glucose level *in-vivo*.

Furthermore, microgel can serve as an optimal candidate for remote drug delivery. It has been demonstrated that microgels can be employed in lubrication medicine as a potential pharmacological treatment for rheumatoid arthritis by sensitizing them via external thermal stimuli (Liu et al., 2013). Thus, it was shown that the loaded microgel poly(*N*-isopropylacrylamide)-poly (ethylene glycol) (PNIPAAm-g-PEG), with lubrication fluids, has a notable response in terms of swellability and collapsing concerning its lower critical solution temperature (LCST), which was 38.4 °C.

6.3. Nanogel

Nanogels attract attention as promising multifunctional drug delivery systems due to their versatile hydrogels and nanoparticles simultaneously. They are three-dimensional hydrogels in the nanoscale size (10–100 nm) with a high capacity to hold large amounts of water while maintaining their structural integrity (Ahmed et al., 2013; Zhang et al., 2016a). They are spherical nanoparticles with tuneable characteristics, including size, softness, porosity, amphiphilicity, and charge (Soni and Yadav, 2016; Soni et al., 2016). Furthermore, designing smart nanogels using specific polymers or monomeric precursors should advance their techno-functionality. For example, hydrogels designed with nanocellulose, including cellulose nanocrystals, cellulose nanofibrils and bacterial cellulose, have significant advantages as drug carriers due to their unique physicochemical properties. Nanocellulose-based hydrogels have shown sustainable delivery patterns of various drugs via different routes of administration due to the diversified tunable capacity (He et al., 2022).

Owing to structural adaptability and flexibility, pharmaceutical and biomedical scientists have been focusing on designing nanogels as exclusive controlled drug delivery systems, in different administration

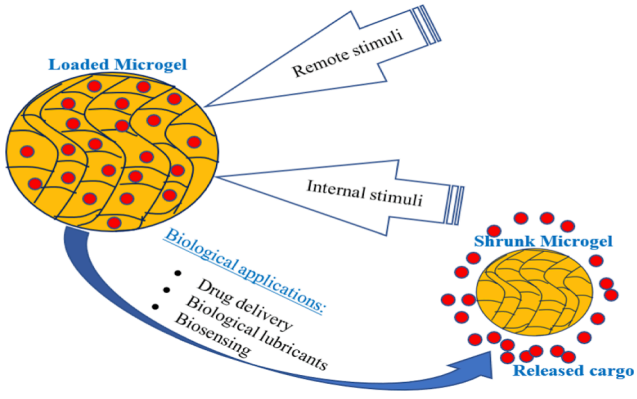

Fig. 9. Schematic representation of the biological applications of microgels depicting different stimuli leads to releasing the entrapped active ingredients.

forms, for specific target sites at which they are subject to specific time-dependent stimuli (Li and Mooney, 2016). Nanogels are effective oral platforms for optimising stability, solubility, and absorption of various APIs, such as hydrophobic drugs, *via* amphiphilic encapsulation (Zhao et al., 2014). They can be designed in an injectable form to deliver compatible APIs systemically. They can leave the small blood vessels via fenestrations in the endothelium infiltrating into the tissue (Li and Mooney, 2016) while they carry and protect sensitive substances such as bioactive peptides and nucleic acids from chemical and biological enzymatic degradation during the delivery process through the bloodstream and other physiological components (Soni et al., 2016).

In terms of specificity and customised delivery of pharmacotherapy, nanogels are suitable for such clinical applications because they can be designed pharmacodynamically to interact with the surface of the targeted cell (Zhao et al., 2014). For example, few scientific attempts have successfully delivered cytotoxic drugs loaded into a nanogel micelle directly to the tumour cells. This way, they enhance the effectiveness of the APIs through higher accumulation and concentration in the vicinity of the cancer cells and by lowering the drug availability around the normal cells (Qiu et al., 2014; Zhao et al., 2014). Therefore, research has been targeting the physicochemical characteristics of the nanogel matrices while trying to elucidate the pharmacokinetic and pharmacodynamic aspects concerning the morphological structure being an interactive integral part of the pharmacological mechanism of medicine (Li and Mooney, 2016; Zhang et al., 2016b). Their morphology uniquely defines nanoparticles. Their structure is built by two main parts, including (i) the inner micellar compartment, where the loaded cargo is protected and then released either in a controlled manner or abruptly, depending on the designed mechanism, and (ii) the corona shell, where the ligands are attached for specific targeting or self-protection and prolonged stay in the bloodstream (Fig. 10) (Alexis et al., 2008; Moritz and Geszke-Moritz, 2015).

The protection of the nanogel in the physiological system (bloodstream and other body compartments) and the functionalization of the outer shell of the hydrocolloid carrier can be enhanced *via* a specific corona design. For example, grafting the hydrophilic poly (ethylene glycol) (PEG) onto the surface of the nanogel provides receptor-mediated drug delivery through PEG-conjugated agonists. These grafted molecules minimise the non-specific interactions with other proteins and reduce the adsorption to biodegradable proteins, which, in turn, reduces the clearance rate of the nanogel (Otsuka et al., 2003; Romberg et al., 2007).

Nanogels are sophisticated systems that require distinctive size, morphology, and functionality tuning. The fabrication of smart nanogels with a specific responsive morphological feature concerning different environmental stimuli such as pH, temperature, electrolytes, glucose, electric or magnetic fields, light, enzymatic activity, or ligand binding can be a convoluted chemical process. This fabrication includes different initiators that further incorporate different functionality groups (Sanson and Rieger, 2010). Exploring the different techniques of nanogel fabrication is not within the scope of the present chapter; however, nanogels are synthesized either through chemical cross-linking and covalent bonding between two low molecular weight monomers or physical crosslinking, where the formed nanogel is stabilised by relatively weak forces such as hydrophobic or ionic interactions (Soni et al., 2016). Conventional chemical synthesis through radical polymerisation provides nanogels with the required architectural structure, including the core–shell and the nanogel hollow (Chiang et al., 2012).

The accumulated scientific data concerning stimuli-responsive polymers has increased remarkably during the last three decades. This plethora of studies is mainly due to the development of new techniques of polymerization, which have an excellent tolerance towards functional group additives such as the atom transfer radical polymerization (ATRP) and the reverse addition-fragmentation chain transfer polymerization (RAFT) (Jochum and Theato, 2013). Stimuli-responsive behaviour is a sequence of events initiated by an indigenous environmental parameter in the vicinity of the nanogel, such as pH or an exogenous stimulus such as light or electric/magnetic field (Soni et al., 2016). These various types of stimuli can alter the balance between the surface hydrophobicity and the lipophilicity of the nanogel, followed by conformational modifications (Li and Mooney, 2016; Soni et al., 2016). Subsequently, these configurational alterations are manifested by changes in the hydrogel's swelling ratio and the trapped material's expulsion (Eichenbaum et al., 1998).

Temperature-responsive hydrogels were popular in drug delivery applications (Jochum and Theato, 2013). This type of response was

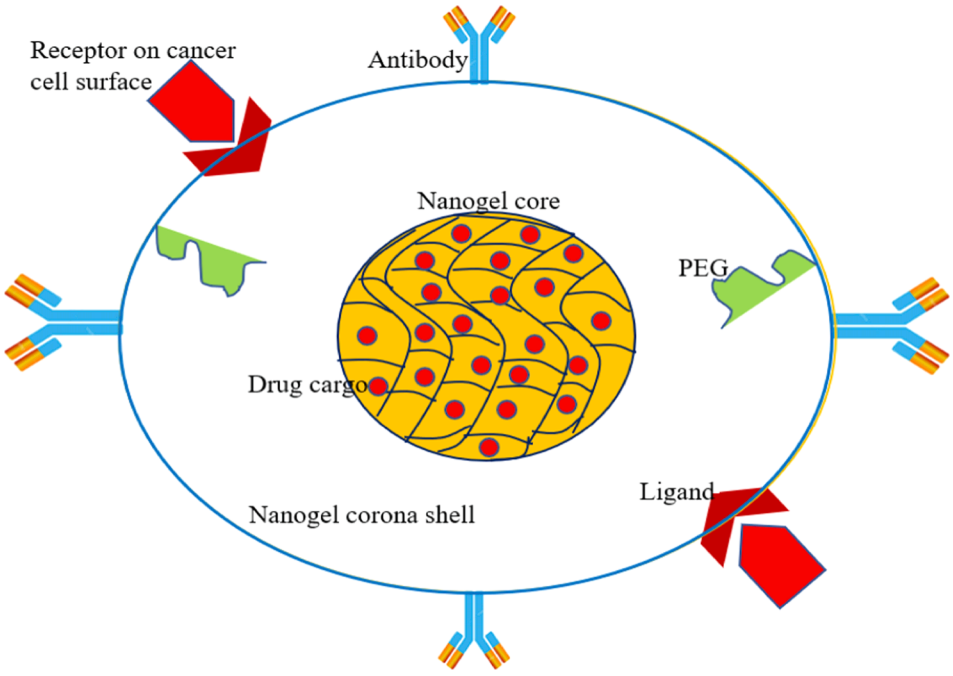

Fig. 10. Schematic representation of a nanogel morphology with a manipulative surface containing various functional groups for targeted delivery of an entrapped bioactive ingredient.

studied intensively by introducing the lower critical solution temperature (LCST) concept. Nanogels show complete miscibility in solution below their unique LCST. However, phase separation occurs above the LCST value (Jochum and Theato, 2013). Poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most common temperature-responsive polymers in the clinical field. It shows inverse solubility in an aqueous medium with a temperature range between 30 and 35 °C due to the macromolecular transition from hydrophilic to hydrophobic structure around its LCST (Schild, 1992). Grafted nanogel with PNIPAM and loaded with API can be triggered externally to initiate the macromolecular transition and release the drug. Similarly, ionic liquid matrices were successfully fabricated to reduce their gelation temperature below 37 ºC, assuring the bioactive cargo's stability without compromising the vehicle's coherence and solubility (Shmool et al., 2022). Hyaluronic acid (HA) is a further example of a viable paradigm of a stimuli-responsive nanogel. HA is a targeting ligand and a common signal molecule in the human body. Moreover, it is ubiquitous in the extracellular matrix. HA is targeted by hyaluronidase (HAdase), a highly expressed enzyme in metastatic cancer and lymph nodes, but indocyanine green (ICG) encapsulated in HA nanogel is a viable enzyme stimuli-responsive mechanism in cancer diagnostic imaging (Mok et al., 2012).

Nanoparticles are considered foreign bodies in the eyes of our immune system. Moreover, the human body is a complex system regarding the existing biological barriers between the different compartments. Hence, nanoparticles must overcome these impediments in order to exert a biological effect. The nanoscale size of the gels increases their accumulation and enhances their diffusion through biological membranes and extravasation across the blood vessel endothelial linings with an average fenestra between 50 and 100 nm across most physiological compartments (Alexis et al., 2008). The long-circulating time for nanoparticles can be enhanced by manipulating the outer shell preventing attraction to digestive enzymes and natural immune peptides. Nanoparticles clearance from the biological system is performed via spleen, renal filtration, or macrophagic phagocytosis, depending on the size of the particles. They undergo renal filtration below 20 nm, whereas larger particles up to 200 nm can be squeezed through the spleen (Moghimi et al., 1991; Soni et al., 2016; Zhang et al., 2012). Thus, phagocytosis may not be a leading clearance mechanism against nanogels except for particles ranked between 0.5 and 10 μm (Alexis et al., 2008).

In summary, hydrogels provide customised and realistic physiochemical properties to carry various therapeutic molecules, including novel atypical remedies such as peptides-based drugs. These active agents have recently become the focus of pharmaceutical scientists. For example, one of the rocky medical areas that have attracted the attention of researchers for alternative therapeutic approaches is the infectious disease field. Multidrug-resistant (MDR) bacteria, or the so-called superbugs, pose a severe threat to human health and existence due to their ability to develop highly sophisticated resistant mechanisms against typical antibiotics. MDR bacteria are also putting tremendous financial stress on health sectors across the globe. The death toll owing to the MDR bacteria is estimated to be nearly 700,000 people. Moreover, it has been projected that by 2050, these global casualties will exceed 10 million people worldwide due to untreated MDR bacterial infections, superseding cancer as the primary cause of global mortality (Dadgostar, 2019). Hence, the necessity for an effective and safe medicine combining the atypical API with a viable drug delivery system against MDR bacteria is eventually crucial.

7. Conclusions and perspectives

In the last 70 years, pharmaceutical and biophysical sciences researchers have considerably advanced the drug delivery field. Their achievements have been translated by the pharmaceutical and biomedical industries, especially in the early years of such explorations. More recently, however, the discovery of a plethora of biologically active molecules has not been accompanied by the same pace of commercial exploitation. This is due to the difficulties encountered in developing delivery systems, which are time-consuming and expensive. This primarily reflects the need to fine-tune the techno-functionality of composite vehicles as bioactive cargo carriers. Hydrogels can be fabricated to provide much-needed thermal stability, mechanical strength, tuneable swelling kinetics and biocompatibility in the role of a delivery vehicle. Concepts of the mechanical glass transition temperature and the free volume theory, as they are a paragon of utility in synthetic polymer science and food technology, can be utilised in the innovative delivery of bioactive compounds from biopolymer matrices that remain stable at 40 ºC for up to twelve months in distribution and storage (Nassar et al., 2021). Such technological achievements provide encouraging evidence of the utility of hydrogels in the delivery of biologics, including vaccines, without the need for costly cold-chain logistics.

CRediT authorship contribution statement

Nazim Nassar: Conceptualization, Writing – original draft. **Stefan Kasapis:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Author contributions

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