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Controlling the diffusion of small molecules from matrices processed by all-aqueous methodologies: towards the development of green pharmaceutical products

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Green technologies for the development of drug delivery systems (DDSs) are important to lower the environmental impact associated with drug manufacturing and may help in decreasing risks associated with common excipients. All-aqueous technologies may be plausible routes to realize the sustainable and safe development of DDSs. In general, the aqueous processing of polymeric materials culminates in the formation of structures that behave as hydrogels, which have been widely used in the fields of tissue engineering and regenerative medicine, agriculture, and food development. Although a high number of studies can be found involving hydrogels for controlled drug delivery purposes, they usually focus on the encapsulation and controlled release of medium to large sized molecules (usually proteins). Concerning the controlled release of small hydrophilic molecules (<1000 Da), few examples are available, and from the point of view of clinical translation and market approval, examples are even scarcer. Retention in the encapsulating matrix normally relies on drug–polymer interactions since the regulation of the mesh size of the network is not sufficient to provide a controlled release of such drugs or depends on steps that lead to low initial drug contents in the matrix. Here, we critically discuss the advantages of green approaches for producing DDSs and highlight the main advances in the challenging task of using matrices fabricated in all-aqueous settings for the encapsulation and release of small hydrophilic drugs.

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1. Introduction

When administered in a free form, most drugs, ranging from small molecules to biopharmaceuticals (Fig. 1a), exhibit a tendency for degradation due to the contact with biological agents and environmental stimuli variations (*e.g.*, enzymes, pH variations). Depending on their nature, mainly biopharmaceuticals are also often recognized and further cleared by the immune system.¹ Therefore, to achieve and improve the therapeutic effect of drugs, the use of high dosages or repeated administrations are normally required, often leading to side effects related to systemic circulation of drugs, including toxicity, and the burden of renal and hepatic clearance mechanisms. The repeated intake of drugs has also been associated with low patient compliance with therapeutics.^{2,3} Short circulation times are common, limiting drug bioavailability and

overall therapeutic efficacy.² In order to overcome such inherent disadvantages associated with drug administration, drug delivery systems (DDSs) have gained momentum in the pharmaceutical industry, with a global market size rated at USD 34.70 billion in 2021 and envisioned to grow to USD 78.76 billion by 2030.⁴ DDSs, defined as a dosage form which comprises the active pharmaceutical ingredient (API) and excipients, often aim at tailoring drug release over time and, for some cases, in space, limiting the actuation region of the delivered drug.⁵ Overall, the main objective of DDSs typically relies on maximizing the timeframe in which drugs are in the therapeutic window (the region between the minimum level needed to achieve efficacy and the maximum level associated with toxicity) and, ultimately, leading to the less frequent administration of lower dosages, with less off-target effects, and expected increasing adherence of patients to therapies.^{2,3,6} The production of DDSs through green and all-aqueous methodologies may be of great interest to overcome the environmental concerns related to the most commonly applied strategies to obtain these drug carriers and will be later explored in this review.

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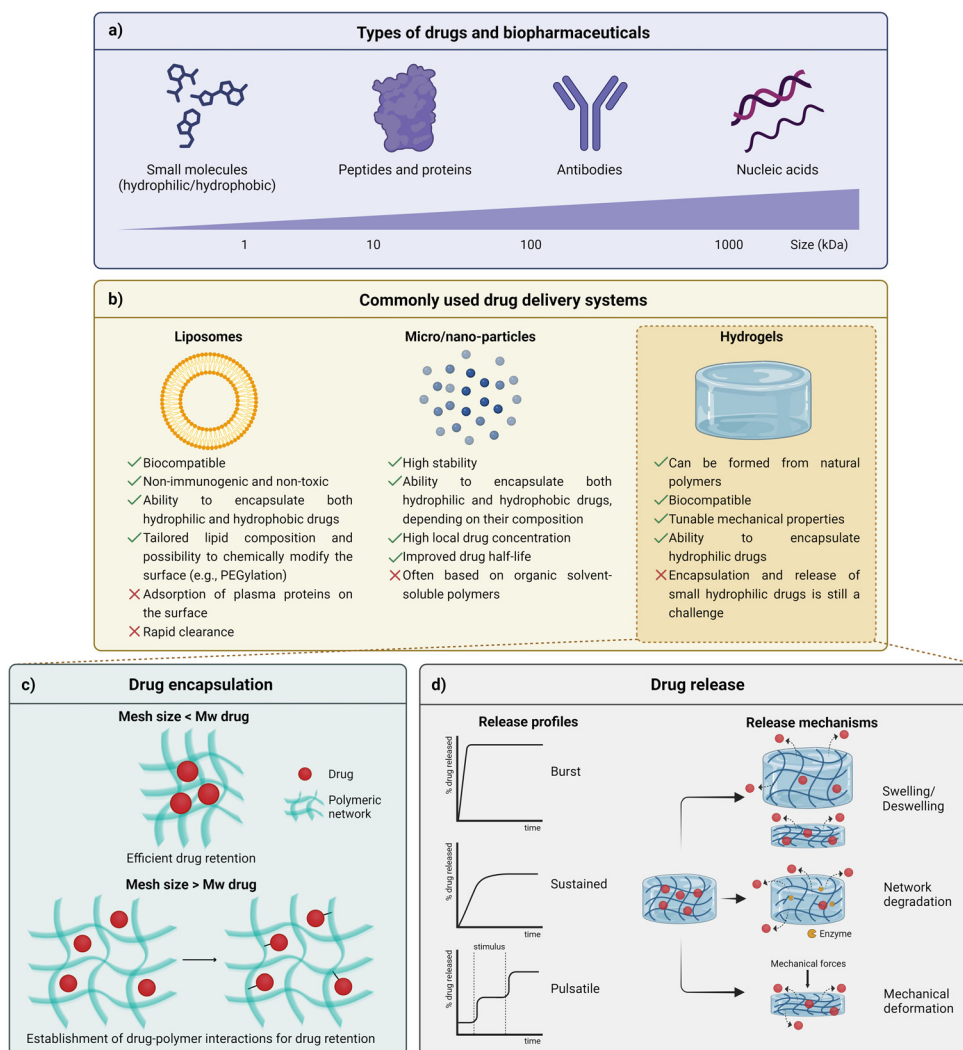


Fig. 1 Key parameters to control the diffusion of drugs from drug delivery systems (created with BioRender.com). (a) Drugs ranging from small molecules to biopharmaceuticals. (b) Most common types of drug delivery systems and their advantages and limitations. (c) Relationship between the mesh size and the molecular weight (M_w) of the drug and its influence on the efficacy of drug retention. (d) Typical drug release profiles obtained from hydrogels with different predominant release mediating mechanisms. (d) was partially inspired by a schematic representation of ref. 2.

1.1. Fundamentals of drug encapsulation, drug release, common types of drug delivery systems and current challenges

1.1.1. Drug encapsulation and drug release. As mentioned above, the encapsulation of drugs in DDSs is an important factor to consider for pharmaceutical purposes due to its contribution to the protection, targeted delivery, and further release of the encapsulated drug. Once drug release fits the expected therapeutic outcomes, drug availability (short or long term) and release profile (continuous or pulsatile; burst or sustained release) are some parameters to consider when designing a DDS.² Additionally, the properties of the drug (e.g., molecular weight (M_w) and hydrophilicity), the properties of the carrier (including membrane thickness and porosity) and the delivery conditions themselves also interfere with the release pattern followed.³

1.1.2. Common types of DDSs. Liposomes, soft to non-soft micro- and nanoparticles, as well as polymeric matrices with

several geometries stand out as some of the most well-characterized and widely explored DDSs in the literature, as well as available in the market (Fig. 1b). These structures share the same objective: maintaining drug bioactivity while preserving chemical and physical properties of the DDS until release. In some cases, they are also targeted at aiding with a controlled and/or on-demand release of drugs.^{2,3} These drug carriers may exhibit tailored features, namely regarding their shape (spherical, cylindrical, disc or thin films), dimensions (nano, micro, or macrometric scale), surface chemistry (neutral, cationic, or anionic; hydrophilic, hydrophobic) and deformability, according to the manufacturing process, chemical composition, properties of the drug to be delivered, and its final target.^{2,3,7}

Sphere-shaped DDSs are the most common systems available both in academic and market approaches.⁸ Their predominance is justified not only because their processing is often considered simple, but also because the achievement of sus-



tained drug release profiles is facilitated by their architecture.⁹ The high surface-to-volume ratio of spherical-shaped DDSs results in more interaction sites between the drug and the encapsulating excipient matrix, which are important for drug delivery purposes, mainly in systems where the degradation of the excipient matrix and molecular diffusion are the forces driving drug release. Therefore, water-insoluble materials susceptible to medium-term degradation under aqueous conditions – including synthetic polymers such as polylactic acid (PLA), poly(caprolactone) (PCL) and poly(lactic-co-glycolic acid) (PLGA) are often employed by the pharmaceutical industry to prepare particles that constitute oral intake tablets.^{10,11} Through the architectonic control of microparticles and their aggregation in tablets, it is possible to regulate their pharmacokinetics, often avoiding the occurrence of the burst release phenomenon.¹²

Liposomes and similar structures. Unlike continuous polymeric particles, liposomes are formed through the hydrophilic/hydrophobic interaction between lipid/water and lipid/lipid molecules, resulting in an aqueous core surrounded by a lipidic bilayer. Several formulations of self-assembled vesicles, that can be categorized based on their size and lamellarity (number of bilayer membranes), have been reported to be generally accepted as biocompatible, non-immunogenic, non-toxic, and capable of encapsulating both hydrophilic and hydrophobic drugs.⁶ Additionally, since they can be tailored by changing lipid composition and/or by chemically modifying their surface, liposomes are considered promising candidates to integrate versatile DDSs. However, these colloidal particles can adsorb plasma lipoproteins on their surface, which limits their stability and contributes to their rapid clearance.⁵ In order to overcome these limitations, it is possible to functionalize the surface of the liposomes with polymers, most commonly using poly(ethylene glycol) (PEG). In fact, this strategy – usually addressed as PEGylation – is a widely adopted strategy to provide liposomes and other nanoparticles with shielding from the action of the immune system. Thus, the use of this polymer to decorate the surface improves the stability of the nanoparticulated DDSs and, consequently, the drug delivery efficiency since it promotes a reduction of clearance while extending the circulation half-time of particles.¹³ Alternatively, functional amphiphilic polymers can self-assemble into structures similar to liposomes, named polymersomes, which are more stable than liposomes and may be tailored to showcase responsiveness to environmental cues (*e.g.*, changes in the temperature or pH).^{5,6} However, the toxicity related to residual organic solvents and some laborious fabrication steps have limited the clinical application of both liposomes and polymersomes.¹³ Nevertheless, it is worth noting that, recently, lipid-based nanoparticles stabilized with PEG were applied as a DDS for the delivery of nucleic acids, namely modified mRNA, in COVID-19 vaccines.¹

Hydrogels. Since most micro-objects currently applied in the clinic are based on organic solvent-soluble polymers, hydrogels have emerged as promising aqueous-based DDSs, which can be formed from natural polymers (*e.g.*, sodium alginate

(SA), gelatin). In fact, due to their usual low toxicity and, in some cases, biodegradability, as well as relatively low cost, natural polymers are appealing materials to surpass toxicity concerns related to the use of organic solvents.^{6,14} Owing to their high-water content (usually in the range of 70 to 99%), hydrogels also display physical similarity to tissues, with some examples showing high biocompatibility. Due to their cross-linked polymer network, which may result from non-covalent or covalent bonds, these three-dimensional (3D) networks also exhibit tuneable mechanical properties. Moreover, hydrogels can be tuned to showcase a myriad of sizes (macroscopic hydrogels, microgels and nanogels) and architectures. When effective drug entrapment is achieved, and no burst release occurs, hydrogels can ensure the protection of the therapeutic agents from degradation. However, drug release from such highly hydrated matrices is often mediated by swelling mechanisms, which condition the mesh size of these structures in the presence of solvents. Drugs and biopharmaceuticals with average sizes higher than hydrogel mesh size have been effectively retained in hydrogel structures (Fig. 1c). Nevertheless, small drugs are normally much smaller than the retentive mesh of the hydrogels, which often culminates in a rapid and burst release of such drugs whenever the hydrogel is in contact with the delivery medium (*e.g.*, *in vitro* medium solutions; blood and other body fluids). Thus, most approaches seeking the retention and controlled release of small molecules from hydrogels have been based on the tailoring of chemical drug-polymer interactions (Fig. 1c).^{2,13}

1.2. Conventional and green techniques to produce DDSs

The pharmaceutical industry adopts a wide range of techniques (common examples in Table 1) to produce DDSs, aiming for the improvement of drug solubility and bio-availability and promoting a proper encapsulation, delivery, and release.^{15,16} Table 1 provides a summary of the main advantages and limitations associated with conventional technologies used in the pharmaceutical industry (relevant reviews about the topic can be found in ref. 17–21), along with a comparison with rising green technologies mostly explored in the literature.

Conventional techniques applied in the pharmaceutical industry often require high energy inputs (*e.g.*, high temperatures) and/or the use of organic solvents – the latter is difficult to remove during the washing steps, requires treatment after discarding, and also may produce toxic and pollutant volatile organic compounds (VOCs). Therefore, there is an urge to develop alternative methods able to surpass the high environmental impact generated, and compliant with the UN Sustainable Development goals.⁵⁶ Aiming to reduce the emission of VOCs in various industrial installations and processes, namely in the pharmaceutical field, several political actions, such as the EU Solvent Emissions Directive (1999/13/EC), have been decreed. The Clean Air Program for Europe also sets objectives for EU air policy up to 2030 in order to reduce the nefarious effects of air pollution on health by half compared with 2005.^{100–102} Thus, some alternative processing techniques



Table 1 Overview of advantages and limitations for both conventional techniques adopted by the pharmaceutical industry and emerging green approaches to produce DDSs. The DDSs marked with * represent functional excipients instead of common DDSs

Conventional Technique	Advantages	Limitations	Materials/equipment	DDSs' carrier molecules
Emulsification-solvent evaporation	<ul style="list-style-type: none"> - Low cost¹⁰ - High speed¹⁰ - Bath-free technique¹⁷ - One-step continuous process¹⁶ - Medium/low energy requirements¹⁶ - Solvent-free^{17,18} - Low cost^{17,18} 	<ul style="list-style-type: none"> - Large amounts of oils and organic solvents¹⁰ - Takes several steps²² - Requires organic solvents²⁹ - Difficult to control the form of the drug¹⁶ 	<ul style="list-style-type: none"> - Need for characterization (microscopy and zeta potential)^{23,24} - It is difficult to collect particles < 2 μm with cyclone¹⁶ - Bulky equipment¹⁶ 	<ul style="list-style-type: none"> - Microparticles^{25,26} - Nanoparticles^{27,28} - Microparticles³⁰⁻³⁴ - Nanoparticles^{35,36}
Spray drying	<ul style="list-style-type: none"> - One-step process^{17,18} - Solvent-free¹⁹⁻²¹ - Low cost^{19,21} 	<ul style="list-style-type: none"> - High energy input¹⁷ - Molten fluid influences the shape and the size of the microparticles¹⁸ - High energy input¹⁹⁻²¹ - Downstream processes to obtain the final product¹⁷ 	<ul style="list-style-type: none"> - Limited number of equipment available (modified/adapted spray dryers)¹⁸ - Limited availability of thermally stable polymers^{19,21} - Highly complex process equipment²¹ 	<ul style="list-style-type: none"> - Microparticles³⁷⁻⁴⁰ - Zmax® (azithromycin microspheres in poloxamer)⁴¹ - Films⁴²⁻⁴⁵ - Capsules⁴⁶⁻⁴⁸ - Nanocomposites^{49,50}
Spray congealing/spray chilling/spray cooling	<ul style="list-style-type: none"> - Continuous manufacturing¹⁹⁻²¹ - High reproducibility¹⁹ 	<ul style="list-style-type: none"> - High energy input¹⁷ - Molten fluid influences the shape and the size of the microparticles¹⁸ 	<ul style="list-style-type: none"> - Limited number of equipment available (modified/adapted spray dryers)¹⁸ 	<ul style="list-style-type: none"> - NuvaRing® (progesterone and an estrogen in polyethylene vinylacetate copolymers)⁵¹ - Lactriset® (hydroxypropyl cellulose)⁵² - Kaletra® (lopinavir and ritonavir)²¹
Hot-melt extrusion (HME)	<ul style="list-style-type: none"> - Mild, environmentally friendly process conditions^{53,54} - Does not require additional post-treatment⁵⁴ - Uniform particle size distribution⁵⁵ 	<ul style="list-style-type: none"> - Limited solubility of polar substrates⁵³ - Insufficient research on the phase behaviour of SCFs⁵³ 	<ul style="list-style-type: none"> - High costs of the equipment (temperature- and pressure-resistant chambers)⁵³ - High cost of some SCFs (e.g., Xe and SF₆)⁵⁶ - Requires safety rules and stringent regulations (e.g., Current-Good Manufacturing Practices (cGMP)) due to the extreme conditions (pressure and temperature)⁵³ - Requires an experienced analyst to run the samples⁵⁵ - Relatively inexpensive products⁷⁵ - Low production cost⁷⁵ 	<ul style="list-style-type: none"> - Microparticles⁵⁷⁻⁶⁴ - Nanoparticles^{61,65-67} - Liposomes⁶⁸⁻⁷² - API-ILs⁷⁶⁻⁸² - Films^{83,84} - Microemulsions⁸⁵⁻⁸⁷ - Microspheres⁸⁸ - Nanoparticles⁸⁹ - API-DESS^{92,93} - Fibers⁹⁴⁻⁹⁶ - Ion-gel⁹⁷ - Microemulsions⁹⁸ - EMLA® cream (eutectic lidocaine/prilocaine cream)⁹⁹
Green approach Supercritical fluid (SCF) technology	<ul style="list-style-type: none"> - Designer solvents⁷³ - Unique tailored properties^{73,74} 	<ul style="list-style-type: none"> - Eventual toxicity^{73,74} - Lack of information about <i>in vivo</i> effects⁷⁴ 	<ul style="list-style-type: none"> - Inexpensive compounds⁹⁰ - Does not need complex facilities⁹⁰ 	
Ionic liquids (ILs)	<ul style="list-style-type: none"> - Mild processing conditions^{90,91} - Produced from low toxic compounds⁹⁰ 	<ul style="list-style-type: none"> - Limited solubility⁹¹ 		
Deep eutectic solvents (DESS)				



have been arising (as showcased in Table 1), mainly at the laboratory scale.

Supercritical fluid (SCF) technology. Supercritical fluid (SCF) technology (Fig. 2a) relies on the use of supercritical solvents, mainly supercritical carbon dioxide (SC-CO₂), that is considered safe for pharmaceutical purposes by the Food and Drug Administration (FDA),⁵³ to improve the bioavailability of APIs, that could be processed by themselves or in combination with biodegradable polymers.¹⁰³ Since this method is based on benign solvents and does not require additional post-treatment, it has emerged as a green alternative to the techniques currently adopted that, mostly, lean on the use of organic solvents. Moreover, this high-pressure technique requires low temperature operating conditions, making it compatible with thermally labile drugs.^{53,54} Owing to its non-toxicity, inert character as well as the ability to form micro- and nano-sized controlled uniform particles faster than other methods and with low residual solvent, this compressed/pressurized fluid bottom-up technique presents great interest and also displays specific features, namely solvating power, antisolvent effect, and high compressibility. Thus, they can be subdivided into (i) solvents or co-solvents, if the SCF dissolves the drug, polymer, and/or other excipients (*e.g.*, for Rapid Expansion of Supercritical Solution (RESS)); (ii) antisolvent, if the SCF is used to precipitate a solute that has been dissolved in an organic solvent (*e.g.*, for Supercritical Antisolvent Recrystallization (SAS)) and (iii) processing additive/co-solute (*e.g.*, for Particles from Gas-Saturated Solutions (PGSS)).^{53,54,56}

RESS uses SCFs for drug encapsulation and comprises two steps: (i) dissolution of both drug and carrier in an SCF, forming a supercritical solution, and (ii) passage of such supercritical solution through a nozzle into an expansion vessel. In this last step, there is depressurization from supercritical conditions to atmospheric pressure, promoting a rapid expansion of the SCF and a reduction of the solvating power that, in turn, leads to the formation of nucleation sites and, ultimately, the creation of particles through the crystallization

of the API inside the matrix. The antisolvent effect of SCFs refers to SAS, which is used to prepare DDSs, namely microparticles, and consists in a previous dissolution of the drug and the polymer in an organic solvent (*e.g.*, acetone, dichloromethane, or dimethyl sulfoxide) which is then sprayed *via* a nozzle to a vessel containing a supercritical fluid which acts as an antisolvent. The SCF promotes the reduction of solubility and, therefore, the precipitation of fine particles. Conversely, PGSS is the most used organic solvent-free processing for encapsulation of small molecules and relies on the melting of the carriers followed by saturation with the SCF which acts as the plasticizing agent. Through the reduction of the melting and glass transition temperatures of the solute, small solid particles are formed during depressurization.^{53,55,104–106} Although both lyophilization technique and SCF technology are suitable for heat-sensitive drugs, SCF methodologies, namely PGSS, exhibit a competitive advantage since they offer better control over uniformity (size and morphology) of the particles.^{104,107}

SCFs are also known for their gas-like diffusivity and viscosity (*i.e.*, high diffusivity and low viscosity) and liquid-like density (*i.e.*, high density) in the supercritical phase.⁵⁶ Their physical properties can be adapted through temperature and pressure regulation above the critical point (as depicted in the graph of Fig. 2a), where these fluids present both liquid-like and gas-like behaviour, acting as a hybrid fluid.^{53,56} This high control over the critical conditions and the flow rate of the SCF leads to the crystallization of a single polymorph and determines the performance efficiency of the SCF technology in DDS design, which is also dependent on the selection of an appropriate solvent. In fact, the solubility of the drug in the SCF depends on the density of the fluid and the size of the particles is related to the pre-expansion concentration of the solute. As mentioned above, SC-CO₂ (critical temperature = 31.1 °C and critical pressure = 7.38 MPa) is the most common choice since it is inert, non-toxic, non-flammable, cost effective and exists in high abundance. It is also related to relatively simple processing and manufacture of pharmaceutical

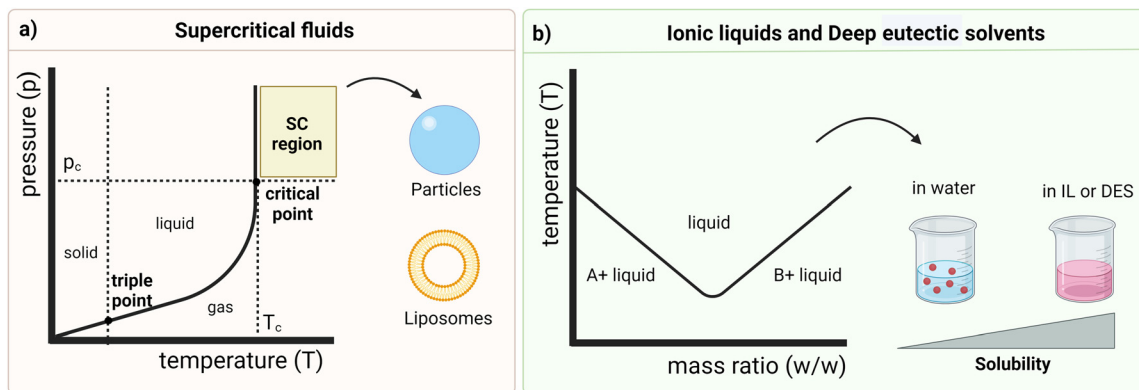


Fig. 2 Green approaches for drug delivery applications (created with Biorender.com). (a) Schematic representation of supercritical fluids' phase diagram and the main DDSs formed through such technology. (b) Schematic representation of a phase diagram of a hypothetical DES (with A and B being the two components that constitute the DES) and the effect of ILs and DESs in the solubilization of APIs (represented as red spheres).



products.^{53,54,56} To encapsulate low molecular weight (LMW) drugs in a polymeric shell, the API is solubilized in the SCF, and the polymer is then added for impregnation. This strategy, which relies on the formation of an initial amorphous form of the API, is particularly relevant for drugs with low solubility in the crystalline state because the API is firstly solubilized and then the crystallization occurs inside the polymeric matrix.¹⁰⁶ One of the key steps in this method is the selection of the polymer, which normally also exhibits low solubility in SCF. Therefore, by increasing pressure and/or temperature, the solubility in these fluids increases and its viscosity decreases.⁵³ The polymer plasticization upon contact with the SCF also contributes to the reduction of its viscosity, leading to the formation of smaller particles, effective entrapment of drugs, and the possible further controlled release from the hydrophilic polymer matrix.⁵³ This green technology also increases the surface area of the particles, that, consequently, enhances the dissolution rate, culminating in higher efficacy and a decreased dosage requirement for delivery.⁵³ Interestingly, it has been shown that the SCF technology is versatile enough to enable the preparation of liposomes, enabling surpassing the excessive use of organic solvents and the multiple steps needed for their preparation and also improving the encapsulation efficiency. The mechanism relies on the simultaneous pressurization and depressurization phenomena that cause CO₂ to be released upon depressurization and dispersed in phospholipids, leading to liposomes with high encapsulation efficiency, improved drug release, high stability as well as narrow particle size distribution.⁵³ However, the application of SCFs is still limited to the poor solubility of polar substrates, including some drugs and polymers, thus requiring large amounts of SCF and, ultimately, increasing the production costs.¹⁰⁴ Such drawback is lightly surpassed by pre-mixing the drug, the polymer and other excipients before the SCF treatment.⁵³ Additionally, owing to the insufficient research defining the phase behaviour of multi-component mixtures in detail, as well as due to the high costs associated with the equipment required to withstand the high pressure and temperature conditions, the extrapolation of this technology to the pharmaceutical field at an industrial scale still presents limitations.^{53,105} However, such high costs of equipment are counterbalanced by their ability to optimize the process, reducing the greenhouse gas emissions and, consequently, the carbon footprint which is quantified according to the life cycle assessment (LCA). The use of SCFs also presents economic benefits by reducing the disposal costs of the solvents typically used in conventional techniques. Moreover, the recovery of some SCFs (e.g., SC-CO₂) further reduces the disposal costs, which contributes to the overall classification of the SCF technology as a cost-effective approach.¹⁰⁸

Ionic liquids (ILs). Ionic Liquids (ILs) (Fig. 2b) are organic-ionic hybrid solvents able to combine numerous asymmetrical organic cations and organic or inorganic anions, and are considered “designer solvents”. These solvents also present melting points at or below 100 °C and, hence, can be liquid at room temperature (so called room-temperature ILs -

RTILs).^{74,75} Moreover, they exhibit unique tailored properties, such as low vapor pressure under ambient conditions and tuneable solubility in both polar and non-polar solvents. In fact, the physicochemical properties of each IL are highly dependent on the combination of ions, therefore determining the biological outcomes.^{73,74} These features as well as their mostly hydrophilic nature contribute to the classification of ILs as greener organic solvent alternatives and make them promising candidates to be applied in the pharmaceutical industry.^{73,109,110} ILs have, then, a wide range of applications, namely in drug delivery (e.g., through topical, transdermal, and oral routes), synthesis and purification of pharmaceutical compounds, solubilization of hydrophobic drugs, and formulation of APIs (API-ILs). Since they can self-assemble into nanostructures when in an aqueous environment, it is possible to increase the solubility of drugs, that is mainly driven by the anion, through the formation of hydrogen bonds.^{73,74} These solvents can also improve pharmaceutical parameters, namely the pharmacokinetic and pharmacodynamic of drugs, and have been used to fabricate micro and nanoemulsions, to enhance their stability and drug loading.^{73,74}

However, the application of ILs as solvents in the pharmaceutical field is still limited due to the eventual toxicity and the lack of knowledge about the microscopic interactions that occur both within the solvent and between the solvent and the drug and, ultimately, their effect *in vivo* (e.g., biocompatibility and biodegradability).⁷⁴ The selection of the cation and the length of the alkyl side chains attached to it are crucial since they define the toxicity and biodegradability of the IL, as it has been reported that a longer alkyl side chain exhibits better biodegradability but is more toxic due to the increase of interactions with the phospholipidic layers in the cell membranes.¹¹¹ In fact, the toxicity of some ILs (mainly, first-generation ILs) is a barrier to developing DDSs, which has been lightly surpassed through the adoption of second- and third-generation ILs that are formed from more biocompatible cations and anions.^{73,75} The adoption of precursors from biocompatible sources is an interesting strategy to develop biocompatible ILs.⁷⁵ Since purified protein-derived compounds are usually considered non-toxic, biodegradable, and biocompatible, they constitute the main building blocks to synthesize cations and anions to, ultimately, form such biocompatible ILs. The selection of cholinium or, more recently, glycine betaine as cations and the use of anions derived from biological buffers (e.g., zwitterionic amino acid derivatives) or organic acids (e.g., malic acid) are also strategies to design biocompatible ILs to be used as pharmaceutical excipients due to their general safety.¹¹¹⁻¹¹³

Besides improving the solubility of drugs and acting as permeation enhancers,¹¹⁴ ILs have been applied in the preparation of biomaterials used for drug delivery.¹¹² For example, Dias *et al.* took advantage of the abovementioned properties of choline-based ILs and loaded choline chloride and choline dihydrogen phosphate in chitosan films, that were further used for the development of a pH-responsive DDS for dexamethasone.⁸³ Hua *et al.* also studied the application of chito-



san to develop stimuli-responsive DDSs but by conjugating such a polymer with a hydrophobic drug using the 1-butyl-3-methylimidazolium chloride IL and, finally, adding poly(*N*-isopropylacrylamide) (PNIPAAm).¹¹⁵

Deep eutectic solvents (DESs). Deep eutectic solvents (DESs) (Fig. 2b) comprise a different branch of green solvents to develop DDSs and consist of a combination of at least two compounds homogeneously mixed that melt at a temperature that is lower than the melting temperature of any of the constituents. Therefore, they deviate from the ideal thermodynamic solid–liquid phase behaviour, being liquid at room and human body temperature (Fig. 2b), and are also considered biocompatible.^{90,91} Starting from low toxic, easily available and inexpensive compounds, DESs are produced by heating, grinding, vacuum evaporation or freeze-drying methods, being considered a green approach.

Furthermore, they are characterized by their low vapor pressure and non-inflammability, can be chemically tailored, have a solvency power for several solutes and are not reactive in water.⁹⁰ Thus, these solvents have emerged as a versatile method for enhancing the solubility, permeability, stability and bioavailability and, consequently, the therapeutic efficacy of drugs.⁹¹

The improvement of solubility, particularly important for hydrophobic compounds, may be due to the hydrotropic effect exhibited by some DESs. Such an effect is defined by altering the solubility, and changing the concentration of the additive. Oliveira *et al.* demonstrated that the solubility of gallic acid is higher using the DES composed of cholinium chloride ([Ch]Cl) and 1,2-propanediol at a concentration of around 80 wt% and using the DES composed of [Ch]Cl and ethylene glycol at a concentration around 60 wt%, compared to pure constituents.¹¹⁶

This improvement in the drug properties may be achieved through the dissolution of the API in DES (DES acts as a pharmaceutical solvent) or by integrating the API as one of the components of the DES (API-DES).⁹¹ Particularly, drug solubilization and stabilization can be adjusted by selecting compounds considering their physical–chemical properties as well as their ratio. Moreover, DESs avoid the thermal and light degradation of drugs.⁹¹ Regarding the API-DES approach, also called therapeutic DESs, it aims to decrease the drug melting temperature to obtain a liquid form of the drug, that is also influenced by the second DES component. The already reported API-DESs display melting temperatures near or below the temperature of the human body and are topically or orally administered. In fact, DESs are mainly used as permeation enhancers and scarcely explored as DDSs. However, owing to the ability of DESs to increase the solubility of both APIs and biopolymers in an aqueous environment, the exploration of novel administration routes and the development of stimuli-responsive systems relying on this technique is envisioned.⁹¹ A study developed by Mukesh *et al.* is an example of the preparation of biomaterials for drug delivery using these solvents. Owing to the abovementioned high biocompatibility and non-toxicity of choline-based solvents, they synthesized chitin nanofibers using the choline chloride-thiourea DES. Such

nanofibers were, then, incorporated in calcium alginate beads, promoting a sustained release of 5-fluorouracil, under physiological conditions, for 24 h.⁹⁴

2. Focus on hydrogel-based DDSs

All-aqueous processing approaches have been gaining more relevance owing to their advantages compared to conventional techniques. As mentioned above, conventional methods are typically associated with the use of organic solvents and the production of toxic and volatile by-products. All-aqueous methods are then a promising alternative which rely on the use of water, under mild processing conditions, and do not produce such compounds, so there is no need for treatment of hazardous solvents and there is a reduction in the emission of pollutant VOCs. Thus, simpler apparatus is required, ultimately leading to a reduction of costs of such technology. However, the use of water as a green approach should be discussed with caution because, despite being a cheap raw material, its global availability is reduced, and its use has become limited by the depletion of water resources. In fact, it has been estimated that millions of gallons of wastewater are produced by several industries, mainly in European countries.^{108,117} Aiming to reduce these numbers, several European policies (*e.g.*, the Blueprint to Safeguard Europe's Water Resources and Environmental Quality Standards Directive) for the preservation and management of water have been applied, involving different activities such as industry. For instance, in LbL approaches applied for pharmaceutical purposes, high volumes of water are required due to the need to maintain the drug-loaded templates immersed in such solvent, which is not appealing from an environmental perspective. Thus, the adoption of all-aqueous structures as DDSs (*e.g.*, hydrogel-based) should rely on the total utilization of the water involved in the process, in order to minimize wastewater and to be considered a green approach.

2.1. Theoretical consideration of drug retention and release from hydrogels

In continuous hydrogel models, it is often considered that – in the absence of relevant chemical interactions between the drug and the matrix – the retention and release profile of the drug is mostly driven by diffusion mechanisms. This process takes over the drug release when the mesh size is bigger than the drug. The value of diffusivity (D) can be calculated according to eqn (1) (Stokes–Einstein equation), where R is the gas constant, T is the absolute temperature, η is the viscosity of the solution and r_{drug} represents the radius of the drug, that relates with its M_w . For small molecules (and, particularly, for hydrophilic ones), this value is high, meaning that these drugs easily diffuse through the network.²

$$D = \frac{RT}{6\pi\eta r_{\text{drug}}} \quad (1)$$

In order to immobilize drugs by steric hindrance, the mesh size could be reduced through the increase of either polymer



or crosslinker concentration, thus defining the molecular weight cut-off (MWCO). Finally, for the release of the entrapped drugs, the value of the MWCO may be modulated over time, according to several strategies (Fig. 1d).²

2.1.1. Swelling. Swelling rate, defined by the equilibrium established between forces that prevent network deformation and osmosis, is the most common approach to manipulating the MWCO in hydrogel-based matrices. In these networks formed from hydrophilic polymers, a significant amount of water is absorbed, causing swelling that leads to an increase in both the inside pressure and porosity of the hydrogel, promoting the diffusion of the incorporated drugs from the swollen polymeric network.^{2,10} This phenomenon can also occur in response to several stimuli (e.g., temperature and pH).^{2,118} Some hydrogels are also prone to the deswelling phenomenon, in which they expel water when their affinity for such fluid is reduced. In fact, the variation in the water absorption culminates in alterations in the MWCO, promoting drug loading during the swelling mechanism while the deswelling is accompanied by drug release.¹¹⁹

2.1.2. Network degradation. Network degradation is another route used to regulate drug release patterns. Degradation, that can occur either in the polymer backbone or at the crosslinking sites, mainly through hydrolysis or enzyme activity, causes an increase in the mesh size, ultimately leading to drug release. This phenomenon can occur in the bulk or on the surface of the hydrogel. When the network is permeable to water or enzymes able to degrade it and the permeation rate is greater than the rate of bond degradation, network degradation will take place in the bulk. On the other hand, surface erosion occurs when the rate of bond degradation is faster than the diffusion rate of water or enzymes to the interior of the gel. Thus, by controlling the permeation of water and/or enzymes, it is possible to manage release kinetics, finally allowing a long-term controlled release. However, the adoption of this mechanism requires that the products are non-toxic and small so that they can be further cleared.² In order to optimize drug delivery and its release through this mechanism, entrapped drugs may act as crosslinking agents, minimizing the use of excipients to play this role while increasing drug encapsulation. Finally, network degradation through the cleavage of drug-polymer bonds allows drug release.²

2.1.3. Mechanical deformation. Another mechanism to trigger and modulate drug release relies on the mechanical deformation of the hydrogel mesh. This phenomenon leads to changes in the structure of hydrogels, normally leading to an increase in mesh size and, consequently, culminating in drug release. This approach is useful to generate an initial burst release of a drug without its accumulation and, therefore, no toxic side effects associated.^{2,3} For hydrogels as drug carriers, the addition of macropores normally enables an easier scaffold deformation, which has been used to trigger drug release.² Despite allowing controlled and pulsatile drug release profiles, the accumulation of damage on the hydrogels due to mechanical deformation may lead to mechanical failure. The emergence of self-healing and tough hydrogels is an alternative to surpass this drawback.²

2.2. Current strategies for the retention and controlled release of small hydrophilic drugs from hydrogels

2.2.1. Strategies mostly based on drug-polymer interactions. The retention and controlled release of small molecules from hydrogels typically rely on the tailoring of chemical drug-polymer interactions, through physical adsorption and covalent conjugation.

Physical adsorption. Physical adsorption (Fig. 3a) is a simple process in which molecules are physically adsorbed through inter-molecular interactions (e.g., ionic interactions, hydrogen bonding, hydrophobic interactions, π - π interactions), presenting high biocompatibility. Polyelectrolytes, that contain charged functional groups, are extensively used for the retention of LMW hydrophilic drugs because they can capture and load such drugs and also form stable nanoparticles through the compression of the polymer chains. Once this strategy is typically based on electrostatic interactions, there are no toxicity concerns related to the use of chemical crosslinking agents or solvents. Moreover, it is possible to obtain entrapment by mixing the drugs and the carrier polymers at room temperature. Despite these advantages, the retention through physical adsorption is highly dependent on the bonds established between the matrix and the drug. Thus, owing to the non-covalent nature of these bonds, physical adsorption is characterized by a less controlled retention, leading to an initial rapid drug release that may also be explained by the saturation of the counter-ions of the polymers or by rapid ion exchange.¹³

Studies performed by Klak *et al.* were focused on evaluating the release profile of small charged molecules (methylene blue, eosin, and bromothymol blue) from gelatin gels, (i) composed of gelatin only, (ii) containing additional viscous non-crosslinking alginate (a semi-interpenetrating polymer network), (iii) with an interpenetrating alginate calcium-gelled network (mixed gels) and (iv) containing pre-formed and mixed alginate beads.¹²² It was verified that molecule release from gelatine gels does not depend on the M_w of the molecules but relies on the ionic interactions between the loaded dyes and the protein network (that was positively charged at the pH of the experiments). Therefore, eosin ($M_w = 692$ Da; negatively charged) diffused slowly, whereas methylene blue ($M_w = 320$ Da; positively charged) was rapidly released due to the ionic repulsion with the gelatin network. Bromothymol blue ($M_w = 624$ Da; uncharged dye) was used as a control to evaluate the effect of ionic interactions in dye release because, owing to the absence of charges in its structure, it would not be retained in the network by electrostatic interactions.¹²² Through the incorporation of alginate (negatively charged polysaccharide) into the protein gel, the effect of the physical state of alginate on the diffusion of these LMW molecules was assessed, indicating that the viscosity of alginate did not exert a great influence. According to the results obtained, it was possible to conclude that ionic interactions were, then, the main players in the regulation of the diffusion of these dyes, so, increasing the concentration of alginate slowed the release of methylene blue but



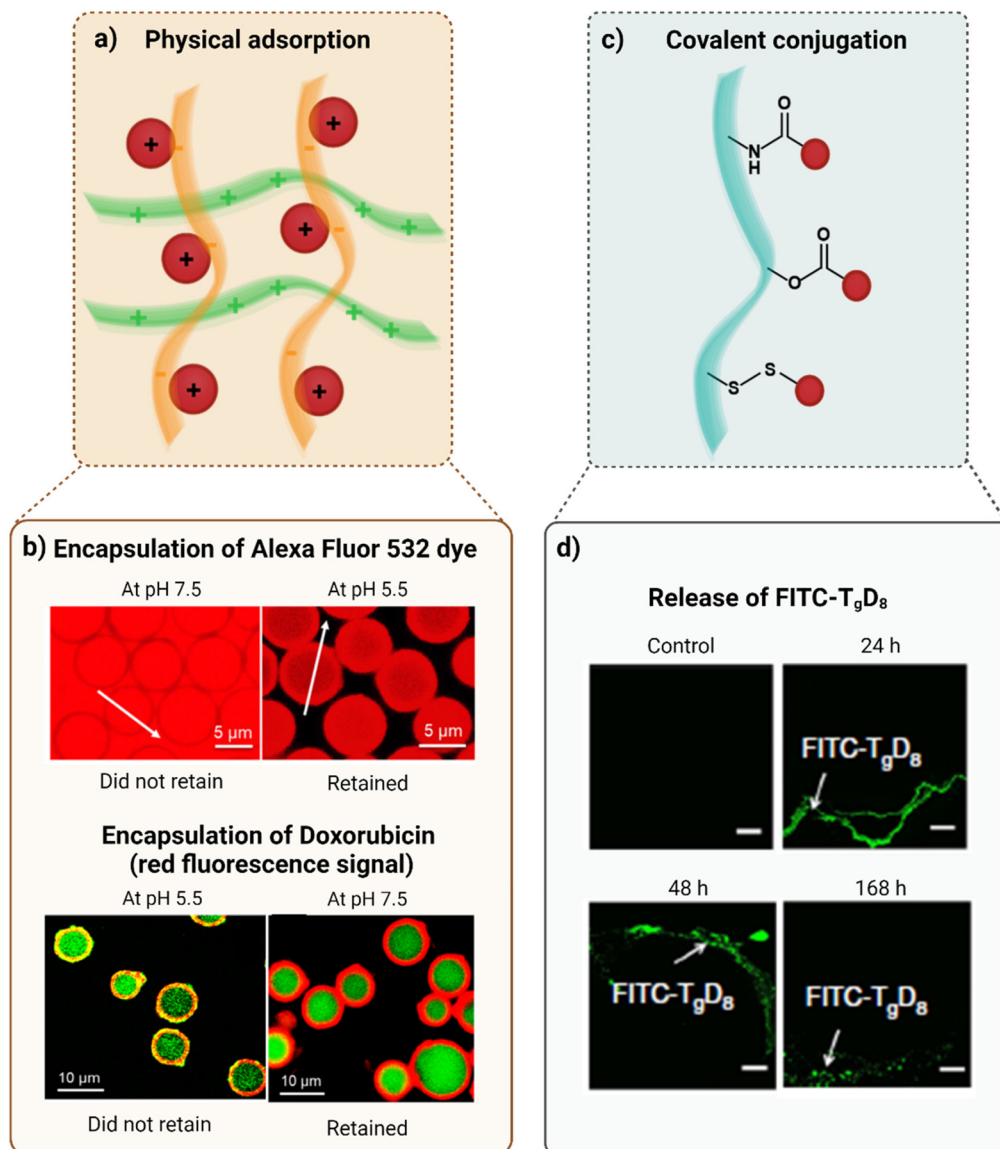


Fig. 3 Strategies to retain small hydrophilic drugs (schematically represented by red spheres) (created with BioRender.com). (a) Physical adsorption. The orange and green polymer dye chains are oppositely charged. (b) Confocal laser scanning microscopy (CLSM) images of the pH-induced encapsulation of the Alexa Fluor 532 dye inside capsules, and of doxorubicin (the red fluorescence signal) into the capsule wall. (c) Covalent conjugation through an amide bond, ester bond and disulfide bond, respectively (from top to bottom). (d) CLSM images 24, 48, and 168 h after sciatic nerve injection of FITC-T_gD₈. Here, FITC represents the interaction that occurred with tetrodotoxin. Figures (b) and (d) were reproduced from ref. 120 and 121, respectively, with permissions from American Chemical Society, copyright 2018, and Nature Portfolio (<https://creativecommons.org/licenses/by/4.0/>), copyright 2019.

the same effect was not verified for the release profile of eosin. Besides, once the bromothymol blue was not retained by alginate, its release was not affected by the concentration of this polymer.¹²² On the other hand, the formation of mixed gelatin–alginate gels (in which alginate was gellified with calcium ions inside the gelatin gel) was also not sufficient to allow the definition of a release profile independent of ionic interactions. The networks remained too loose, with large mesh sizes, and the entrapment of small molecules by simple steric hindrance was not possible. Consequently, the negatively charged polysaccharide delayed the release of the positively

charged molecules (methylene blue), through ionic interactions.¹²² Regarding gelatin gels containing pre-formed alginate beads with calcium ions (that, in turn, contained methylene blue), the release of molecules occurred more slowly than in the previously mentioned approaches since here the diffusion firstly occurred from the polysaccharide gel to the protein gel and, afterwards, for the external medium. Concerning eosin encapsulation in alginate beads following this method, this dye was rapidly released from alginate (due to the opposite charges) but was then retained by the gelatin gel through ionic interactions, delaying its release into the



external medium. Furthermore, the effect of alginate lyase on alginate beads degradation, within the gelatin gel (in which the enzyme was incorporated), was analysed as well as the respective impact on the release kinetics of the dyes. While for methylene blue it was demonstrated that the release rate of the dye was directly related to the concentration of enzyme, this effect was not observed for the negatively charged eosin due to lack of interaction with the alginate gel.¹²²

This drug retention approach was also tested by Kozlovskaya *et al.* who reported the pH-induced post-loading of hydrophilic compounds both in the inner cavity and in the shell of multilayer hydrogel capsules, that were then resealed with 40 000 Da dextran. The negatively charged Alexa Fluor 532 dye ($M_w = 723.8$ Da) was retained inside the positively charged capsule cavity, at pH 5.5, while the cationic doxorubicin ($M_w = 543.5$ Da) was encapsulated in the anionic shell, at pH 7.5, as showcased in Fig. 3b.¹²⁰

Another study in this field refers to the one performed by Moreno-Villoslada and colleagues, in which LMW hydrophilic cationic molecules were immobilized in chitosan/poly(sodium 4-styrenesulfonate) nanoparticles through aromatic-aromatic interactions. It was demonstrated that the intensity of the binding between the entrapped molecules and the particles increased with decreasing hydrophilicity. Regardless of the abundance of negative charges, poly(sodium 4-styrenesulfonate) exhibited a lower ability to bind the LMW cationic molecules as it complexed with chitosan. Thus, aromatic-aromatic interactions dictated the association efficiency between positively charged aromatic groups of the molecules and poly(sodium 4-styrenesulfonate), that also contained aromatic groups and was negatively charged.¹²³

In order to provide a sustained release of hydrophilic drugs for a few days, Schulze and co-workers established a polyelectrolyte-layered system composed of alginate beads (in which the drug was incorporated), formed through electrohydrodynamic atomization, that were further coated with polyelectrolyte layers. The addition of polyelectrolyte layers proved to delay the burst release, as verified with adenosine 5'-triphosphate (ATP) (water soluble; $M_w = 507$ Da). The application of five alternating layers of poly(allyl amine) (polycation layer) and alginate (polyanion layer) led to a more successful sustained release since ATP electrostatically interacted with the polycation layers.¹²⁴

Covalent conjugation. As opposed to physical adsorption, covalent conjugation (Fig. 3c) exhibits improved stability due to the strong linkages between LMW molecules and the polymers or lipid chains, that can be highly stable (*e.g.*, amide bonds) or cleaved in response to stimuli (*e.g.*, ester bonds and disulfide bonds). Furthermore, by modifying polymer composition and the number of reactive sites as well as the drug-to-polymer ratio, it is possible to control the drug entrapment with high precision. However, coupling agents and solvents, that have inherent toxicity and, consequently, environmental implications and regulatory issues, are often required in this type of drug retention.^{2,13,123}

Studies performed by Zhao *et al.* have proven that tetrodotoxin ($M_w = 319$ Da) remained retained in PEGylated and non-

PEGylated polymers through hydrolysable ester bonds and its release rate could be controlled, as represented in Fig. 3d, based on the hydrophilicity of the polymers, in a proportional way.^{13,121}

2.2.2. Systems with highlight on physical barriers

Exploration of multicompartimentalized hydrogel-in-hydrogel devices. Since multilayer hydrogels have emerged as an excellent alternative to the drug leakage phenomenon that monolayer hydrogels face, Hu *et al.* created a double-layer hydrogel sustained-release system (Fig. 4a) consisting of a polysaccharide (SA and carboxymethyl cellulose) inner core, formed through physical crosslinking of Ca^{2+} , and a synthetic polymer (poly(acrylamide) or its derivatives) outer layer, added by chemical crosslinking. Considering the advantages of these systems, namely the possibility to control both layers, that can be relatively independent from each other, it was possible to control the release profile of LMW drugs (indomethacin and metformin), by changing not only the inner layer composition but also the thickness of the outer layer of the hydrogel. The inner interpenetrating network hydrogel, formed by natural polymers, exhibited an alkaline pH-sensitive behaviour, avoiding the burst release phenomenon in the stomach and providing a sustained release in the intestinal environment. This effect was reinforced by the synthetic polymer outer layer that, owing to its residual swelling capacity, could prevent the inner hydrogel expansion and further drug diffusion, controlling drug release. It was proven that the inner hydrogel layer tended to gradually erode, due to the weak physical crosslinking, while the outer hydrogel kept its integrity towards swelling. Thus, it was possible to achieve a sustained-release effect, that was also positively affected by increasing the thickness of the outer layer. When exposed to the intestinal pH, indomethacin ($M_w = 358$ Da, hydrophobic molecule) was gradually released due to the equilibrium between the swell of the inner layer and the diffusion resistance offered by the thickness of the outer layer. However, this behaviour was not displayed by metformin ($M_w = 129$ Da, hydrophilic drug), that, by contrast, exhibited a burst-release effect, being almost totally released in 2 h. These results, depicted in Fig. 4b, corroborated how challenging it is to control the release of hydrophilic LMW drugs because, owing to its water solubility, metformin easily diffused through the hydrogel, even before the occurrence of swelling.¹⁴

Exploration of the layer-by-layer (LbL) technology. In order to try to obtain a more controlled release of small hydrophilic drugs, recently, a strategy based on the formation of polyelectrolyte multilayer capsules (PEMCs) in vaterite CaCO_3 crystals templates has been applied (Fig. 4c).¹²⁶ As previously mentioned, the adoption of multilayer systems is an alternative to delay the drug release process,¹²⁷ so PEMCs were produced according to layer-by-layer (LbL) technique, from which core-shell complexes were formed. Oppositely charged polyelectrolytes were alternately deposited onto degradable core templates, that were further removed, leaving behind the polymeric shell, that culminated in a PEMC.¹²⁸ Although PEMCs are already used to encapsulate macromolecules, these multi-



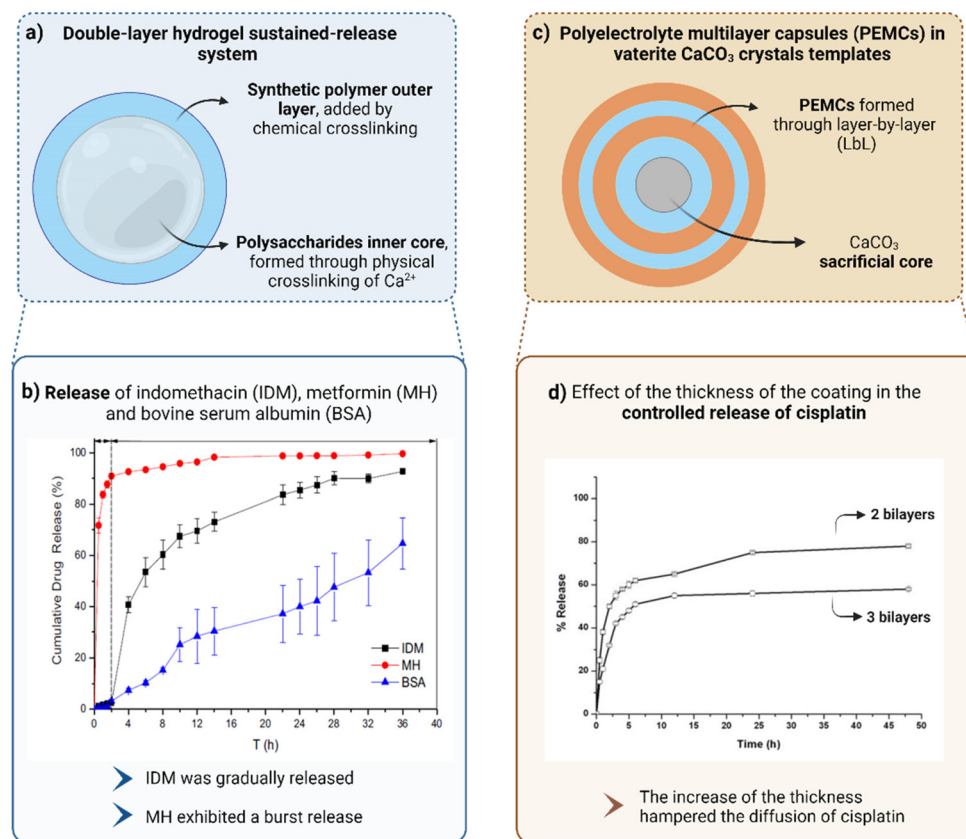


Fig. 4 Strategies to retain low molecular weight molecules with highlight on physical barriers (created with BioRender.com). (a) Double-layer hydrogel sustained-release system. (b) Graphical representation of the cumulative release of indomethacin (IDM), metformin (MH) and bovine serum albumin (BSA) (high molecular weight molecule). BSA and IDM were gradually released while MH exhibited a burst release. (c) Polyelectrolyte multilayer capsules (PEMCs) in vaterite CaCO_3 crystal templates. (d) Graphical representation of the effect of the thickness of the coating in the controlled release of cisplatin from layer-by-layer (LbL) nanocapsules. (b) and (d) were reproduced from ref. 14 and 125, respectively, with permissions from Nature Portfolio (<https://creativecommons.org/licenses/by/4.0/>), copyright 2021, and Elsevier Ltd, copyright 2015.

layer capsules often exhibit low capacity to retain LMW drugs. Therefore, they were combined with biocompatible and readily decomposable vaterite CaCO_3 crystals that acted as sacrificial cores and led to the high retention of LMW drugs (that might occur during the formation of the capsules – co-synthesis – or after this process – physisorption) as well as allowed the reduction of release rate while hindering the initial burst release. In studies performed by Trushina *et al.*, capsules were subjected to heat-treatment, that annealed the polymer multilayers, resulting in a shrunk structure, with reduced permeability, that promoted the sustained release of LMW drugs from the capsule lumen.¹²⁹ It was also proven by Vergaro *et al.* that the release rate was influenced by the polymer density within the capsule matrix or shell, that, in turn, could be tuned by changing the polymer deposition time or the number of deposition steps. Thus, it was verified that increasing the thickness of an (alginate/protamine sulfate)_n system or raising the polymer shell density hampered the diffusion of cisplatin ($M_w = 301$ Da, hydrophilic drug) (Fig. 4d).¹²⁵ The release profile of this drug was also studied by Mehnath *et al.* who encapsulated it in poly(diallyldimethylammonium chloride) (PDADMAC)/poly [di(sodium carboxyphenoxy)phosphazene]

(PDCPP) coated CaCO_3 nanoparticles and, through the formation of pores in the shell, the matrix swelled, causing cisplatin diffusion, following a release profile characterized by a previous burst-release phenomenon, followed by sustained release.¹³⁰ However, owing to the time-consuming multistep process behind the processing of the inorganic templates, this strategy is not ideal to release LMW molecules independently of the chemical interactions with the matrix.

2.2.3. Filler-based strategies. In order to reduce the MWCO of hydrogel matrices and exert a high control on drug release rates, strategies based on filling the hydrogel pores have been emerging. Pan *et al.* reported the use of supramolecular phenolic-based nanofillers (SPFs) to both tune the mesh size and promote dynamic interactions between the encapsulating network and drugs.¹³¹ Through this strategy, a multiscale porous structure was formed, composed of 3 main types of pores in the following descending order of size: macropores (of the hydrogel network itself), mesopores (between the several SPFs) and micropores (in the inner side of each SPF structure). Besides the retention promoted by such a multiscale porous structure, the molecular interactions between the SPF aggregates and the drug also determined the drug release



profile. Non-covalent interactions (*e.g.*, hydrogen bonds and electrostatic interactions) were the main driving forces for drug retention, displaying an improved effect on higher molecules due to the larger number of binding sites. However, smaller molecules (*e.g.*, rhodamine B; $M_w = 479$ Da) were also retained through such bonds since these molecules modulated their conformation in order to promote binding sites with the SPF aggregates, resulting in transient binding-diffusion cycles and, ultimately, following controlled release profiles.¹³¹ They proved the concept with different hydrogels (single and double networks), formed from several building blocks and cross-linked by either physical or chemical bonds, and with different types of drugs with respect to their M_w and overall physico-chemical properties. Thus, this study demonstrated that, by tailoring the SPF content, it is possible to establish a system that can be widely applied to deliver a broad range of drugs, regardless of their chemistry and/or hydrogel matrix.¹³¹

2.3. Aqueous two-phase systems (ATPSs)

Aqueous two-phase systems (ATPSs) are totally aqueous systems with low energy requirements, with potential to be used as DDSs (core-shell capsules and continuous hydrogel systems).¹³² In fact, the mild and all-aqueous environment provided by these systems is advantageous to maintain the bioactivity of hydrophilic drugs such as proteins and prevent their denaturation as well as broaden the range of drugs that can be used. Another important feature is the very low interfacial tension between the aqueous phases, which enhances their contact area and, therefore, the free diffusion and exchange of solutes.^{133,134} The most common ATPS relies on the use of dextran (DEX) and PEG since these two polymers are biodegradable, biocompatible, and exhibit a stabilizing effect on most biological products.¹³³ Oppositely charged polyelectrolytes can be added to each aqueous phase, thus promoting single-step interfacial reactions and the formation of microparticles and capsules.^{132,135} For example, Ma *et al.* proved that the addition of poly(sodium-4-styrenesulfonate) (PSS) and poly(allylamine hydrochloride) (PAH) to DEX and PEG, respectively, resulted in microparticles, while the addition of these two polyelectrolytes to the opposite ATPS phases, PAH + DEX and PSS + PEG, led to the formation of stimuli-responsive microcapsules with liquid cores. An outside-to-inside encapsulation was performed with FITC-DEX, confirming the potential of such systems to encapsulate, protect, and trigger the release of several compounds.¹³⁶ A system with similar potential was developed by Jiang *et al.* who fabricated pectin-chitosan-collagen microcapsules through their self-assembly in ATPS phases. Pectin (anionic polysaccharide) was added to the DEX phase whereas both chitosan (cationic polysaccharide) and collagen were added to the PEG phase. The addition of collagen promoted the formation of more robust capsules with anti-swelling and anti-shrinkage properties from which FITC-DEX ($M_w = 70$ kDa) was sustained released when exposed to certain stimuli.¹³⁷ Vilabril *et al.* proposed the combination of PEG/DEX ATPS with the oppositely charged polyelectrolytes ϵ -poly-L-lysine (EPL) and alginate, respectively, to also form robust cap-

sules with an opaque semipermeable membrane with potential to be applied as a DDS. However, it was reported that molecules with a molecular weight of 150 kDa easily diffused from the microcapsules, emphasizing the incompatibility of their application to retain LMW molecules, mostly due to the polyelectrolyte complex hydrogel-like nature of the formed membranes.¹³⁵ A similar conclusion was drawn from the study performed by Zhang *et al.* in which platelet-derived growth factor-BB (PDGF-BB; high M_w) was effectively encapsulated and released from polyelectrolyte microcapsules while small polyelectrolytes easily diffused from such capsules.¹³⁸ All these studies proved that, although ATPSs are a promising green technology, the encapsulation of LMW molecules using this method is still a challenge.

3. Conclusion and future perspectives

The development of DDSs has enabled disruptive advances for the pharmaceutical industry since these systems are broadly applied to encapsulate and release high to low molecular weight drugs. However, the conventional methods followed for their production still face some limitations, namely the use of organic solvents. In order to fulfil legislative requirements and substantially decrease the environmental impact of pharmaceutical manufacturing, there is an urge to employ greener alternatives. The use of SCFs has been one of the most explored methods to prepare DDS + API formulations in the pharmaceutical research field. However, solubility limitations and the use of specific equipment associated with SCF technologies still justify the development of alternative versatile techniques compatible with green processing of drug and drug-carrier formulations. The use of ILs and DESs has been mostly addressed to improve drug permeability in tissues, namely through skin. Additionally, they have also been used to improve or promote the concomitant solubility of drugs and DDS carrier precursors upon processing, although such applications are still scarce, namely, for DESs. The use of simpler technologies based on the processing of hydrogels made of water-soluble polymers and directly encapsulated drugs is also a growing trend for the preparation of drug delivery formulations. However, its application has been mostly limited to the encapsulation and release of biopharmaceuticals. While the latter are mostly constituted by proteins and their derivatives, with molecular weights in the range of dozens or hundreds of thousands of Daltons, the encapsulation and effective controlled delivery of small molecular weight drugs and therapeutic molecules using all-aqueous and easily processed hydrogels remains a challenge.

Conflicts of interest

There are no conflicts to declare.



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