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Review article

Sustained and targeted delivery of hydrophilic drug compounds: A review of existing and novel technologies from bench to bedside

Daniel Hawthorne [a,*], Ananth Pannala [b], Susan Sandeman [c], Andrew Lloyd [d]

[a] Centre for Regenerative Medicine and Devices, School of Applied Sciences, University of Brighton, Brighton, BN2 4GJ, UK
[b] Biomaterials and Drug Delivery Research and Enterprise Group, School of Applied Sciences, University of Brighton, Brighton, BN2 4GJ, UK
[c] Centre for Regenerative Medicine and Devices, University of Brighton, Brighton, BN2 4GJ, UK
[d] School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, BN2 4GJ, UK

A B S T R A C T

The sustained and/or targeted delivery of hydrophilic drugs is an important field within drug delivery, presenting unique challenges when compared to that of hydrophobic drugs. Yet relatively few comprehensive reviews specific to hydrophilic drug delivery have been published recently. In this review, therefore, we seek to establish the recent trends in the delivery of hydrophilic drugs in particular, and recent developments including electrospun core-shell nanofibrous materials, stimuli-responsive hydrogel carriers, amphiphilic drug-drug conjugates (ADDCs), and nanomaterials including polymer nanoparticles (PNPs), solid lipid nanoparticles (SLNs), micelles, liposomes, and mesoporous silica nanoparticles (MSNs). A recurring trend in the field has been the relatively slow translation of novel technologies into viable pharmaceutical products, with few reaching clinical trial phase. Furthermore, we consider the bench-to-bedside potential of these novel technologies, taking into account the capabilities of these concepts to overcome the technical, legislative, and commercial requirements that must be met in order for a viable device to be adopted in the real world.

1. Introduction

Whilst the objectives of using novel technologies in both hydrophilic and hydrophobic drug delivery are by and large very similar – i.e., predictable and constant sustained release, triggered and/or targeted release, and increased membrane permeation and bioavailability [1] – the methods used to reach these goals can be very distinct due to the opposing natures of these two classes of drugs [2]. In many cases, the aqueous solubility of hydrophobic drugs must be modified to improve its initial dissolution into the aqueous fluids. On the other hand, aqueous solubility is an inherent property of hydrophilic drugs. While this enhances initial mobility within the body fluids, the drugs are susceptible to rapid elimination, and are also unable to cross lipid barriers (e.g. the blood-brain barrier), leading to reductions in drug lifetime, bioavailability, and productive absorption [3].

Therefore, common approaches used both historically and contemporarily in hydrophilic drug delivery technologies have included encapsulation within nanocapsules, microemulsions, or nanoparticles, conjugation to hydrophobic moieties such as lipids and polymers using labile bonds, and immobilisation within macromolecules and three-dimensional structures such as hydrogels [1–4]. Innovations to improve site-specific targeting have included conjugation to biomolecule ligands for use in targeting pathologies which overexpress certain biomolecules, for example [5,6], while those to improve membrane permeation have included lipid conjugated and encapsulation in lipid vesicles [7,8]. Improved drug lifetime, for example, by instilling a resistance to drainage, has been achieved by conjugating, entrapping or otherwise embedding the drug within mucoadhesive polymers, and nanoparticles of the same [9,10].

There are, undeniably, technologies which can be used to improve the sustained and targeted delivery of both hydrophilic and lipophilic compounds. Indeed, co-delivery systems for the simultaneous targeted and sustained release of hydrophilic and hydrophobic drugs together have become more commonplace; these have included amphiphilic drug-drug conjugates (ADDCs) and amphiphilic vehicles such as polymersomes and polymer nanoparticles [11–14]. However, while many review articles have detailed various approaches to specific diseases, drugs, classes of drug delivering device, and their applications, relatively few have been dedicated to the sustained and targeted delivery of hydrophilic compounds specifically [3,11].

Another important aspect which will be considered in this critical review is the feasibility of the bench-to-bedside conversion and commercial viability for these technologies and devices. The so-called 'translational medicine' approach will be considered in this review

* Corresponding author.
E-mail address: d.hawthorne@brighton.ac.uk (D. Hawthorne).

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[15]. For a technology in the stages following laboratory inception to complete the translation into clinical trial and commercial adaptation, there are numerous regulatory requirements and physicochemical prerequisites that must be met and demonstrated [16,17]. Some of these relate to shelf life, processing and suitability for scale-up, and – crucially, in particular, for implant-based technologies – the ability of the device to withstand aggressive sterilisation conditions [18]. These considerations are, in many research articles, inadequately explored or not considered at all, since many publications for devices at the primary research stage are initial, proof-of-concept investigations.

We therefore aim to provide a unique perspective in recent trends in the drug delivery review literature; one which focuses primarily on systems for the sustained and targeted delivery of hydrophilic drugs, and one which emphasises the long-term uptake of these systems and drugs. The systems will also be contextualised in terms of applicability to industrial processing and sterilisation requirements, and viability for uptake as medical devices.

2. Electrospun nanofibers and nanofibrous materials

Electrospinning allows facile fabrication of polymer-based devices with desirable properties including nanometric dimensions, high surface area to volume ratio, and high porosity, leading to excellent drug encapsulation and release [19–21]. In electrospinning, polymer solutions are driven through an electrically charged tip, or spinneret, using a syringe pump. The application of a high voltage to the droplets exiting the tip results in the stretching of the droplet, forming a charged liquid jet which accelerates towards an oppositely charged collector. Charge repulsion within the fibre itself, as it accelerates in flight, leads to the formation of fibres of a reproducible size. Parameters which can be adjusted to influence the structure of the deposited fibres include the tip/collector voltage, the solution flow rate(s), collector/tip distance, polymer solution concentration, and the solvent volatility [19].

Recently (within the last 15–20 years), coaxial electrospinning has been increasingly important in the synthesis of core-shell-type fibres with tuneable properties [19–21], allowing hydrophilic drugs to be encapsulated in a hydrophilic or hydrophobic matrix, within a predominantly hydrophobic outer sheath layer. To achieve this, a second polymer solution is introduced to the electrospinning spinneret at a perpendicular angle to the first solution. When the two polymer solutions have differing properties, this results in a core-shell fibrous structure of the deposited fibre. Additional secondary interactions, such as hydrogen bonding, can improve the compatibility of the hydrophilic drug core with the hydrophobic shell [19–21]. A typical setup for a coaxial electrospinning experiment is shown in Fig. 1.

Coaxial electrospinning provides a rapid way to produce core-shell fibres in a single step, reducing processing time. Moreover, coaxial electrospinning reduces the burst release profile of weakly surface-bound hydrophilic drug molecules from the fibre, when compared to singly electrospun fibres [22]. This can otherwise be achieved by post-treatment including cross-linking or coating the formed fibres in a second processing step, though both of these options have disadvantages such as increasing cellular toxicity [22]. Fibres can be further processed into mats or membranes [23–25], from which the rate of release of a drug is typically diffusion controlled and dependent on the wettability of the fibrous matrix [23]. As aqueous channels form through the predominantly hydrophobic material slowly, the drug is able to diffuse outwardly only at a rate dependent on the permeation of water through it. Thus, a plot of drug release over time is theoretically very similar in shape to the plot of hydration or swelling over time. In turn, the wettability of the fibres is affected by their physical properties such as their hydrophilicity.

2.1. Recent advances in electrospun delivery devices for hydrophilic drugs

Both synthetic and natural polymers have been used successfully in the synthesis of electrospun nanofibers. A selection of recent publications detailing these devices is presented in Table 1. Formulations of electrospun fibre systems have been optimised to encapsulate drugs in a variety of materials, including synthetic and natural polymers. The polyesters poly(caprolactam) (PCL), poly(lactide) (PLA), poly(glycolide) (PGA), poly(lactide-co-glycolide) (PLGA), and their copolymers feature in many published articles; they are well-known biocompatible and biodegradable polymers, with biologically compatible degradation products [26–28]. PCL fibres formed the basis of several recently published articles [22,23,29], and fibres composed of PCL and other polymers have been used to encapsulate hydrophilic drugs including ampicillin, tetracycline and doxorubicin hydrochloride [24,30–32].

Sultanova et al. produced coaxially electrospun fibres of the hydrophilic antibiotic, ampicillin, in PCL, achieving near zero-order release for >72 h [22]. The core was spun from a 10% w/v solution of PCL containing 2% w/ampicillin, and the shell was made of a 4% w/v PCL only. Shell thickness was modulated by modifying the flow rate of the shell solution relative to that of the core solution. In a core-only fibre, almost 80% of the drug was released in 4 h; by comparison, a core-shell fibre released just 15% of drug in the first 4 h, with 90% release eventually reached after 72 h. Further experiments showed that increased shell thickness led to a decrease in rate of drug delivery, supporting the

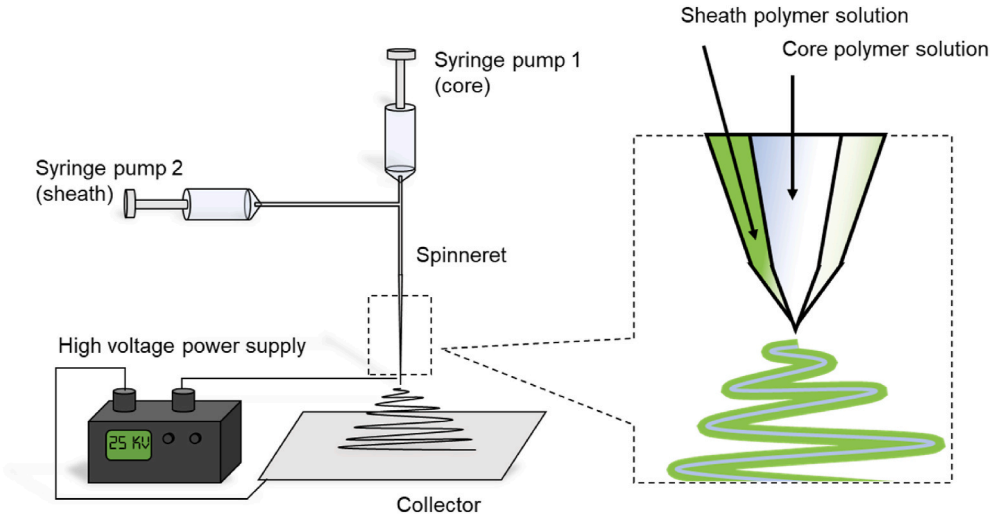

Fig. 1. Apparatus configured for the coaxial electrospinning of core/sheath fibres from two polymer solutions.

Table 1
Electrospun nanofibres and nanofibrous materials used in the delivery of hydrophilic drugs in the recent literature.

Ref	Drug compound	Description of electrospunfibre system	Release characteristic
[22]	Ampicillin	Drug-loaded core/shell PCL[a] fibres produced through coaxial electrospinning	Pseudo-zero order kinetics over 72 h with shell, cf. << 24 h burst release in core only fibre
[23]	Metronidazole (MTZ); ciprofloxacin (CIP)	Periodontal antibiotic delivery; Electrospun PCL nanofibre mats	MTZ release dependent on mat thickness; CIP release dependent on wettability. Maximum lifetime for MTZ = 200 h; for CIP = 30 h
[33]	Ampicillin	Amyloid-like bovine serum albumen fibres produced by electrospinning	Sustained release for up to 150 h, Fickian diffusion at ≤ 10% w/w ampicillin/BSA
[34]	Tamoxifen citrate	Colonic delivery; pH-sensitive coaxially electrosprayed hydrophilic poly(vinyl pyrrolidone) (PVP)-drug core/shellac shell nanocomposite particles	6% release in 2 h at stomach pH of 2.0. Triggered release at pH 7.4100% in 5 min.
[29]	Tetracycline	Alginate/soy protein isolate core-PCL sheath scaffold constructed *via* coaxial electrospinning	Initial burst release of 49% in 6 h, followed by slow release for a ≥14 days.
[12]	Doxurubicin HCl	Electrospun nanofibre mats composed of regenerated silk fibroin	*Ca.* 70% release over 8 h
[35]	Diclofenac sodium	Electrospun cellulose acetate nanofibrous mats	Linear release for initial 10 h (20%); then sustained release up to 100% for 48 h.
[30]	Tenofivir, azidothymidine, maraviroc, raltegravir	Electrospun PCL-PLGA fibres	Sustained release for up to 240 h, dependent on loading and ratio of PCL:PLGA
[31]	Naproxen	Layered double hydroxide particle-loaded electrospun PLA fibres	Sustained release for up to 66 days with no burst phase; dependent on thickness of hydrophobic PLA layers
[32]	Doxicycline hyclate	Coaxially electrospun PCL/poly(ethylene glycol) (PEG) core-shell nanofibres	Burst phase of 40% in 1 h, followed by 60% in 8 h
[24]	Metformin	PCL/chitosan electrospun nanofibrous membranes	50% released within initial 24 h, followed by lag phase (90% in 24 days)
[36]	Rosmarinic acid	Electrosprayed nanoparticles of PLGA	Sustained release for up to 96 h

conclusion that drug release was controlled by the permeability of the hydrophilic drug through the hydrophobic core. Ampicillin was also the target drug in a study [33] in which electrospun nanofibrous mats of amyloid protein-like bovine serum albumin were used as a biopolymer encapsulating agent for the drug. A concentration of 10% w/v ampicillin sodium in these protein fibres was found to sustain release of 81.5% of the encapsulated drug over 96 h. A follow-up study [37] compared the drug release properties of monoaxial electrospun fibres to fibres of amyloid-like BSA spun coaxially, from a drug-containing core and a drug-free shell. In these studies, flow rate ratio of drug-free to drug-containing solutions was 0:1, 2:1 and 3:1. It was found that the core-shell structured fibres slowed the release of the drug significantly, as expected due to the increased thickness of the relatively hydrophobic sheath.

The mechanism of hydrophilic drug delivery from hydrophobic fibres was studied in more detail recently by Zupančič et al. [23]. Here, nanofibrous mats were produced by monoaxial electrospinning of PCL solution containing metronidazole (MET) and/or ciprofloxacin hydrochloride (CIP), intended for sustained delivery to the periodontium. By electrospinning onto a rotating drum which also moved back and forth along its axis, nanofibrous mats of reproducible, varying thicknesses could be deposited, controlled by the length of experiment. The material properties found to affect release profile most were the thickness of the nanofibrous mat, its surface area, and the temperature of the release medium. For MET release, mat thickness was found to be of high significance (release rate was inversely proportional to mat thickness), while for CIP, drug release rate was independent of mat thickness. Varying surface area was found to be far less significant in release of MET from the thickest mat tested. Increasing temperature from 22 °C to 37 °C had the effect of increasing the maximum amount of drug released from 60% to 100% over an 8 day period, for the thickest mat tested. Contact angle measurements showed no difference in wettability between drug-loaded and drug-free mats, implying that the properties of the bulk polymer, and not the drug, are the major influence in wettability and drug release in nanofibre and nanofibrous mat drug delivery devices.

Copolymer and mixed polymer solutions are also commonly used for the adjustment of material properties when compared to single-polymer fibre components, allowing fine-tuning of the drug release profile according to the properties of the carrier system. For example, while PCL is by far the most used polymer due to its low price and biological compatibility, both synthetic and natural polymers such as PLGA [30], PEG [32] and chitosan [24] have all been used to modify physicochemical properties of the spun fibres. In a recent example [30], electrospun PCL/PLGA fibres were developed as sustained delivery devices for various hydrophilic antiretrovirals, with the ratio of PCL to PLGA having significant effect on the release of the drugs. For example, the release of tenofovir from PCL-only fibres was complete within 48 h (100% of encapsulated drug); on the other hand, fibres comprising a 40:60 ratio of PCL:PLGA released *ca.* 70% of encapsulated drug in 240 h. The difference in the relative flexibilities of the two polymers control the diffusivity of the material; PLGA's rigidity inhibits mobility of the drug, while the contrasting flexibility of PCL encourages diffusion of drug outward from the fibres.

Similarly, mixtures of hydrophilic and hydrophobic polymers at different ratios have been used to adjust the release rate of drugs from electrospun fibres. Eskitoros-Togay et al. [32] encapsulated the antimicrobial agent, doxycycline hyclate (DCH) in mixed PEG/PCL fibres. The ratio of hydrophobic PCL to hydrophilic PEG was optimised to give fibres of desirable smoothness and release properties; a fibre with a 3:1 ratio of PCL/PEG with 3.2% drug loading was found to be the optimal formulation for sustaining drug release, with 80% release over 6 h; other fibres with different drug loading typically released the majority of their payload within 2 h.

Biopolymers, such as chitosan (which are already widely used in drug delivery and as tissue/bone scaffolds [38–40]) have also been used in mixed material fibres, for example with PCL in the recent work of Zhu and co-workers for the encapsulation and sustained release of metformin [24]. Here, the electrospun fibres not only acted as a drug delivery device, but also formed membranes to guide localised bone regeneration. *In vitro* studies performed on fibres of ratio 7:3 PCL: chitosan revealed a release rate of 95.8% over a period of 24 days, albeit with initial burst release of 50% within 1 day. Other biologically derived material fibres have recently included a dual-drug delivering electrospun nanofibre of silk fibroin [12], encapsulating doxorubicin hydrochloride (hydrophilic), and curcumin (hydrophobic), with sustaining their release for over 12 h.

Nanofibre mats of another plant-derived polymer, cellulose acetate, were studied by Adepu and co-workers [35], for the transdermal delivery of diclofenac sodium (a hydrophilic non-steroidal

anti-inflammatory drug). In this work, the deposition of the hydrophilic, drug-containing polymer onto the surface through a mesh of 100 μm produced micropatterned mats with favourable drug release properties. This was due to the introduction of air pockets in the mat, reducing wettability of the micropatterned mats when compared to the hydrophilic, non-patterned mats. Thus, the micropatterned mat sustained a near-zero order transdermal release profile for over 20 h (80%), with lag phase up to 48 h; for the non-patterned mat, transdermal detection was much more rapid, with >75% encapsulated drug released in 12 h.

Stimulus-responsive fibres have also been synthesised using polymers with temperature or pH-responsive properties to ensure drug release occurs only under physiological conditions. The main advantages of these 'triggered release' systems come in their specificity and enhanced stability in storage. In a recent example [41], a temperature-sensitive electrospun fibrous system comprising temperature-sensitive poly(N-vinylcaprolactam) (PNVCL), with poly (methacrylic acid), was used to encapsulate a hydrophilic drug, captopril, and a hydrophobic drug, ketoprofen. PNVCL has a lower critical solution temperature (LCST; the temperature above which the polymer is insoluble in water) of 33 °C. The release of both drugs in PBS at 20 °C and 40 °C was monitored; at 20 °C, the maximum concentration of released drug was reached rapidly (<250 s), indicating uninhibited release. However, at 40 °C, the maximum concentration was not reached until after 24 h. Mechanistic studies revealed Fickian diffusion dominates below the LCST, and non-Fickian anomalous diffusion above it; drug absorbed close to the surface is released rapidly, while drug deep within the hydrophobic form of the fibres diffuses outward slowly. Release is therefore dependent both on the drug and the morphology of the polymer. Differences between observed total dissolved concentrations of ketoprofen and captopril in the release study were explained by the tendency of hydrophobic ketoprofen to aggregate in water (rather than dissolve), compared to the rapid dissolution of captopril. Such responsive systems, while promising in laboratory settings, suffer from poor long-term stability and would have to be carefully stored to avoid undesired triggered release, especially in warm climates.

In summary, electrospinning is a versatile and effective tool for the encapsulation of hydrophilic drugs within a predominantly hydrophobic matrix, providing a readily tuneable release profile controlled by machining parameters and polymer blends (with polymers and co-polymers which contrast in hydrophilicity/hydrophobicity, or flexibility/rigidity). Other approaches have included micropatterning, to introduce of air pockets within fibrous mats [35], and the use of temperature-sensitive polymers for physiologically-triggered drug release [41]. In any case, the attributes of critical clinical importance include mechanical properties, surface structure, morphology, and porosity, which are controllable through varying processing parameters (including solvent composition, polymer/copolymer composition and concentration, flow rate, spinneret voltage, and annealing time) [19–21]. Mechanical properties are most important where drug-eluting electrospun nanofibres are used in scaffolds for tissue regeneration; for example, tensile strength must be sufficient to withstand strain exerted e.g. during suturing [42]. Stiffness also plays a crucial role in the ability of scaffolds to mimic the extracellular matrix that they seek to imitate; Nam et al. showed that even if the chemical composition is identical, differing elastic moduli of electrospun scaffolds resulted in differentiation of stem cells into either chrondrocytes or osteocytes [43]. Encouraging cell adhesion is also crucial in drug-eluting scaffolds for the scaffolds to be successful in tissue regeneration; cell attachment is initially driven by electrostatic interaction, which can be controlled in the initial stages by incorporating charged polymers into the feed polymer solution, or by applying a positive or negative voltage to the spinneret (thus influencing orientation of dipoles within the polymer fibre and resulting in a net surface charge) [44].

Whilst electrospinning presents a simple, rapid way of producing such sustained delivery devices with desirable properties *in vitro,* their practicability as clinical devices remains to be assessed. In order to receive regulatory approval to enter clinical trials, manufacturers must demonstrate capability to produce sufficient volumes of material as appropriate for the number of participants in the trial and its duration (typically in the region of 10–100 participants over 18 months for a Phase I trial) [45,46], while adhering to current good manufacturing practices (cGMP). For electrospun nanofibres, the rate of production in laboratory settings is typically in the region of less than 1 g per hour [47]; managing scale-up is therefore a significant early barrier for many novel investigational medical products, and especially nanopharmaceuticals/nanofibres [45,46]. However, more recent methods have enabled outputs of several hundreds of grams per hour [47]. Other important barriers for clinical acceptance of nanofibres include their stability with respect to the amorphous-to-crystalline transition of the drug and polymer (since the improved bioavailability of fibre-encapsulated drug is due to it existing in an amorphous state [47]), and the dosage, since most drug-loaded nanofiber systems can only incorporate <10% drug by weight. Thus, for drugs of a higher threshold therapeutic range, the physical size of tablets would have to be uncomfortably large, creating a patient compliance issue [47].

Finally, for any medical device which is to be inserted into the human body, it is critical that the product is sterile. However, selection of a suitable sterilisation technique is heavily dependent on the material; for example, the majority of the electrospun fibres reviewed here are based on biologically compatible polyesters such as PCL, which have relatively low melting points (50–60 °C for PCL and some PCL/PLGA blends [48]), making them unsuitable for certain procedures in downstream processing required for use as medical devices (e.g. steam sterilisation). Even when steam sterilisation can be avoided, other commercial sterilisation techniques such as hydrogen peroxide plasma and ethylene oxide were shown to modify the physicochemical properties of PCL fibres undesirably. UV sterilisation was effective in sterilising the surface, but is poorly penetrating and unlikely to be effective in sterilising thicker mats or fibres [49]. Hydrophilic polyesters (e.g. PGA) are also typically unstable with respect to hydrolysis in extended periods of storage in humid conditions or aqueous solutions [50]. Moreover, since the drug delivery profile of nanofibrous devices is based on wettability, storage in a humid environment for an extended period would result in the gradual loss of drug compound from the fibres, hence specialised packaging may be required to extend the shelf life of the material.

The future of nanofibres, nanofibrous mats and implants in bench-to-bedside translation will be dictated by advances in polymer chemistry (with desired tuneable properties in drug loading, hydrolytic degradation, and biological compatibility), and also in improved understanding of cellular toxicity long term. The final obstacle will be in development of efficient, high yielding, and standardised method for scale-up in their manufacture [51], though some organisations have already developed regulatorily compliant manufacturing protocols and facilities for electrospinning of nanofibrous materials, and some promising clinical trial results have been obtained (e.g. Afyx's Rivelin® corticosteroid-delivering nanofibrous oral patch) [52].

Our second field of consideration focusses on different polymer systems; those based on hydrogels and the range of drug delivery approaches that have been developed using these materials.

3. Hydrogel systems for hydrophilic drug delivery

Hydrogels are insoluble, yet hydrophilic, cross-linked polymer systems which readily absorb water and become swollen, to the degree that the gel's composition is more water than polymer, and the gel characteristics are consequently dictated more so by water than by the polymer [53,54]. This physical stability is a product of their three-dimensional structure and cross-linking of polymer chains due to either physical interactions (ionic, dispersion, polar, hydrogen bonding) or chemical (covalent) cross-linking [55]. Aside from the nature of their cross-linking, hydrogels are commonly categorised in terms of their

origin: synthetic or natural [56]. Synthetic hydrogels are, by and large, more mechanically robust and resistant to degradation, as well as having tuneable properties (e.g. controlled by degree of cross-linking agent, or derivatisation of pendant groups). Naturally-derived hydrogels are mechanically less stable, but are inherently biologically compatible due to being formed from degradable polysaccharides or proteins, and thus (unlike many synthetic polymers) do not require post-modification such as PEGylation to enhance their biological compatibility [53–56].

The high water content and low-leakage properties of hydrogels make them suitable polymeric vehicles for hydrophilic drug delivery; dissolved drugs can be entrapped in the aqueous nodes of the swollen cross-linked polymer matrix [53–55]. However, the relative free movement of small, hydrophilic compounds through the swollen gel network facilitates rapid diffusion of drug into the aqueous surroundings, resulting in an undesirable burst release [55]. The so-called 'second generation' of stimuli-responsive hydrogels were able to combat this by reversibly collapsing into insoluble, densely cross-linked polymeric gels from a dissolved polymer solution, in response to changes in their surrounding environment. Thus, these systems reversibly entrap or release drug molecules within the gel by a change in conformation [53], which may be ionotropic, thermotropic, or pH-dependent in nature. Fig. 2 depicts the reversible collapsing and swelling of a polymeric hydrogel, resulting in drug entrapment/release.

The most useful systems in sustained release of hydrophilic drugs, then, are those which undergo this sol-gel transition under physiological conditions of pH or temperature [55,56]. *In-situ* gels are easily handled polymer solutions delivered in topical drops or injectable formulations; gelation under physiological conditions increases viscosity and thus slows the rate of elimination of the dissolved drug and polymer by transfer in aqueous fluids [55]. Polymers with the opposite behaviour have also been used in formulations with targeted delivery properties - for example, oral formulations which must withstand the acidity of the stomach to deliver drugs in the more alkaline intestinal tract. In these cases, the drug remains immobilised and entrapped in the cross-linked polymer network until exposed to the desired physiological conditions, at which point the polymer matrix will dissolve and the drug is released rapidly [55].

A selection of recent publications detailing hydrogel based materials, including those responsive to various stimuli and with self-healing properties, is displayed in Table 2. Subcategories of some of the novel hydrogel systems which have been recently developed in the field of hydrophilic drug delivery are summarised and examined in the subsections below.

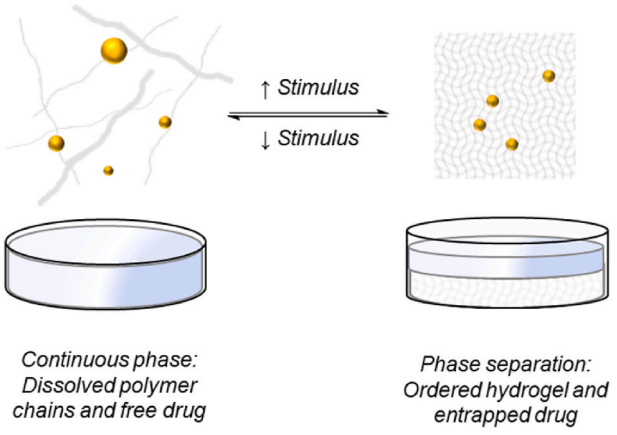

Fig. 2. The reversible entrapment of drug molecules in a polymer hydrogel solution, which gels (becomes cross-linked) or de-gels in response to an environmental stimulus.

Table 2
Recent publications detailing hydrogel devices used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of hydrogel system	Release characteristic
[57]	Levofloxacin	Chitosan/acryloylphenylalanine physically cross-linked hydrogel	Release sustained for *ca.* 60 h
[58]	Naltrexone HCl (NTX), polypeptide LXT-101	Temperature-sensitive, PLGA-PEG-PLGA *in-situ* gel	Systemic lifetimes for LXT-101 and NTX increased by a factor of 10x and 4x, respectively.
[59]	Ornidazole	Mucoadhesive hydrogel composed of drug embedded in quaternised dextran-*graft*-poly (dimethylaminoethylmethacylate)	Controlled release for ≥200 h
[60]	Levofloxacin	Self-healing hydrogel formed from L-lysine crosslinked guar gum/poly (acrylic acid) copolymer	Biphasic release profile; 50% release in 24 h, 90% release at 110 h
[61]	Rivastigmine hydrogen tartrate	Intranasal delivery; In-situ gel of Poloxamer 407 hydrogel-embedded PLGA nanoparticles prepared by nanoprecipitation	Burst release of ≥25% in « 1 h; sustained release up to 60% up to 8 h
[62]	Selegiline HCl	Nasal delivery; Thermosensitive *in-situ* gels of Pluronic F-127	Release sustained for 8 h
[63]	Acetamidophenol	Temperature-and pH-responsive *in-situ* forming gel formed from chitosan and poly(N-vinyl caprolactam)	<5% dermal permeation after 24 h at 32 °C. 30% release after 24 h at 39 °C at pH 7.4.
[64]	Fluorescein isothiocyanate	Silicone hydrogels containing PVP, poly(hydroxyethylmethacrylate) (PHEMA) and ethylene glycol dimethacrylate	Sustained release for over 24 at neutral and alkaline pH; rapid release in « 10 h in acidic media
[65]	Rhodamine B	Ocular delivery; PLGA-PEG-PLGA thermosensitive *in-situ* forming gel	Dye retained for up to 4 weeks in *in vivo* testing
[66]	Doxycycline HCl	Temperature-triggered phase transforming lyotropic liquid crystal capsules of glycerol monooleate and Gelucire® surfactant	Sustained release of drug for 24 h, (burst release of 30% in first 2 h, near linear release until 80% at 24 h)
[67]	Bimatoprost	Solid lipid nanoparticles prepared from glycerol monostearate, soya lecithin, and Tween 80 embedded in a pH-sensitive gel of Acrypol 941	*Pseudo*-first order release (>99% over 19 h)
[68]	Benzydamine HCl	Mucoadhesive, thermoresponsive polymer gels of poloxamer, PVP, and chitosan	Sustained release for at least 3 h (49%).
[69]	Acetylsalicylic acid	Double networks of responsive polymer gels, of poly(butyl acrylate)/poly(acrylic acid) (pH-responsive) and poly(N-isopropylacrylamide) (PNIPAM) (thermoresponsive).	Release sustained for 7 h.
[70]	Mitomycin	Thermoresponsive gels synthesised from methylcellulose and oxidised	Sustained release of drug

(*continued on next page*)

Table 2 (*continued*)

Ref	Drug compound	Description of hydrogel system	Release characteristic
		carboxyl nanocellulose, conjugated to drug.	for up to 14 days
[71]	Methadone HCl	Drug-loaded PCL microspheres embedded in a PEG and pentaerythritol-based hydrogels	Linear release profile up to 50% release in 67 h
[72]	5-fluorouracil	Colonic delivery; pH-sensitive core-shell structured polyelectrolyte complex microparticles synthesised from alginate, Pluronic F127 (core) and Eudragit RS 100	35% maximal release at pH = 1; burst release for 30 min followed by sustained release to 100% after 3 h at pH = 6.8
[73]	Procaine	Poly(styrene maleic anhydride)-*b*-PNIPAM temperature-sensitive *in-situ* forming micelles	Maximal 10% released over 700 min at 25 °C; *ca.* 50% release at 200 min at 37 °C

3.1. Stimuli-responsive hydrogels

The thermotropic gelation of polymeric hydrogels has been explored and exploited for many years in the field of drug delivery, especially in topical, transdermal, and injectable applications [55,56]. Since the human body has a core temperature which is typically significantly higher than the temperature of the surrounding environment, hydrogels which collapse upon surpassing a temperature of 32–37 °C are particularly useful in *in-situ* gel formulations [55,74]. Such behaviour is observed in polymers such as poly(N-isopropyl acrylamide) (PNIPAM), which have the property of lower critical solution temperature (LCST). Below the LCST, hydrogen bonding between the polymer and water is favourable, thus the polymer is solvated fully by water. Above the LCST, however, the inter- and intra-chain interactions become more favourable than those with solvent molecules, thus the polymers collapse and form gels. This is complicated by changes in behaviour resulting from tonicity – for example, the LCST of hydroxypropyl cellulose (HPC) is known to decrease with increasing salinity [75].

Triblock copolymers of PEG-PLGA-PEG exhibit temperature sensitivity and gel at temperatures which increase according to the ratio of lactic:glycolic acid in the hydrophobic portions. These systems have been used in the delivery of hydrophilic agents including drugs and proteins [58,65]. In the work of Zhang et al. [58], an injectable, thermoresponsive *in-situ* PEG-PLGA-PEG gel was shown to sustain release of high molecular weight compound LXT-101 (a gonadotropin-releasing hormone) tenfold, and low molecular weight naltrexone hydrochloride (a hydrophilic opioid antagonist) four-fold, when compared to the free drugs alone. In their 2019 article, Chan *et* al. [65] describe a topical drop containing PEG-PLGA-PEG for topical delivery of hydrophilic drugs to the ocular surface; thermogelation at ca. 30 °C was useful in increasing the viscosity of the drug-containing polymer matrix at the ocular surface, so that the gel was able to resist elimination *via* nasolacrimal drainage. The delivery of model hydrophilic dye, Rhodamine B, was of zero order type in a release medium of PBS at 34 °C, releasing ca. 90% of the encapsulated hydrophilic compound over 20 days.

Another family of triblock copolymer systems are the Pluronics®/Poloxamers comprising hydrophilic PEG units with a hydrophobic polymer, poly(propylene glycol), PPG, which exhibit thermoresponsive gelation. Pluronic® F-127 (PF-127) in particular, with a ratio of 1:0.65:1 PEG:PPG:PEG, has been consistently identified as a candidate for thermoresponsive gel hydrophilic drug delivery systems. Recently, PF127 has been employed in the nasal delivery of selegiline hydrochloride (SEL), a drug used in the treatment of Parkinson's disease [62], and the oral delivery of benzydamine hydrochloride (BZD), a drug used in the treatment of mucositis [68]. Gelation temperatures in the useful range of 30 and 34 °C were achieved through variation of concentrations of PPG, PF-127, and drug, in the pre-gel solution [62], granting slow release of SEL for up to 8 h in PBS (pH 7.4). Drug lifetime in mucosal tissues such as the nasal passage can be enhanced by using mucoadhesive drug delivery vehicles [9]. Therefore, in the work of Pagano et al. [68], the authors blended PF-127 with polyelectrolytes including poly(acrylic acid) and chitosan, to give the polymers mucoadhesive properties by ion pairing interactions. The drug/polymer solutions could be sprayed onto the affected area and would gel *in-situ* due to increased temperature, be retained on the negatively charged mucosa, and provide sustained release of BZD for at least 3 h.

As well as the ratio of hydrophilic/hydrophobic blocks, the degree of cross-linking in a thermogel also controls the release rate of drug molecules, as was investigated by Kang Derwent and Mieler [74]. In their mechanistic study, the ratio of cross linker PEG-diacrylate in a PNIPAM thermogel was varied, and the release of large molecular weight compounds such as proteins to the ocular surface was measured. The initial release was rapid and driven by shrinking of the swollen polymer as gelation occurred; the contraction in volume led to the ejection of the large drug. The second, slow phase was limited by diffusion of the relatively large proteins as they travelled through the densely cross-linked polymer matrix. As such, high cross-linking density was associated with a slower second phase release, but a more rapid and dramatic initial burst release.

Another ocular in-situ gelling polymer was developed by Prasannan, Tsai and Hsiue for the sustained delivery of epinephrine to the anterior eye in order to alleviate intraocular pressure (IOP) in conditions such as glaucoma [76]. Their system comprised cross-linked drug-loaded nanogel particles, themselves entrapped within a graft copolymer of poly acrylic acid and pNIPAM. Applied as an eyedrop, the *in-situ* gel formed as a thin film over the ocular surface, providing extended release of epinephrine for approximately 2 days in PBS. Animal models revealed reduction in IOP for 36 h, as opposed to 8 h for an epinephrine eyedrop containing no polymer vehicle. Such *in-situ* gel formulations are also suitable not just for direct encapsulation of drugs, but also for secondary encapsulation of polymeric or nanoparticulate drug delivery vehicles. For example, rivastigmine hydrogen tartrate (RHT), a hydrophilic salt of the cholinesterase inhibitor used in treatment of Alzheimer's and Parkinson's diseases, was encapsulated in PLGA nanoparticles which were subsequently embedded in a thermoresponsive hydrogel of poloxamer 407 [61]. This composite nanomaterial sustained the release of RHT for up to 8 h (60%), following an initial burst release of *ca.* 25% in 2 h.

Though rarer, there are recent examples of gels which behave in the opposite manner to those described above, and instead dissolve at higher temperatures and precipitating at lower temperatures. Poly(N-acryloyl glycinamide) (PNAGA), has a tuneable upper critical solution temperature (UCST) of between 38 and 94 °C, influenced both by M_w of the polymer and its concentration in solution [77]. Boustta et al. published work which showed that an injectable PNAGA solution would gel at human body temperature as it cooled, and would sustain the release of methylene blue, a hydrophilic dye, for up to 300 h at body temperature [77]. However, the size and shape of the gel could not be controlled *in vivo*. Many other gels with UCST in useful range of 32–34 °C tend to be synthetic ureido group-containing polymer derivatives [78]. In general, it should be noted that UCST behaviour in (clinically) useful temperature ranges is uncommon, and useful drug delivery systems using UCST behaviour are few and far between when compared to LCST polymers.

Polymers with ionisable functional groups (e.g. amine or carboxyl moieties) can reversibly form pH-responsive gels as result of protonation/deprotonation [53–56]. Increased charge density of a polyelectrolyte results in inter-chain repulsion, allowing water to solvate the

polymer chain. Removal of charge facilitates agglomeration and precipitation due to inter-and intra-chain interactions such as hydrogen bonding. Chitosan, a naturally ubiquitous glucosamine/N-acetylglucosamine copolymer, has ionisable amine groups which become protonated in acidic conditions, thus making it one of very few naturally occurring polycations. Its availability, biocompatibility, and interesting properties in pH-sensitivity and enzyme degradability have made it one of the most heavily cited natural biopolymers in the drug delivery literature [39,79,80]. Applications for pH-sensitive hydrogels in drug delivery have included ocular *in-situ* gels which collapse at the neutral pH of the tear film [81–83], and hydrogels with the opposite behaviour which swell in the neutral pH of the intestines after remaining collapsed to entrap drug in the acidic gastric tract [72]. However, as the polymer is produced from the deacetylation of natural chitin (extracted from fungi, arthropods and crustaceans [84]), chitosan of known purity, molecular weight, degree of deacetylation, and uniformity of frequency of deacetylation, is difficult to produce; these issues in synthetic reproducibility are a major issue in the approval of chitosan-based pharmaceuticals by regulatory bodies [85,86].

Dual and multi-responsive gels provide additional specificity in terms of environmental trigger, thus improving control over drug delivery by increasing the specificity of the conditions required to initiate drug release. For example, pH-responsive chitosan was grafted to temperature-sensitive poly(N-vinyl caprolactam) to form a dual-responsive, on-demand topical pain relief system for transdermal delivery of hydrophilic acetamidophenol and hydrophobic etoricoxib in recent work by Indulekha et al. [63]. The hydrogel had an LCST of 35 °C, and chitosan's pK_a is *ca.* 6.5. Therefore, application of the device to the skin (of pH typically <5 [87] and temperature typically in the range of 33.5–36.9 °C [88]) results in the most rapid rate of drug delivery. At temperatures below the LCST and pH above the pK_a of chitosan, the release rate is slowest. The effect of temperature was much more significant than that of pH; less than 20% of hydrophilic acetamidophenol was released at 25–32 °C at either pH 5.5 or 7.4. On the other hand, at 39 °C, 100% drug release was achieved in 90 min at pH 5.5, while 100% release took 180 min at pH 7.4.

Dual-responsive hydrogels sensitive to both pH and glucose concentration have recently been developed for the triggered delivery of insulin to the open wound area of diabetic foot ulcer sufferers [89], employing a system comprising a phenylboronate ester of chitosan, polyvinyl alcohol, and end-capped PEG-dibenzaldehyde. The reaction of chitosan with the benzaldehyde groups crosslinks the chitosan, while the electrostatic interaction of PVA with the boronic acid moieties cross-links forms the 3-dimensional network. Boronic acid preferentially binds to glucose over PVA, thus granting sensitivity to the glucose, while the pH-sensitive Schiff base grants sensitivity towards acidic media. Thus, release of insulin from the hydrogel proceeds slowly at typical physiological pH of 7.4 and in the absence of glucose, but is rapid at pH 6.5 and more so in the presence of glucose. In terms of real wound healing activity, wound area was reduced by 50% in *ca.* 3 days with the hydrogel dressing, compared to 6 days for a PBS control, and was nearly 0% in 18 days cf. >15% in the same period for the PBS control. By combining environmental and biological stimuli, this work provides an example of a truly intelligent material which is specific and selective to the disease it seeks to target.

3.2. Self-healing and miscellaneous hydrogels

Self-healing hydrogels have received considerable attention in the recent literature, approaching the forefront of hydrogels in engineering applications in the last 20 years [90], especially as biomaterials [91]. These materials, upon mechanical damage such as tearing or cracking, will repair themselves through interactions of compatible moieties constituting the material's fractured edges. These so-called autonomous self-healing hydrogels, self-repairing *via* hydrogen bonding and electrostatic interactions (without requirement for energy input or chemical activation), have applications in medical technology applications including wound healing, scaffolds, and drug delivery [91,92]. The self-repair process typically occurs rapidly (<1 h [57,60]), *via* attractions between the two edges as a result of secondary interactions, eventually reforming the solidified material. This process is illustrated in Fig. 3.

Embedding antimicrobial drugs into self-healing scaffolds and dressings offers a facile method to support the body's natural repair mechanisms and simultaneously offer sustained protection from infection. Two self-healing hydrogels designed for the release of the hydrophilic antimicrobial, levofloxacin, were described by Sharma and co-workers recently [57,60]. In the first, the self-healing material was chitosan/acryloylphenylalanine/methylenebisacrylamide, synthesised through template polymerisation [57]. Even when the hydrogel film is cracked completely by razor blade scission, the gel reforms within 30 min with no visible deformity. In one example, a self-healing hydrogel soaked in lexofloxacin sustained the release of the drug over 60 h in aqueous buffer solution (PBS, pH 7.4). The same authors later published another system for the release of levofloxacin with improved properties, synthesised from self-healing guar gum/acrylic acid hydrogels [60]. The *in-situ* polymerisation of acrylic acid in the presence of guar gum created an entangled hydrogel, cross-linked by hydrogen bonding of the hydroxyl groups in guar gum with the carboxylic acid groups of acrylic acid. In comparison to their previous system, this self-healing hydrogel exhibited excellent elasticity even after one cracking and healing cycle, and favourable drug release profile of nearly 98% in 120 h, after an initial burst phase of *ca.* 55% in the initial 24 h.

In both cases, the impressive drug release profiles, coupled with excellent elasticity and self-repair properties, offer clear advantages over currently existing antimicrobial wound dressings. Existing hydrogel wound dressings, made from materials such as alginate [93], are prone to fail mechanically by tearing, cracking or ripping on movement of the patient, and thus require regular replacement and re-dressings [94]. Furthermore, these drug releasing dressings offer advantages over traditional, non-drug releasing dressings, in that the wound does

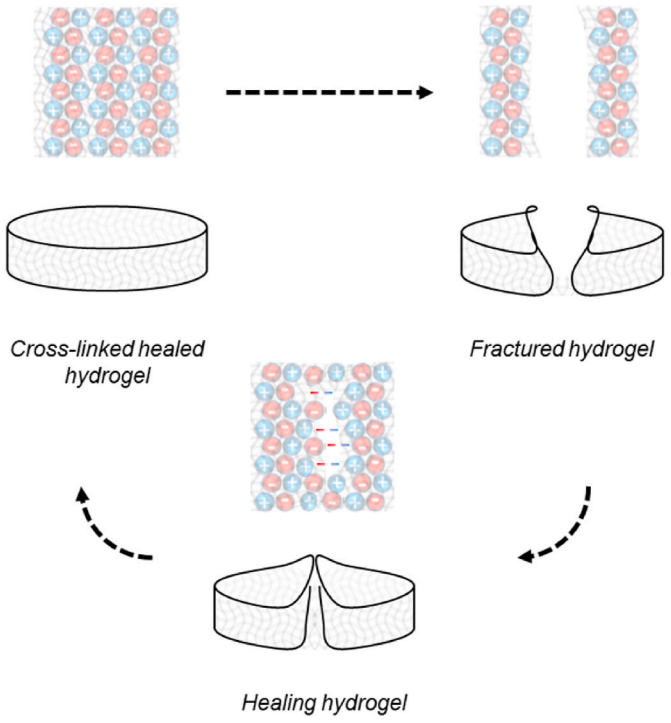

Fig. 3. The self-healing of an electrostatically cross-linked hydrogel, as secondary interactions rapidly form between oppositely charged components of the fractured edges, repairing the gel macrostructure.

not need to be exposed for repeat dosing of antimicrobial agents, thereby increasing risk of infection. These properties therefore make these self-healing, drug-releasing hydrogels excellent candidates for use in home, hospital, and emergency settings.

3.3. Hydrogel soft contact lenses

Since the patent was filed for their invention in the late 1960s, soft contact lenses (CLs) constructed from hydrogel-forming synthetic polymers such as pHEMA have been envisioned as drug delivery devices for ophthalmic pharmaceuticals [95–98]. Most common, commercially available ophthalmic medications are available to the consumer as topical eyedrops, yet drugs delivered by aqueous eyedrops suffer from premature precorneal elimination and thus poor bioavailability [95–98]. This results in a need to re-administer the drugs often (and sometimes even overnight), commonly resulting in poor patient compliance [95–98]. Frequent re-administration can also lead to undesired systemic side effects, if sufficient concentrations of drug enter the bloodstream after absorption by the conjunctiva [99]. CLs, as polymeric platforms, can effectively act as removable implants and reservoirs for absorbed drugs. However, unmodified CLs alone are typically unable to significantly sustain drug release for hydrophilic drugs, due to the tendency of these compounds to elute relatively unencumbered from the hydrated CL [100], as the mesh voids (typically <10 nm [101]) are significantly larger than even large pharmaceutical compounds. Thus, the unmodified CL is a poor diffusion barrier.

Nonetheless, the nature of CLs allows drug delivery devices to be constructed to be a part of the hydrogel itself. Methods used to achieve this have included the polymerisation of the CL around a template of drug molecules (i.e. molecular imprinting), as in the work of Chu et al., who embedded dexamethasone sodium phosphate (DSP) into molecularly imprinted CLs, considerably improving the drug loading efficiency, and extending the drug release lifetime from several min to >2 h [102]. Incorporation of photonic crystals allowed the CL to self-report drug release progression, as the refractive index of the CL changes with swelling. As an alternative to loading or imprinting the drug molecule by polymerising the CL monomers around a template of the drug, the anchoring or coating of drug delivery devices onto the preformed CL can be performed instead. For example, a study by Mehta et al. [103] used a novel template device to coat exclusively the outer perimeter of a silicone CL with nanofibers of timolol maleate-containing mixed fibres of poly(N-isopropylacrylamide) (PNIPAM) and poly(vinylpyrrolidone) (PVP). Thus, the central portion of the contact lens was transparent and retained its desired vision-correcting properties. The delivery profile in aqueous buffer comprised a biphasic release, whereby 50–75% encapsulated drug was released over 6 h, followed by up to 65% release over 24 h. As is common for these nanofibre systems, the total % of drug released, and the rate of drug release, was inversely proportional to the thickness of the fibre. While the authors ensured that the centre of the lens remained transparent and uncoated to maintain visual correction efficacy, the smoothness and comfort of the lens were not assessed. Its true viability as a wearable implant for the delivery of ophthalmic drugs therefore remains to be fully established.

Another common method for embedding drug delivery systems into CLs is through entrapment of the durg in nanoparticles which are then secondarily embedded into a CL. Maulvi et al. described such a system, where pH-sensitive, drug-loaded nanoparticles of Eudragit® S100 were incorporated into a CL during curing [82]. The CLs were stored at a pH of <6.5 and, when exposed to simulated tear fluid at a pH of around 7.4, released cyclosporine for up to 156 h. A shelf-life study showed that drug loss to bulk solution in the 90 days following autoclave sterilisation was reduced by a factor of 16, in comparison to a lens soaked in a solution of drug rather than a NP suspension. The sizes of NPs measured were 45–61 nm. Maulvi's is one of fairly few studies in the recent literature which studies the feasibility of these particles in a real-world setting, i.e. by including shelf-life and autoclave stability studies. However, the impact of the nanoparticle impregnation of the hydrogel contact lens on its visual clarity was not assessed, nor oxygen permeability or user comfort – each examples of additional considerations in translational therapeutics not commonly addressed in the literature [104]. In summary, with tuneable multi stimulus-responsive behaviour and enhanced biocompatibility due to the nature of the materials used and their high water content, hydrogel reservoirs for drugs and drug-encapsulating nanoparticles are versatile and can be used in topical, injectable and oral applications, as we have seen. Their disadvantages include low mechanical strength, poor physical stability, and the non-biodegradability of certain synthetic hydrogel polymers [55]. Indeed, the mechanical properties of hydrogels are highly variable, and tuneable depending on the materials used, and their desired purpose. For example, injectable hydrogels must have the necessary fluidity to be injected, yet must also possess the rigidity required to remain in place once injected. For these applications, shear-thinning polymers and non-covalent gelation are the most common forms of forming a hydrogel *in-situ*. Examples of noncovalent gels used in clinical and commercial successes include carboxymethylcellulose (e.g. Osteogenic protein 1 (OP-1®) implant, OP-1® Putty (Stryker Biotech)), hyaluronic acid (e.g. EUFLEXXA® (Ferring Pharmaceuticals Inc.) and alginic acid (e.g. Algisyl-LVR® Hydrogel Implant (LoneStar Heart, Inc.)) [105].

On the other hand, covalently cross-linked hydrogels, made from (commonly) acrylate-based polymers, have more easily tuneable properties including porosity, water content, and mechanical strength. However, their drawbacks are that due to their nature and method of formation, they are not injectable. and that these hydrogels must undergo careful post-processing to remove any toxic unreacted initiators and monomers. Therefore, any loaded drug must be retained during these wash stages, but remain releasable at the target tissue for the required lifetime of the drug. Examples of covalently cross-linked, synthetic polymers used in clinically and commercially successful products include PHEMA (e.g. Vantas® (Endo Pharmaceuticals)), and poly (acrylamide) (Bulkamid® hydrogel (Searchlight Pharma)) [105]. More recently, as we have seen, hybrid materials have been becoming increasingly common; grafting of a biologically compatible co-polymer, such as PEG or a biopolymer, to an otherwise poorly tolerated synthetic polymer backbone can give linear polymers and hydrogels with the desired mechanical strength and biological compatibility.

By far the most common synthetic hydrogels already used as medical devices worldwide are CLs, for vision correction [105]. However, despite a wealth of scientific literature indicating they may be suitable for use as drug delivering systems, no drug-eluting CLs are available commercially today [98]. The main barriers preventing their mainstream adoption have been the significant alteration of material properties as drug load in the CL changes during drug release, issues with sufficiently extended wear, which increases the risk of developing ocular diseases such as microbial infection, corneal hypoxia, and dry eye disease [98].

Challenges for any drug-eluting hydrogel to be clinically and commercially successful are manifold – firstly, as with all preclinical investigational medicine products, simply scaling up the manufacturing operation in line with cGMP and producing a sufficiently robust process is often difficult, especially when working with materials of natural origin whose characteristics may themselves vary from batch to batch of raw material. Pharmacologically, the fates of each component (polymer (s), drug(s), cross-linker(s)), must be understood and demonstrably reproducible, with predictable behaviour and stability both *in vivo*-eye and under storage conditions. This may be difficult to achieve depending on the manufacturing methods used, especially given the sheer number of variables required for synthesis of the hydrogel, loading with drug, and packaging/storing the drug-loaded hydrogel. For CLs specifically, clinical uptake may be hindered by a limited willingness of physicians to prescribe (and for patients to accept prescription of) drug-eluting CLs products, due to psychological reasons such as predicted discomfort, or simply a technical inability to insert CLs safely and efficiently [98].

Sterilisation of hydrogels is relatively simple, as most are compatible with the commonly used steam sterilisation process. However, there is evidence that drug release from drug-eluting hydrogels following steam, γ-radiation or ozone sterilisation result in a decrease in the amount of drug delivered, with γ-radiation and ozone both resulting in the chemical degradation of the embedded drug itself [106]. Numerous hydrogel materials have entered the clinical trial phase in recent years, evidencing the bench-to-bedside applicability of these materials [107]. Overall, while many hydrogels are now entering clinical trials, the final limitation is simply one of resources; it can take up to 10 years and $800 million for a product to translate from the preclinical to commercial stage [105].

The library of hydrogel materials is constantly evolving, and the focus on commercialisation expanding. Remaining challenges include the balancing of costing, shelf life, and differences in patient-to-patient interactions between synthetic and living tissues, as well as the current lack of any standardised testing procedures for monitoring the efficacy of the devices, and their fate in the body [107]. The current landscape in the literature is one of a sustained interest (from researchers, clinicians and investors alike), in biologically compatible hydrogels. Thus, these materials are likely to remain among the strongest candidates for approval in biomedical applications, including tissue scaffolds and drug delivery.

An alternative approach is to use encapsulated micro- and nanoparticulate carriers. The next section explores this expanding field of nanomedicine and its potential application for the delivery of hydrophilic compounds.

4. Micro- and nanoparticulate carriers

Nanomedicine is arguably one of the most widely used approaches in contemporary drug delivery, due to the ability of nanoparticles to encapsulate drugs in vehicles with desired properties of biological compatibility, targeting, and size [4,108,109]. These properties differ significantly at the nanoscale in comparison to the bulk material [110]. Furthermore, the small size range of these particles enables particles of an appropriate size to interact with, and enter, cells and release drugs directly into the cytoplasm, *via* endocytosis [111]. Drug release from these particles can either be driven mechanistically by diffusion through the nanoparticle matrix, erosion of the particle, or a combination of the two [109]. Self-assembling liposomal formulations have already proven successful in enhancing the delivery of poorly soluble, hydrophobic cancer drugs, and are used today in real-world healthcare applications [4].

In the delivery of hydrophilic compounds specifically, then, the requirements are the reverse of those for hydrophobic compounds; aqueous solubility must be reduced instead of increased, thus modulating of the drug's lifetime in the body and ability to penetrate lipophilic barriers (e.g. the blood-brain barrier, BBB). This has been achieved by encapsulation into an amphiphilic or hydrophobic particulates, including lipid carriers (solid lipid nanoparticles and nanostructured lipid carriers), polymeric matrix nanoparticles and capsules, functionalised porous silica nanoparticles, and self-assembling structures such as micelles and liposomes. Recent advances in these technologies are explored below.

4.1. Lipid carriers

The two main types of lipid carrier used in contemporary drug delivery are solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). While similar, the two differ in that the SLN particles have a solid lipid core at room and body temperature, often being prepared from a solution of molten lipid at a raised temperature. Upon cooling, drug molecules are entrapped between fatty acid chains, between lipid layers, or within imperfections in the particulate crystal structure (as illustrated in Fig. 4) [112]. Thus, for reasonable entrapment efficiency,

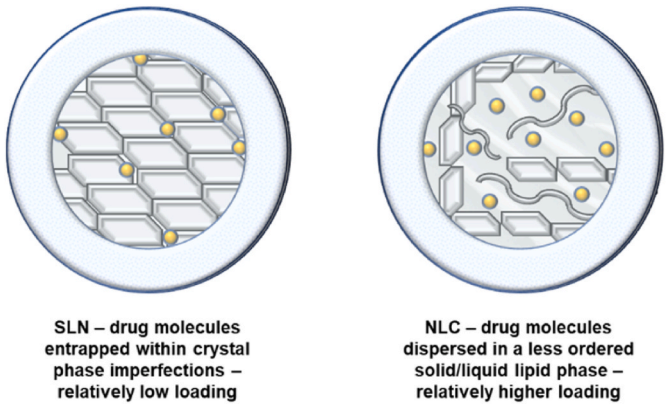

Fig. 4. Comparison between lipid core of SLN and NLC particles and the consequent effects on drug loading capability and encapsulation efficiency.

there is a requirement for a certain degree of imperfection in the structure [113]. Typically, therefore, SLNs are associated with lower drug encapsulation and a less desirable, burst release profile, when compared to NLCs [114].

NLCs, on the other hand, use mixtures of lipids with high and low melting points to give a nanoparticle comprising both solid and liquid core character, permitting encapsulation of much more drug per volume (since the prerequisite for crystalline imperfections is met inherently). Thus, the drug may be entrapped within liquid nano-compartments dispersed throughout the particle, within imperfections in the particle semi-crystalline structure, or dispersed relatively more homogeneously within an amorphous particle matrix [114]. This leads to higher drug loading efficiency and a more favourable diffusion- or erosion-controlled release.

In both cases, the entrapment of hydrophilic drugs within a hydrophobic lipid core is understandably more complicated than the entrapment of lipophilic drugs. There are two methods commonly used to synthesise lipid particles in the nano scale. For example, the double emulsion solvent evaporation technique, in which the water soluble drug is dissolved in water and emulsified in an oily phase, which is then further emulsified in an aqueous phase; the solvent is then removed to form the particulates [115,116]. Alternatively, a single emulsion method is used in which a drug-lipid dispersion is formed by adding the hydrophilic drug to a molten lipid phase, which is then added to a surfactant-containing aqueous phase and homogenised [67,117–121]. Table 3 contains a list of recent work in which hydrophilic drugs have been encapsulated in nanoparticulate lipid carriers.

NLCs and SLNs have been used to modulate the solubility and bioavailability of hydrophilic drugs, making them useful in delivery vehicles for the brain [115,117,119] and ocular surface [67], for example. Furthermore, surface modification of the particles can be used to induce site-specific targeting (e.g. conjugate of biomolecules for recognition by cancerous tissues [116]) or enhanced cellular/mucosal adhesion [117]. In each example, maximal entrapment of the hydrophilic drug in a hydrophobic lipid matrix is accomplished by optimising blends of different solid and liquid lipids, at differing ratios, and with different surfactants. Details of the individual formulations in terms of lipids and surfactants used in various recent articles can be found listed in Table 3. Some of the novel and innovative modifications, which have increased specificity by conjugation of targeting moieties to the particle surface, for example, are explored in more detail below.

SLNs with biological targeting for the specific treatment of breast cancer were the subject of work by Radhakrishnan and co-workers [116], in which the targeting moiety, bombesin, was conjugated to the outer surface of lipid particles containing the drug epigallocatechin gallate. Bombesin, a short chain peptide, has a high affinity for gastrin releasing peptide receptors which are overexpressed in breast cancer.

Table 3
Recent publications detailing SLN/NLCs used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of lipid nanocarrier system	Release characteristic
[117]	Almotriptan	Brain delivery; Chitosan-coated nanostructured lipid carriers composed of Compritol, Labrafil, Tween 80 and lauroglycol	Final drug brain concentration over 7 x greater for the lipid carrier than the free drug
[115]	Baclofen	Brain delivery; Nanostructured lipid carriers based on soy lethicin and glyceryl, mono-, di-, and tristearates stabilised by Tween 80	Sustained delivery of 74.6% encapsulated drug over 28 h. Typical brain permeation *ca.* 2 x that of the free drug solution
[118]	Sulforhodamine 101	Solid lipid nanoparticles of stearic and capric acid stabilised by lecithin and polysorbate	No release data. Encapsulation efficiency of 63%
[67]	Bimatoprost	Solid lipid nanoparticles prepared from glycerol monostearate, soya lecithin, and Tween 80 embedded in a pH-sensitive gel of Acrypol 941	*Pseudo*-zero order release (>99% over 19 h)
[116]	Epigallocatechin gallate	Targeted release to tumour cells; solid lipid nanoparticles of stearic acid, glycerol monostearate, and lecithin, conjugated to bombesin	Tumour growth inhibited over 30 days *in-vivo*.
[119]	Rasagiline Mesylate	Poloxamer 407-stabilised stearic acid SLN	Initial burst release (30%, 2 h); sustained release for 24 h
[120]	Valacyclovir	Ocular delivery: SLNs formed from stearic acid and tristearin, stabilised by surfactants Poloxamer 188 and sodium taurocholate	Burst release 20–40% in 90 min; 80% release in 12 h
[115]	Baclofen	Brain delivery; Nanostructured lipid carriers based on soy lethicin and glyceryl, mono-, di-, and tristearates stabilised by Tween 80	Sustained delivery of 74.6% encapsulated drug over 28 h. Typical brain permeation *ca.* 2 x that of the free drug solution
[121]	Alendronate sodium	Glyceryl monostearate and Tween 80 SLN carrier, emulsified in drug-containing aqueous phase containing Poloxamer 127	93.2% drug release (of the optimised formulation) over a period of 102 h.
[122]	Berberine	Poly(glycerol sebacate) gel macrostructures	Biphasic release; 15% drug released over 62 days.

Over a 30 day period in tumour-implanted mice, the bombesin-conjugated SLN system was found to inhibit tumour growth while maintaining body weight, indicative of specificity for the tumour environment.

In another example of targeting, bimatoprost-containing SLNs were recently embedded in a pH-sensitive hydrogel of poly(acrylic acid) by Wadetwar et al. [67]. In comparison to SLN-only formulations (i.e. those not encapsulated in a hydrogel matrix), the pH-sensitive hydrogel was found to sustain release of the drug with near zero-order kinetics, releasing 99.7% of the drug in *ca.* 19 h (cf. 10 h for the NP-only formulation) due to the additional diffusion barrier provided by the cross-linked matrix. This formulation was designed for use in ophthalmic therapeutics, thus the hydrogel was useful in increasing the viscosity of the formulation and reducing premature elimination of the lipid particles from the tear fluid.

The main benefits of SLNs and NLCs are in their ability to entrap and sustain the release of both hydrophilic and hydrophobic drugs in aqueous media and stabilise otherwise unstable drugs for periods of months or more, due to protection from oxidative and hydrolytic degradation when in the lipid surroundings [112,123]. However, these lipid matrix nanoparticles gradually undergo a transition from an imperfect crystalline structure containing amorphous regions to a highly ordered lipid crystal structure. Given that the drug is encapsulated in these amorphous regions, the restructuring of the lipid crystal phase results in the expulsion of drug molecules [112,113]. Typical high pressure steam sterilisation of these particles at 121 °C is likely to result in the loss of efficacy due to the melting of the lipids, and flocculation of polymer stabilisers [112,124]. Aseptic preparation and pre-filtering therefore remain the most common form of sterile manufacture of SLNs, though little research has been made into the effects of γ-radiation sterilisation on the formulations and their pharmacology as a whole [125], other than in specific, recent examples [121,126]. In the latter example, γ-radiation was effective in sterilising the particles, but nearly halved the total amount of drug released [126].

4.2. Polymer nanoparticles, spheres and beads

Polymer nanoparticles (PNPs), as an umbrella term, can relate to any sub-micron sized structure which is formed from polymer materials, but is most used to refer to polymer nanospheres and nanocapsules. Unlike self-assembling nanocapsules and SLNs/NLCs, PNPs are formed of polymers and are therefore constructed from a covalent, drug entrapping network rather than less stable secondary interactions. They can be synthesised from a 'top-down' or 'bottom-up' approach; i.e. from pre-made polymers which are manipulated through solvent control to form nanoparticles, or from monomers which are polymerised to form nanoparticles, respectively [127]. These methods include emulsion-diffusion or solvent evaporation methods, coacervation, and nanoprecipitation, as well as emulsion and interface polymerisation for the bottom-up methods.

Particle size control is achieved by optimising parameters including solution concentration, surfactants concentration, polymer molecular weight, homogenisation technique, and characteristics of the solvent and solvent environment. Loading of hydrophilic drugs into predominantly hydrophobic polymers is typically achieved either through double emulsion solvent evaporation polymerisation [128,129], complex coacervation [130,131], or nanoprecipitation [132]. These nanoparticle synthesis techniques are illustrated in Fig. 5.

Many different polymers have been used in the fabrication of nanoparticles, but in drug delivery applications, most are typically based either on biologically compatible acrylate polymers, alkylene oxides such as PEG, or, more recently, biodegradable polyesters such as PLA, PLGA, and PCL [127,133]. pH-sensitivity and biorecognition can be instilled to the particles through construction using pH-responsive materials or through conjugation to targeting moieties [134,135]. Other modifications, such as PEGylation, are necessary since hydrophobic particles are recognised as foreign by the body and are eliminated by the reticuloendothelial system [111]. Table 4 summarises recent publications in which polymer nanoparticles have been used in the sustained release of hydrophilic drugs.

An uncommon, novel system for the on-demand topical delivery of drugs from a nanoparticulate preparation was detailed by Rajamanickcam et al. [129]. In this device, compressible silicone elastomer microparticles were impregnated with the model hydrophilic dye, sodium fluorescein. Upon application of mechanical stress to the elastomer, compression of these particulate-containing void spaces resulted in the release of drugs from the particulates. By embedding these particles in a thin film of PDMS, an applicable, thin film device could be fabricated, which releases the drug when force is applied. Release

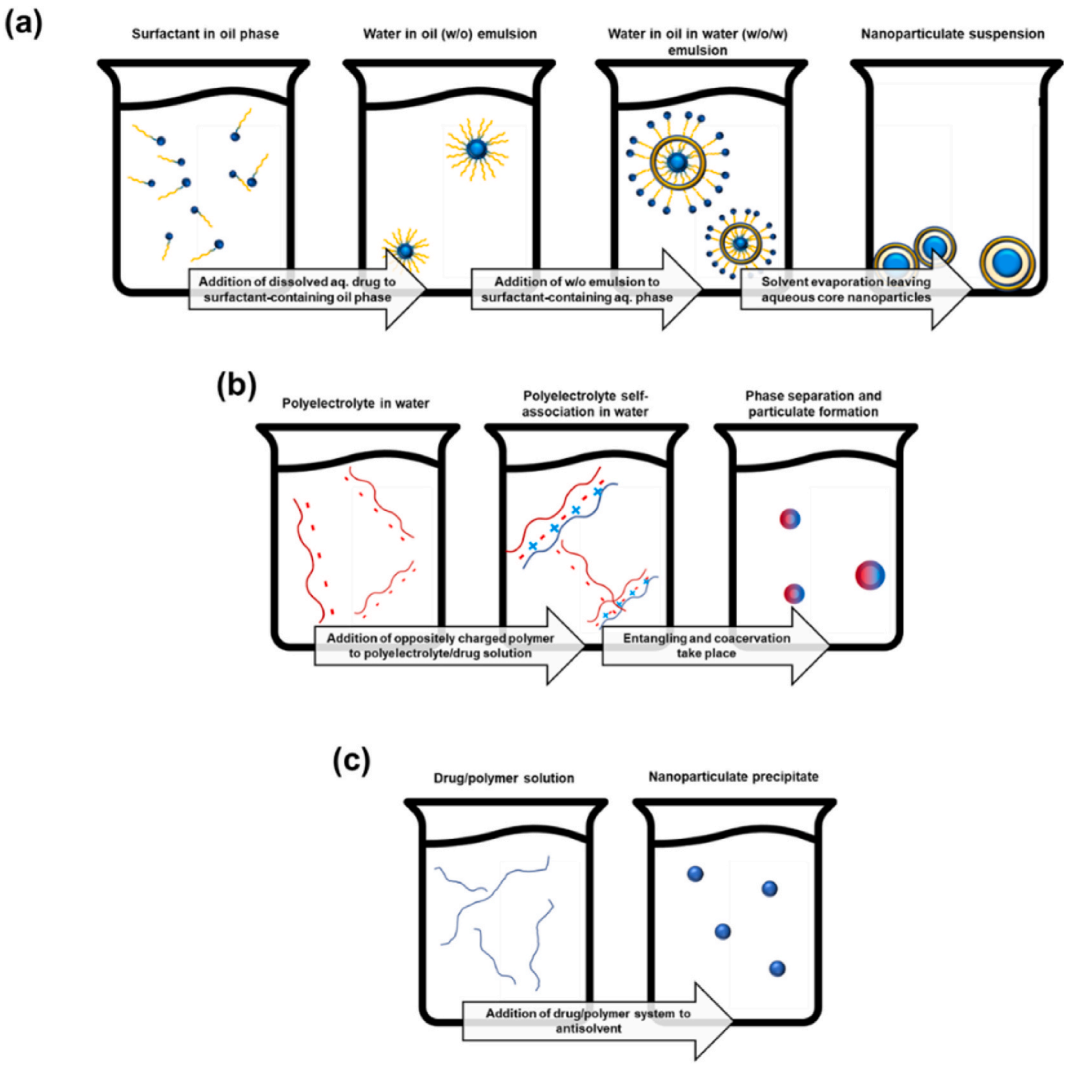

Fig. 5. Schematic representing the processes behind (a) double emulsion solvent evaporation, (b) polyelectrolyte complex coacervation, and (c) nanoprecipitation, in the formation of hydrophilic drug-loaded nanoparticles.

studies on this device conducted in PBS showed that release of drug was proportional to the amount of pressure applied to the film, and a maximum of 5% encapsulated sodium fluorescein was released in the absence of an externally applied force. Such a technology has potential for the on-demand elution of e.g. painkillers and antibiotics from compressible wound-healing dressings.

As an alternative to aqueous core, or matrix nanoparticles, novel, solid-core nanoparticles were synthesised by Toorisaka et al. recently [136]. Here, solid, powdered hydrophilic drug (theophylline) was dissolved in water and dispersed in hexane containing sucrose palmitate. The emulsion was then lyophilised, producing a solid, surfactant-coated drug in powdered form. The emulsion/solvent evaporation technique was then used to create solid drug-core PLGA nanoparticles. The advantages of particle synthesis by the solid-oil-water method, as opposed to the solvent diffusion method or traditional double emulsion solvent evaporation, were facile size control and greatly increased encapsulation efficiency (almost three-fold for comparable formulations of aqueous core PNPs).

The biodegradable polyesters PLA and especially PLGA (which have received attention in the drug delivery landscape at large), have also been extensively investigated for drug-encapsulating nanoparticles, due to attractive features of biodegradability, biocompatibility, approval by regulatory bodies, applicability to sustained and targeted release, and its applicability to encapsulation of high and low molecular weight drug compounds, both hydrophilic and hydrophobic [111]. PLA nanoparticles have been used for dual drug delivery applications (for hydrophilic theophylline and hydrophobic budenoside) [140], which were found to sustain the delivery of theophylline for $\geq$24 h in diffusion cell studies. PEG-PLA nanoparticles were synthesised by Surwase et al. [139], for the sustained delivery of gemcitabine. These particles were prepared using the double emulsion solvent evaporation technique, and sustained the release of the drug for up to 15 days. The release rate was dictated by the ratio of PEG: PLA, which in turn affects the crystallinity of the polymer system, and the polymers' molecular weights.

PLGA has been heavily featured in recent publications in the drug delivery literature, PLGA nanoparticles have been the subject of studies to encapsulate hydrophilic drugs 5-fluorouracil [145], tacrine [147], and diclofenac sodium [13]. In these examples, modifications of the PLGA particles either by co-polymerisation or functional coating, have been used to improve the properties of the particles for specific applications. The modification of PLGA with another biologically compatible, biodegradable polyester (3-hydroxybutyrate-co-3-hydroxyvalerate acid), PHVB was investigated by Handali and co-workers recently [145]. In the optimum formulation, the entrapment efficiency was 54%, and *in vitro* release was slow, with 20% fluorouracil released within 5 h and 54% released after 48 h.

PLA has also been employed as a drug entrapment matrix in the entrapment of isoniazid, an antibiotic, by Zhang et al. [150]. In their

Table 4
Recent publications detailing lipid drug-conjugate vehicles used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of particulate system	Release characteristic
[129]	Sodium fluorescein	Compressible PDMS[a] elastomer films containing drug filled microcapsules for mechanically-stimulated release	Initial burst release of 10% in 30 min in absence of force, followed by a force-sensitive response with no further release in the absence of mechanical stimulation.
[128]	5-fuorouracil	Microsphere capsules of natural gum katira with Eudragit pH-sensitive polymers	83% drug release after 12 h
[132]	Caffeine	Hydrogen-bonded PCL nanoparticles	90% cumulative release at *ca.* 4 h cf. 100 min for free caffeine.
[131]	Verapimil HCl	Glutaraldehyde-crosslinked Chitosan-κ-carrageenan polyelectrolyte complex beads	VP release sustained for 8 h, cf. < 2 h for a marketed tablet product Isoptin ®, with significantly lower initial burst release
[136]	Theophylline	PLGA nanoparticles prepared by solid-in-oil-in-water method	Release not determined, but encapsulation efficiency much greater than *w/o/w* emulsions
[137]	Donepezil	Nanocomposite particles formed from one-pot microwave assisted synthesis: ZnO with 2-acrylamido-2-methyl-1-propanesulfonic acid, acrylamide, and methylene-bis-acrylamide	Release of drug sustained for ≥120 h
[138]	Blue dextran	Keratin microspheres	Sustained release for 6 h
[139]	Gemcitabine	PEG-PLA nanoparticles	Sustained release for >14 days *in-vivo*
[140]	Theophylline	PLA nanoparticles[a]	Sustained release for ≥24 h in *in-vitro* studies
[141]	Rivastigmine hydrogen tartrate (RHT)	Poloxamer 407-stabilised Eudragit RL nanoparticles prepared by nanoprecipitation	Initial burst of 55% in 2.5 h, followed by gradual release up to 60% in 6 h. Cf. 100% in « 40 min for free RHT.
[130]	Bovine serum albumen; Bovine haemoglobin	Auricularia auricular polysaccharide and chitosan polyelectrolyte complex nanoparticles	Sustained delivery of 81.6% over 12 h.
[142]	Methylene blue	Nanoparticles formed from nanoprecipitation of regenerated cellulose	Pseudo-zero order release at a particle size dependent rate, for up to 96 h (100%)
[143]	Doxurubicin HCl	PLA-encapsulated Fe_3O_4 microspheres	64.8% release in 50 h
[144]	Gentamicin	Supercritically foamed PLGA[a] particles	Initial release of 60% in 8 h, followed by sustained release up to 80% in 2 weeks
[145]	5-fluorouracil	Nanoparticles of PLGA and PHVB[a]	Sustained release for 48 h (50%) after initial burst (30% in 6 h).
[146]	Epirubicin HCl	Poly (3-hydroxybutyrate) (PHB) and Poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) nanoparticles	Sustained release for 2 days (PHB) or 8 days (PHBV), moderate drug release of 60% and 30% respectively,
[147]	Tacrine	Nose-to-brain transport: Drug-loaded, protamine-coated cell-penetrating PLGA nanoparticles	Up to 45% release over 120 h
[148]	Doxorubicin	Dual-functionalised core/shell nanoparticles of chitosan-graft-polyacrylic acid-conjugated drug, coated in dual-functionalised chitosan-glycyrrhiznic acid/lactobionic acid	Biphasic; negligible release for initial 5 h, followed by near-linear release for 11 days (>80%) for the dual-ligand particle. Single and no-ligand particles ≤20% release over same period.
[149]	Doxorubicin	PHEMA-ran-glycidyl methacrylate polymer nanoparticles	Burst phase (50% in 10 h) followed by lag phase (80% in 48 h)
[13]	Diclofenac sodium	PLGA stabilised by Pluronic F68	Initial burst release (25% in <2 h) followed by linear release (75% in 48 h)
[150]	Isoniazid	Spray-dried PLA microspheres	*In-vivo* drug concentration sustained for 4 weeks

work, microspheres were produced by spray drying methodology. Solid-core microspheres were favoured over the w/o/w double emulsion method, as the absence of an external aqueous layer assists in maintaining the stability of the drug in the nanoparticle with respect to diffusion into the external aqueous layer. The drug was first micronized by ball milling, prior to dispersion in an organic solvent, and subsequent spray drying to form microparticulates. The release of isoniazid from these particles was slow and sustained over a period of over 21 days (70% encapsulated drug released) though the majority of the encapsulated drug was released in the initial *ca.* 8 days.

Protamine-coated PLGA nanoparticles have been recently developed for the transport and sustained release of hydrophilic drug tacrine to the brain, *via* the nose [147]. The function of the protamine coating is to enhance cell permeation, since protamine belongs to a family of cell-permeating peptides which have been shown to assist in the transfer of even high molecular weight proteins across the blood-brain barrier. The protamine-coated nanoparticles were embedded in a poly(acrylic acid) gel by mixing a suspension of nanoparticles in aqueous media with the dissolved polymer. *In vivo* studies showed that this particle-embedded gel enabled the drug to penetrate much more successfully than the particles or solution alone, with maximal concentration 2.5 x greater after 1 h.

While such synthetic polymers have advantages in versatility thanks to their readily tuneable properties, natural polymers can be processed into nanoparticles with relative ease and with their own advantages in sustainability, improved biological compatibility and biodegradation [151]. Nanoparticles of biopolymers such as gum katira [128], keratin [138], and chitosan [130,131,148] have all featured in recent literature. Chitosan has been used in the formation of polyelectrolyte complexes with naturally derived polyanions such as κ-carrageenan [131]. and auricularia auricular polysaccharide (AAP) [130]. To enhance drug encapsulation, novel techniques such as the deposition of polymer/drug solution on superhydrophobic glass and the subsequent cross-linking of chitosan by glutaraldehyde vapours have been developed [131].

Other pH-sensitive nanoparticles have included the mixed material synthetic/natural polymer microparticles detailed by Karan and co-workers [128], in which 5-fluorouracil was entrapped in a gum katira/Eudragit® system. The particles were synthesised using the double emulsion solvent evaporation technique, in which the aqueous gum katira/drug core was encapsulated in the hydrophobic Eudragit® coating. Due to the pH-sensitivity of the Eudragit polymer, the particles withstand the acidic conditions of the stomach, permitting

pH-controlled delivery to the more alkaline environment of the colon for treatment of colon cancer.

PNPs, since their inception as drug delivery devices, have been a mainstay of the researchers' arsenal in the targeted, efficient, and biologically compatible delivery of drugs to the human body. In this section of the review, we have seen interesting recent advances including the use of targeting moieties and pH-sensitive conjugates, as well as material advances which have led to novel drug delivery mechanisms rarely seen previously. The typical obstacles to commercial uptake and viability as pharmaceutical devices have included processability, upscaling, stability, and ease of sterilisation prior to clinical uptake. Nevertheless, a significant number of nanoparticulate drug delivering formulations have been approved by the appropriate bodies and have entered and succeeded in clinical trials [152]. The relevant properties are stability of PCL, PLA, PGA, and PLGA nanoparticles showed that long-term stability as a room temperature, water-borne suspension is relatively poor, with particle sizes and molecular weights significantly decreasing after 12 months for each polymer and polymer blend [153]. PGA is particularly unstable, with almost entire degradation of the nanoparticles in 5 months in a PLGA formulation of 2:1 PGA:PLA. However, the materials withstood sterilisation both by filtration and γ-radiation [153].

4.3. Mesoporous silica nanoparticles

Mesoporous silica nanoparticulates (MSNs) have been in use in drug delivery applications since 2001 [154], and are widely successful due to favourable properties such as high drug entrapment, favourable release profile, and ease of surface modification to grant targeting and/or environmentally responsive release. The synthesis of these particles is relatively straightforward, and is driven by the polymerisation of a silicone precursor such as tetraethyl orthosilicate (TEOS) around a template of micellar rods [155]. Calcination of the structure removes the micelle template, leaving a hexagonal, mesoporous structure. Typical pore sizes are therefore relative to the size of the micelles formed, which is in turn directly proportional to the alkyl chain length of the surfactant tail. This process is illustrated in Fig. 6, and Table 5 lists recent publications in which drug-releasing MSNs were developed.

Drug entrapment in these pores is usually achieved by passive absorption (i.e. by adding MSN to a solution of dissolved drug). While this approach is typically associated with burst release and poor drug lifetime for non-porous, matrix particles (due to limited superficial surface adsorption), the porosity of MSNs leads to much slower outward diffusion of drugs due to the small diameter of the pores, effectively creating a bottle neck for outward molecular diffusion. Nowadays, this favourable drug release profile has been enhanced through the grafting of site-specific, stimuli-responsive polymers or functional groups to the MSN surface *via* anchoring of carboxyl-, amino- or thiol-terminated triethoxysilanes. For example, in recent work by Zaharudin and co-workers [156], 3-aminopropyl triethoxysilane (APTES) was used to formulate amino-functionalised MSNs, while thiolated MSNs were synthesised by reaction of the bare MSNs with the analogous compound, 3-mercaptopropyl trimethoxysilaine (MPTMS). Carboxylic acid-functionalised MSNs were produced by reaction of the amino-functionalised MSNs with succinic anhydride. The surface functionalisation influenced the loading efficiency of hydrophilic gemcitabine and hydrophobic quercetin, due to the relative compatibility of functional groups with the drugs and the modified MSN surface. Gemcitabine loading was enhanced by a factor of *ca.* 2 for –COOH coated MSNs as opposed to bare MSNs. For the same reason, release of gemcitabine was also slowest from the –COOH coated MSNs, with only 15% of the encapsulated drug released over 48 h, followed by thiolated MSN (*ca.* 17%), amino-MSN (*ca.* 25%) and bare MSN (35–40%).

Table 5
Recent publications detailing nano and mesoporous nanoparticulates used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of porous particle system	Release characteristic
[14]	Doxorubicin HCl	pH- and glutathione-sensitive hyaluronic acid and PAMAM[a] dendrimer-coated mesoporous silica nanoparticles.	Release sustained for 5 h after exposure to pH 5.5. None detected if pH maintained at 7.4.
[156]	Gemcitabine	-COOH, –SH, and $–NH_2$ surface-functionalised mesoporous silica nanoparticles	Initial 12–26% release of loaded drug in 10 h, sustained release up to 15–30% in 48 h (dependent on surface functionality)
[157]	Levofloxacin	Mesoporous silicate functionalised with biodegradable PLA shell	90% release in 80 min @ pH 2.01; 50% release in 80 min @ pH 7.01
[158]	Acetaminophen	Mesoporous silica nanoparticles functionalised with polydopamine and graphene oxide	Sustained release biphasic, 90% in 60 h; initial burst of 50% in 10 h
[159]	5-fluorouracil	Urea-pyridyl ligand-functionalised mesoporous silica hybrid material	Release of drug sustained for 12 h
[160]	Methylene blue	Nanoporous silica nanoparticles dual loaded with hydrophilic methylene blue and hydrophobic fluorescein	Sustained release, linear phase 175 days followed by lag phase up to 1 year.

Biodegradable, PLA-coated MSNs have been used in the sustained delivery of levofloxacin (LF), with rate of release controlled by the degradation of the PLA coating [157]. The PLA coating was incorporated on the surface of the MSN through the APTES route, with the drug encapsulation taking place following amine modification but prior to instillation of the PLA layer. LF release from these particles was monitored in aqueous buffer over 5 h; a maximum release of 90% in 150 min was observed at pH 2.01, and a slower release of *ca.* 48% in 180 min at pH 7.4.

A notably long drug lifetime of up to 232 days has been observed for

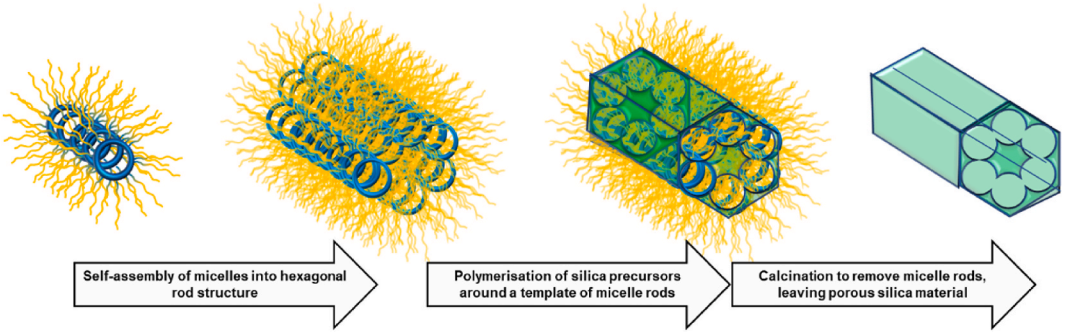

Fig. 6. Representation of the synthesis of MSNs *via* assembly around a micelle rod template.

hydrophilic dye, methylene blue, in the nanoporous silica nanoparticles [160]. These hybrid, core-shell morphology particles were synthesised using typical MSN formulation methodology for the porous silica core, followed by encapsulation in a porous organosilica shell layer. This was achieved by dispersing the initial MSNs in a solution of surfactant and adding the organosilica precursor, 1,4-bis(triethoxysilyl)benzene (BTEB). The unusual and important features of these particles are that both the core and shell are entirely porous, with Brunauer-Emmett-Teller (BET) surface area measurements of 1000 m^2 g^{-1} and 600 m^2 g^{-1} for the core-only and core-shell particles, respectively. Dual loading of hydrophobic and hydrophilic dyes demonstrated that hydrophilic model drug release was significantly slower in the presence of a hydrophobic dye, due to the deeper absorption of cationic methylene blue into the particulate pores. Comparatively nonpolar fluorescein, on the other hand, resides closer to the surface, effectively blocking the pores and inhibiting methylene blue efflux. Hence, the hydrophobic drug must first be liberated before significant hydrophilic drug release can occur, giving a lifetime for methylene blue of 232 days, following an initial near linear release of 80% in *ca.* 175 days.

The uniquely high surface area and surface functionalisation capability of MSNs makes them a powerful tool in the delivery of drugs in almost any pathology of the human body. As we have seen, even ionic, hydrophilic model drugs such as methylene blue can be sustained in the system for almost 6 months upon a single dosage *in-vivo*. Their fate *in-vivo* is of gradual degradation to biocompatible orthosilicic acid, a source of silica absorbed by the body [161]. However, MSNs have yet to be approved for drug delivery applications by the relevant regulatory bodies and are difficult to process at the industrial scale, unlike the lab scale [162]. Significant research remains to be performed on MSN safety in the body, with regards to accumulation in the spleen, liver and tissues [161], and robustness of the trigger mechanism (since MSNs can encapsulate far more drug per unit volume than other particulate formulations, any failure of the slow release mechanism may result in the burst release of high concentrations of drug with life-threatening consequences) [161]. However, if subsequent research and clinical trials give evidence for safety and efficacy, MSNs are likely to offer huge promise for drug formulations in future.

4.4. Self-assembling nanocapsules

Self-assembling capsules and vesicles used in drug delivery have primarily comprised micelles and liposomes, which are stable aggregates of amphiphilic surfactant molecules and lipids, respectively, relying on secondary interactions of nonpolar tails in an otherwise polar continuous phase. Micelles form above the critical micelle concentration (CMC), a threshold concentration above which the nonpolar tails of a surfactant aggregate to form an oily-core capsule, surrounded by a shell of polar headgroups [163]. Liposomes, on the other hand, form a bilayer sheet with an oily core sandwiched between two hydrophilic shell layers, which results in the formation of a hydrophilic core particle, with an inner oily layer, and an outer hydrophilic shell [164]. This lamellar configuration thus permits the formation of not only single layer liposomes (both small unilamellar vesicles, SUVs, and large unilamellar vesicles, LUVs), but also multilamellar vesicles (MLVs) which may contain numerous smaller vesicles enclosed in a larger vesicle, not necessarily in a concentric configuration [164] (see Fig. 7).

The terms ‘micelle’ and ‘liposome’ originally referred only to particulate structures of surfactants and ionic headgroup-containing lipids, respectively [163]. These terms now also commonly include similar structures made from amphiphilic block copolymers [163–165]. Rather than being polar/nonpolar head/tail types, these copolymers instead have hydrophilic polymer blocks hydrophobic polymer blocks. To distinguish them from ‘traditional’ liposomes, polymeric liposomes can be more correctly termed ‘polymersomes’ [164]. Common hydrophobic and hydrophilic blocks include poly(caprolactone), PCL, and poly (ethylene glycol), PEG, respectively. Other configurations have included niosomes (based on nonionic, surfactants) [164], and bilosomes (liposomes synthesised using bile acid salts) [166].

Synthesis of amphiphilic block copolymers of controlled structure and size distribution has been made possible in recent years since the advancement of reversible deactivation radical polymerisation techniques such as reversible addition/fragmentation chain transfer (RAFT) polymerisation, and atom transfer radical polymerisation (ATRP) [163–165]. Both techniques allow finely tuned, structured block copolymers to be synthesised from multiple monomers, but through differing mechanisms. Their versatility and compatibility with numerous different functional groups enables hydrophobic and hydrophilic polymer chains to be combined into micelle and polymersome precursor copolymers with relative ease and speed [165].

In the following sections, a selection both of typical representative technologies and novel modifications from the recent literature are compared for their synthesis, encapsulation efficiency, and drug delivery efficacy. As with other technologies, their viability as real-world devices will be discussed and summarised for each type of material and vehicle. The subsections are divided into the two major classes of self-assembled amphiphilic compound-based capsule structures: liposomes and micelles.

4.4.1. Liposomes, polymersomes and vesicular structures

Whether from lipids or amphiphilic block copolymer starting materials, drug-loaded vesicles are commonly synthesised using the thin film hydration technique or the organic solvent dissolution/evaporation technique [164], though many derivatives and alternatives of these methods have been developed in recent years [167]. Both processes

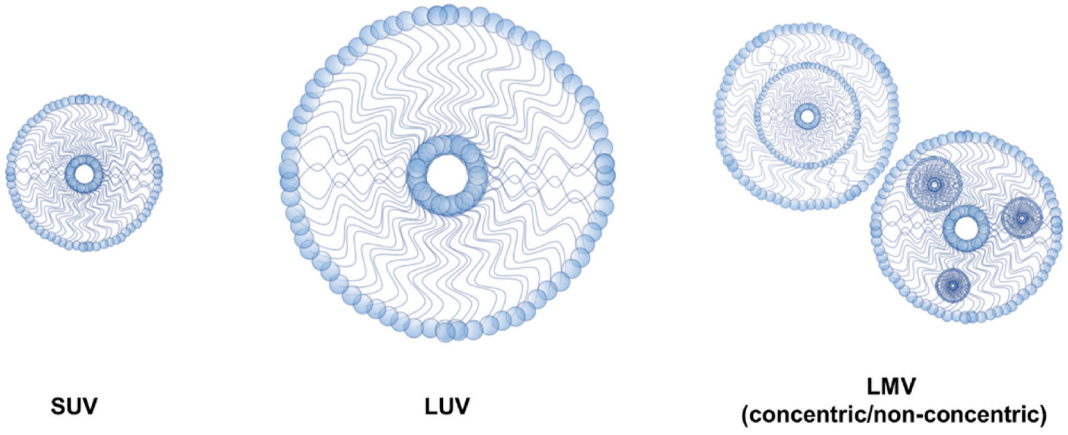

Fig. 7. Structural configuration of the three major liposomal configurations: small, unilamellar vesicles, large multilamellar vesicles, and large unilamellar vesicles.

result in the spontaneous formation of vesicles, but they are usually large and polydisperse; therefore, further processing and refinement is often required to form the desired nano-sized, predictably-sized nanocapsules. Common homogenisation techniques include sonication, freeze-thaw cycling, extrusion through pores of controlled size, or high pressure homogenisation [164,167]. While lipid and polymeric starting materials for liposomes in drug delivery applications have tended to remain similar throughout the years, recent trends in the literature have placed emphasis on the incorporation of targeting moieties or stimulus-responsive functionality. Table 6 shows a selection of recent publications in which liposome, polymersome, or other vesicular drug delivery vehicles have been used for the sustained or targeted delivery of hydrophilic drugs.

Photocleavable liposomes were synthesised by Goto et al. for the ultraviolet light (UVA)-triggered release of hydrophilic penicillin G [169]. This was achieved by modification of the drug first with a hydrophobic, photocleavable moiety, 2-nitro-3-naphthalenemethanol (2-NNM), making it sufficiently hydrophobic to be incorporated into the hydrophobic membranes of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DPMC) liposomes. Release of the hydrophilic penicillin G was controlled by the cleavage of the hydrophobic moiety, thus resulting in the rapid expulsion of the hydrophilic drug from the lipid membrane. Drug release was sustained over a period of 6–12 h (under constant irradiation at 365 nm). Such a device is unlikely to be of significant use internally due to the need for light activation, though it may be useful in external applications such as skin wound healing. However, penetration of UV light into any liposome-infused dressing is likely to be poor and limited to the surface.

Table 6
Recent publications detailing polymer and lipid vesicles devices used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of liposome system	Release characteristic
[168]	Calcein	Transdermal; Liposome and ethosome nanovesicles formed from cholesterol and Phospholipon 90G, and Phospholipon 90G only, respectively.	Calcein skin permeation greatly improved through use of ethosomes in combination with sono/electroporation, cf. liposomes and dissolved calcein only
[166]	Risedronate	Intestinal; anionic and cationic bilosomes formed from soya phosphatidylcholine, cholesterol, sodium deoxycholate, sodium glycocholate, and bile salts.	Anionic bilosomes withstand the gastrointestinal tract and sustained intestinal release for up to 2 h
[169]	Penicillin G	Photocleavable modified penicillin G in dipalmitoylphosphatidylcholine (DOPC) liposomes	Release triggered only after exposure to UVA radiation
[170]	Tetracycline	Lysine-based gemini surfactant-cholestrol niosomes	Sustained release for 24 h (20–50%), 15–40% at initial 8 h
[171]	Fluorescein isothiocyanate-dextran	Prolate (oval) polymersomes formed from PLA-PEG block copolymer	Sustained release for 48 h
[172]	Doxorubicin	Tumour-specific: folate-conjugated, oxidation-responsive liposome containing DOPE and polyhydroxyethyl acrylate-*co*-allyl methyl sulfide	Rapid release (80% in $\leq$30 s) when in an oxidising environment; zero release otherwise
[173]	Tapentadol	Sublingual treatment for osteoarthritis; chondroitin-conjugated drug-containing nanovesicles of cholesterol, soy phosphatidylcholine, and stearylamine	60% release over 8 h, after burst release of 20% in 2 h
[174]	Rhodamine B and doxorubicin HCl	Hybrid nanoparticles of DOPC and Poloxamer 407[a]	Sustained release for 24 h, cf. 4 h free rhodamine

Non-spherical polymersomes were synthesised using the organic solvent removal technique in Ref. [171]. Briefly, diblock PEG-PLA copolymers were dissolved in DMSO and dialysed against water to slowly remove the DMSO and result in vesicle formation. The spherical vesicles were then exposed to hypertonic conditions, resulting in the formation of an osmotic gradient and the outward diffusion of water from the liposomes, leading to their collapse into a prolate structure. Reported advantages of vesicles of this structure over spherical structure include increased cellular uptake due to the similarity in morphology to endogenous cells. Hydrophilic FITC-dextran conjugate was loaded into the vesicles during their synthesis, and was slowly released over a monitored period of 48 h in citrate buffer (pH = 4.8). The release profile was equivalent to spherical polymersomes *in vitro*, with total release after 48 h of 25–30% of the encapsulated drug. Neuronal cell penetration studies confirmed an increase in FITC fluorescence intensity of prolate polymersomes over the spherical morphology, and both were significantly higher than a free drug solution.

Conjugation of targeting bodies to liposomes and polymersomes can be utilised to increase specificity and result in rapid drug release at a target tissue. For example, overexpression of folic acid receptors in tumours is a well-known property of many cancers, thus folate-conjugation represents an effective method of improving drug delivery vehicle penetration into cancerous tissues [175]. The folate conjugation of acrylate polymer liposomes was the subject of Kim et al.'s recent work [172]. In this system, hydrophobic blocks of amphiphilic hydroxyethyl acrylate-co-allyl methyl sulfide (HEA-*co*-AMS) were incorporated into the lipid bilayer of the liposomes, and targeting functionalisation was achieved through carbodiimide coupling of folic acid to HEA. The sulfide moiety of AMS is readily oxidised to a sulfone, thus providing a trigger mechanism in the presence of reactive oxygen species (ROS) generated in the tumour environment. The sulfone formation would greatly increase the hydrophilicity of the hydrophobic AMS block, destabilising the liposome, and resulting in drug release. Release of model hydrophilic fluorescent drug, calcein, from these liposomes, was complete in 80% within <20 s of exposure to H_2O_2 in test experiments, with 0% released in its absence. DOX (4 μg mL^{-1}) encapsulated in folate-conjugated HEA-*co*-AMS stabilised liposomes were found to reduce tumour cell viability by *ca.* 70% when compared to 40–50% for free DOX.

Biorecognition-equipped liposomes system were developed as a novel treatment for osteoarthritis by Bishnoi et al. [173].; these incorporated the polymer, chondroitin sulfate, and the opioid, tapentadol into a liposomal formulation. Chondroitin sulfate, a natural component of chondrocytes, has a high affinity for cartilaginous tissues, and is therefore employed as a targeting moiety and permeation enhancer. The chondroitin-conjugated nanovesicles were assessed for drug delivery properties in *in-vivo* studies in rats, which revealed that, following sublingual administration, drug recovery from both conjugated and non-conjugated liposomes was improved significantly to that of an orally administered free drug in serum and tissues (knee cartilage, kidney, liver, heart, lungs), with the drug recovery from the conjugated liposomes persisting for longer in the cartilaginous tissues. *In-vitro* release studies followed Higuchi model release, with *ca.* 60% drug released over 8 h in PBS (pH 6.8).

Due to the leakage of hydrophilic drugs associated with lipid vesicle encapsulation, the work of Ahmed and co-workers fortified the lipid

layer of their DOPC liposomes using Poloxamer 407, forming a hybrid liposome/polymersome nanoparticulate drug delivery vehicle [174]. The hybrid nanovesicles were prepared by either coating pre-formed DOPC liposomes in a Poloxamer solution, or by hydrating DOPC in an aqueous solution of Poloxamer, thus producing either a polymer-coated vesicle or a hybrid liposome/polymersome material. The mixed polymer-lipid liposomes were more effective than the polymer-coated liposomes, due to the decreased stability of the liposomes resulting from poloxamer's disruption of the liposomal lipid membrane. On the other hand, when poloxamer was a part of the hybrid particle formulation, the formation of gel-core vesicles rather than aqueous core vesicles was found to enhance their stability, with no change in size noted over 58 days at 4 °C. A typical loading concentration of RB and DOX of up to 80% at 0.5 mg mL^{-1} was possible, with controlled release over 24 h (75%) and 30 h (80%) for each drug, respectively, compared to $\leq$ 6 h for the free drug.

4.4.2. Micelles

Whilst diblock copolymeric micelles are useful in stabilising insoluble lipophilic drug in their hydrophobic core, with hydrophilic tails oriented outwards into aqueous solution, hydrophilic drugs can also be encapsulated in triblock copolymer micelles comprising a double-hydrophilic body (A_1BA_2 type, where A is hydrophilic polymer and B is hydrophobic polymer), rather than the single hydrophobic head/hydrophilic tail model used in the formation of hydrophobic drug core micelles, (BA_1 type). Thus, water-soluble drugs can be encapsulated in the aqueous core A_1, with micellar stability granted by the hydrophobic B-block, and aqueous solution stability is improved by the hydrophilic corona A_2 [176]. Table 7 lists recent research articles which have encapsulated hydrophilic drugs in micelles of this type.

Self-assembled reverse micelle-structured nanoparticulates were recently prepared by nanoprecipitation of copolymers of PLA/dextran or PLGA/PEG, to form polyester-*b*-polyether amphiphilic block copolymer micelles [183]. These biodegradable, biologically compatible, hydrophilic core nanoparticles were synthesised by the dropwise addition of a solution of polymer in DMSO, into an aqueous solution of HCl, thus displacing the 'good' solvent, DMSO, with the 'bad' solvent, aqueous acid. Ciprofloxacin, a hydrophilic drug, was entrapped in the hydrophilic corona as well as in the entangled, hydrophobic polyester core. *In-vitro* release studies revealed that the PLA-Dextran nanoparticulates released up to 67.5% ciprofloxacin in the initial 2 h, followed by a lag phase of 96.7% in 144 h. The PLGA-PEG particles had a slightly slower initial burst release, of 56.1% in 2 h, followed by 96.4% at 144 h. For comparison, a free drug solution released 83.2% of the free drug within 2 h.

As with all drug delivery systems, targeting specificity and/or triggered release of drugs from micelles is desirable not only for maximal dosage efficiency and productive absorption, but also in reducing cytotoxicity (e.g. of chemotherapeutic agents) to healthy tissues [163,184]. Stimuli-responsive amphiphilic block copolymers have been employed to instil a triggered release system to polymer micelles in recent publications. The environmental stimuli exploited for triggered release have included temperature, pH, and reduction – the latter of which are often exploited in cancer treatments, since cancerous tissues have a lower pH and produce more reducing agents than healthy tissues [163,184].

The thermoresponsive micelles of Xu et al. were synthesised through RAFT block copolymerisation of PNIPAM (temperature sensitive) with poly(tetraphenylethylene acrylate) (PTPEA, hydrophobic) and poly (oligoethylene glycol methacrylate (POEGMA; hydrophilic) [177]. Thus, at temperatures below 35 °C, the polymer exists as random coiled chains in solution; an increase in temperature to above the LCST of PNIPAM leads to a micelle formation with hydrophobic PNIPAM core, PTPEA hydrophobic block, and POEGMA hydrophilic corona. FTIR data confirms that the hydrophilic immunostimulant drug, thymopentin, is retained in the PNIPAM core through hydrogen bonding of the amide carbonyl group with the amine of PNIPAM. Release of the drug from these micelles was sustained over *ca.* 9 h, compared to just 6 min for the free drug.

In the recent work of El Jundi et al. [182], pH-responsive, doxorubicin·HCl-releasing double-hydrophilic micelles were synthesised through functionalisation of PEG-PCL amphiphilic block copolymers, with advantages in increased degradability and biocompatibility compared with some existing double-hydrophilic block copolymer micelles. The thiol-yne click chemistry reaction was used to instil either carboxylic acid groups onto propargylated PCL, with high yields. Electrostatic interactions between the DOX·HCl cation and the carboxylated interior groups inhibited drug release at pH 7.4, with DOX release reaching a maximum of *ca.* 30% after 7 h over the course of a 24 h experiment. At pH 5.0, on the other hand, due to protonation of the acid groups (pK_a *ca.* 6.0), electrostatic interactions were reduced, and the drug was gradually released (*ca.* 70% after 7 h).

Ma et al. developed a dual-responsive micellar drug delivery system, sensitive both to pH and to the reducing environment of cancerous tissues [178]. This system was composed of the hydrophilic polymer, poly (lysine)-*co*-PEG, and a drug complex of a diol-containing chemotherapeutic agent, capecitabine and 2-formylphenylboronic acid. Borate ester complex formation between the boronic acid group and the diol within capecitabine, as well as the reaction of the aldehyde group and the ε-amine group of lysine to form an imine, led to formation of a stable complex at the core of the self-assembled micelles of 127 nm in size. Relative stability of the imine bond under neutral pH compared to acidic pH resulted in pH sensitivity of the micelle, while the boronate ester complex is sensitive to reduction. Thus, this dual responsive system, drug release still occurred at pH 7.4 and in the absence of a reducing agent, glutathione (reaching a maximum of 60–65% over 24 h in each case) but was much more rapid at pH 5.0 and in the presence of at least 10 mM glutathione (reaching a maximum of *ca.* 90% over 24 h, in each

Table 7
Recent publications detailing self-assembling micelles used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of micelle system	Release characteristic
[177]	Thymopentin	Micelles formed from a PNIPAM-*co*- tetraphenylethene acrylate-*b*- poly[oligo(ethylene glycol) methacrylate triblock copolymer	Sustained release for 9 h cf. 6 min for free TP5
[178]	Capecitabine	Dual-responsive micelles formulated from PEG-b-poly (lysine) and 2-formylphenyl-boronic acid.	Sustained release for up to 26 h
[179]	Nicotinamide	pH-responsive magnetic micelles of gelatin-*g*-poly (NIPAAm-*co*-DMAAm-*co*-UA)-g-dextran/Fe_3O_4 (GPDF)	Sustained release for >36 h at pH 6.6; comparatively very little release at pH = 7.2
[180]	Dexamethasone	Ocular delivery; PLA–PCL–PEG–PCL–PLA[a] micelles	Sustained delivery to > 90% in 12 h
[181]		PCl-PEG-PCL micelles	Uveitis inhibition in animal model sustained for 36 h; results not significantly different to commercial topical eye drops
[182]	Doxurubicin HCl	pH-sensitive, –COOH, –OH, and $–NH_2$ functionalised PEG-PCL[a] block copolymer micelles	50% release in 2 h; 70% release at 7 h at pH = 5; maximum release <30% at pH = 7
[183]	Ciprofloxacin	PLA-dextran and PLGA-PEG nanoparticles	Sustained release for up to 6 days

case). Given this relative non-specificity of the programmed trigger system, it is worth noting that no studies were performed which detailed the effects of the drug delivery system on healthy *vs.* cancerous cell models.

Nanotechnology remains at the forefront of medical research and drug delivery literature, with a vast array of materials and particle classifications (matrix nanoparticles, core/shell type capsules, self-assembled liposomes and micelles, and lipid-based nanostructures) available to researchers, to tailor the properties of drug-loaded nanoparticulates to any imaginable drug, disease, or delivery route. Nanoparticles of late are becoming increasingly more intelligent in terms of their capability to target specific cells, organs, environments or diseases [185–187]. Despite this progress, the translation of nanomedicines into bedside pharmaceutical preparations in industry has not been straightforward, not least because of the numerous clinical obstacles (e.g. unpredictable immune responses to nanoparticles between individuals due to genetics [188]) and regulatory challenges which exist [185,187]. As we have seen, the umbrella term, 'nanoparticle' itself encompasses all manner of materials, morphologies, sizes, and delivery mechanisms, with lack of regulation effectively meaning that the definition of what a nanoparticle is can be freely defined by their manufacturer. Therefore, there exist additional considerations when compared to 'traditional', bulk medicinal preparations, including development and validation of regulatory body-recognised methods to regulate and standardise the differing behaviour of particles in terms of safety and efficacy. Leading regulatory experts of the European Commission recently published a white paper in which the anticipated regulatory challenges expected for approval of future nanomedicines were explored [189]. A summary of all the quality management and clinical considerations required for approval of novel investigatory medicines in the nanoscale is displayed in Table 8.

Nanoparticle devices which have successfully reached clinical trials and commercialisation have included some PNPs, micelles, and liposomes – perhaps simply by virtue of these technologies existing for longer and therefore being subject to more scrutiny than the more novel systems (e.g. MSNs and lipid-based nanoparticles) [185–187,190]. These materials generally have well-characterised, desirable properties such as efficacy, patient tolerance, body distribution/accumulation, and processing parameters (including shelf-life and sterilisation routes) [185,186,190]. On the other hand, the more recently developed technologies (MSNs, SLNs, and NLCs), require more evidence to support their safety and efficacy – for example, MSNs are generally well tolerated, but some ultrafine particle sizes have been known to exhibit cytotoxic effects [191]. More research is also needed into these particles' fates after delivering their payload (e.g. the degradation of MSNs to orthosilicic acid [161]), their shelf lives (e.g. the stability of lipid carrier nanoparticles [112,123]), and the methods used to sterilise them. For all of these nanomaterials, then, given the strength of the research literature that surrounds their efficacy in cell and animal models, and the sustained interest from the medical and research communities, it seems to be a matter of when – and not if – these materials will enter the pharmacist's library.

We have highlighted in the previous sections the challenges and potential benefits of a range of different polymer-based and other carrier systems. An alternative strategy involving the linking of the drug to a carrier system in the form of drug-conjugate systems is explored in the next section.

5. Drug-conjugate delivery vehicles

A drug-conjugate delivery vehicle, or prodrug, is a non-pharmaceutically active compound which undergoes a chemical conversion in the form of a bond cleavage to generate the active form of a drug [192]. Such modifications are typically intended to give the drug favourable characteristics to improve its membrane permeation, specific tissue targeting, and lifetime in circulation or at the tissue of interest. In the recent literature, hydrophilic drug conjugates have been made with lipids [193–195], polymers [196–198], and even with other, hydrophobic drugs [199,200], to create amphiphilic prodrugs which may be further processed into drug-conjugated nanomaterials such as micelles and NLCs/SLNs. The major configurations for drug-conjugate delivery vehicles are illustrated in Fig. 8.

Common linking groups used in the formation of the conjugate-drug bond have included esters, anhydrides, carbonates, carbamates, imines, and amides [196,197], as well as noncovalent, ionic bonds. Disulfide bonds have been used in many amphiphilic drug-drug conjugates, as reduction-sensitive linkages which will degrade to release both a hydrophilic and hydrophobic drug only in a reducing environment, such as that of a tumour [201]. Benefits of these conjugate systems are primarily that the release of the drug, or hydrophilic compound, is controlled by the chemical hydrolysis of a covalent bond, rather than solely a weaker secondary interaction such as physical entrapment, diffusion barriers, polar interaction, or electrostatic interaction. Conjugates are therefore useful for sustaining the release of hydrophilic drugs and compounds, since these compounds' hydrophilic nature otherwise results in rapid partitioning into the external aqueous surroundings. In this section, we review recent advances in hydrophilic drug conjugate entities including lipid conjugates, polymer conjugates, amphiphilic drug-drug

Table 8
Anticipated chemical, material, biological, and pharmaceutical properties which must be reproducible in order for regulatory approval of novel nano-sized medicines and drug delivery systems [189].

Chemical and Material Properties	Biology, Pharmacodynamics and Pharmacokinetics
• Detailed description of all components	• Bioburden control
• Chemical composition	• Sterility and endotoxin levels
• Chemical structure	• Pharmacokinetic parameters
• Structural attributes that relate to function (e.g., lamellarity, core-shell structure	• Stability in blood and serum
• Crystal form	• Biological fate
• Impurities	• Accumulation issues
• Particle size and size distribution	• Absorption, distribution, metabolism, and excretion (ADME)
• Shape and morphology	• Plasma Protein Binding (formation of PC over time)
• Surface properties (e.g., surface area, surface charge, chemical reactivity, ligands, hydrophobicity, and roughness);	• In vivo degradation/solubilisation rate and place of degradation Pharmacodynamical parameters
• Particle concentration	• Biocompatibility with blood and serum
• Porosity (if it relates to a function)	• Additional risks associated with the exposure route: topical application: skin penetration, distribution in lymph nodes, subcutaneous administration: sensitisation to allergens, inhalation: effect on the respiratory system, iv: hemocompatibility
• Degradation path, kinetics and degradation products	• In vitro uptake and cytotoxicity of nanomaterials to the phagocytes
• Stability, both physical and chemical	• Interaction with enzymes e.g. Cytochrome P450
• In-use stability studies at clinically relevant concentrations and under relevant storage conditions	• Immunogenicity (ICH S8)
• Drug loading efficiency	• Complement activation
• Assay and distribution of any active ingredient associated with the nanomaterial and free in solution (e.g., surface bound or liposome encapsulated versus free active ingredient)	
• Physical state of the active substance	
• *In vitro* drug substance/siRNA release rate in physiologically/clinically relevant media	

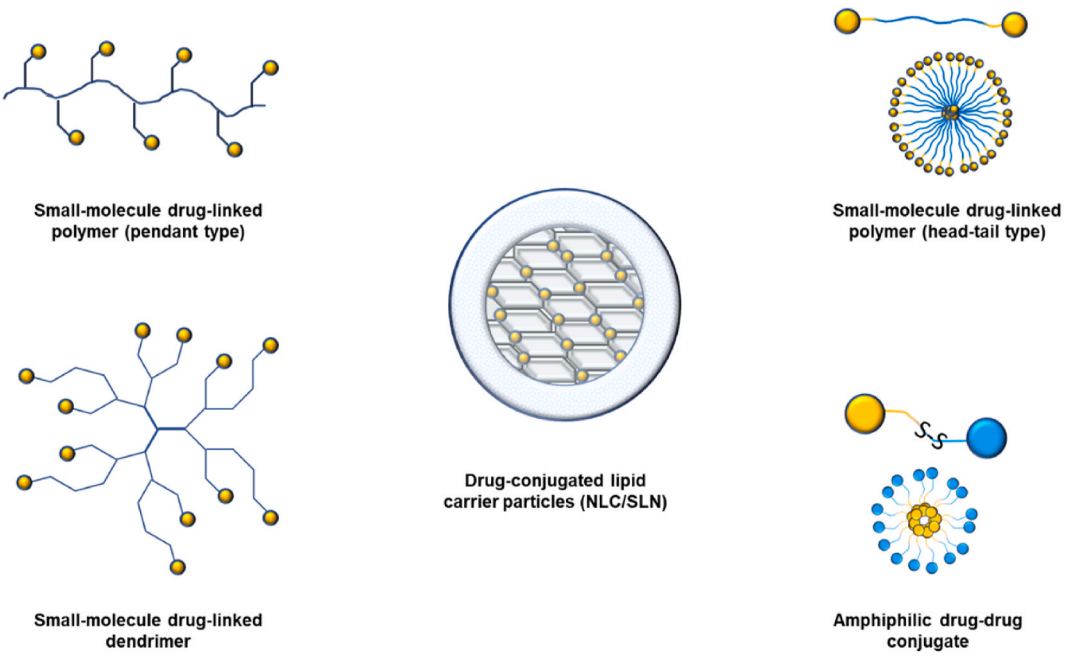

Fig. 8. Various forms of drug-conjugate carrier commonly used in the entrapment and targeted or sustained delivery of hydrophilic drugs in recent years.

conjugates, and drug-dendrimer conjugates.

5.1. Drug-lipid conjugate nanoparticles

As opposed to physical entrapment of drugs in a SLN or NLC, synthesis of a lipid-drug conjugate allows for facile formulation of lipid drug delivery vehicles with the additional benefits that (i) the drug, now an integral hydrophilic head of the lipid structure, is incorporated into the crystalline structure of the lipid carrier more efficiently and (ii) drug release is controlled by degradation of the drug conjugate bonds, rather than solely diffusion of drug/degradation of the particle [194]. A selection of recent drug-conjugated lipid nanoparticles is shown in Table 9.

Zhao and co-workers [195] synthesised ionic complexes of doxorubicin oleate lipid conjugates by vigorous mixing of drug and lipid in a basic, aqueous solution. This complex was then encapsulated in a lipid carrier nanoparticle *via* the addition of molten drug conjugate dissolved in mixtures of lipids to an aqueous phase containing surfactants, at various ratios. Particles of a size typically in the region of 75–160 nm were formed, with entrapment efficiency of 97.8% DOX. With a pK_a of 4.99, oleic acid forms conjugates with cationic compounds which are stable at neutral pH. Therefore, the lipid conjugate carrier is stable at neutral pH, but releases doxorubicin in acidic media, making this system suitable for pH-based targeting of cancer cells. *In-vitro* release studies demonstrated the sustained release of doxorubicin for 108 h, with 80% of the loaded drug released during this period (at pH 3.8). By comparison, at pH 7.4, only 22% of the drug was released over the same period.

An ionic conjugate of the surfactant, lauryl sulfate, with the hydrophilic drug, mirabegron, was prepared in a similar manner by Kasashima et al. [202], who prepared microparticles of the salt complex by spray drying various formulations of mirabegron, sodium lauryl sulfate, ethylcellulose (binder) and triethyl citrate (plasticiser). Particle sizes were typically in the range of 60–100 μm, with *in vitro* drug release of around 80% encapsulated drug within 12 h, even following prior storage of the particles in aqueous media for 30 days at 40 °C. This indicates excellent shelf life, as a result of the insolubility of the particles in aqueous media. The stability of the particles upon heat sterilisation, however, was not investigated.

Covalently bonded conjugates with the hydrophilic drugs, isoniazid and 5-fluorouracil, were detailed in recent publications by Pandit et al. [203] and Sauraj et al. [204], respectively. Isoniazid, an antitubercular drug, was covalently conjugated to stearic acid *via* nucleophilic acyl substitution of stearyl chloride to form a N-stearyl amide of isoniazid [203]. This lipid solution was cooled and added to an aqueous solution containing the surfactants Tween® 80 and Poloxamer 188, producing lipid drug carrier nanoparticles of size 124 nm. Isoniazid release from these lipid carriers was biphasic, with 60.7% encapsulated drug released over the initial 12 h, and 97.8% released after 72 h. The 5-fluorouracil stearic acid conjugates of Sauraj et al. [204] were synthesised by the hydroxymethylation of 5-fluorouracil with formaldehyde, and subsequent esterification of the hydroxyl group with stearic acid. These conjugates were encapsulated in lipid core micelles of stearic acid conjugated with the hydrophilic sugar polymer, xylan. Thus, the biphasic release of the drug was controlled by the degradation of the micelle, and additionally by the subsequent hydrolysis of the prodrug conjugate bond. The release of the drug was pH-controlled, with a total of 28% of

Table 9
Recent publications detailing lipid drug-conjugate vehicles used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of drug conjugate system	Release characteristic
[202]	Mirabegron	Lauryl sulfate complex to modulate aqueous solubility of hydrophilic drug	Controlled release for 12 h, cf. < 1 h when complexed with hydrophilic κ-carrageenan
[203]	Isoniazid	Stearic acid conjugate lipid nanoparticles	Initial burst phase of 20% release in 1 h; intermediate phase of 60% in 10 h; final phase of >90% in 70 h
[204]	5-fluorouracil	Drug-stearic acid conjugates embedded in xylan-stearic acid conjugate nanoparticles	Sustained release for 60 h (55%) at pH = 5; 30% release over same period at pH = 7.4.
[195]	Doxorubicin	Oleic acid conjugate nanoparticles	pH-sensitive release profile – (80% in 108 h at pH 3.8; 20% at pH 7.4)
[194]	Nicotine	Drug-lipid ionic salt conjugate nanoparticles of Kolliwax® S and stearic acid	Release not determined; encapsulation efficiency up to 60%

the drug released over 60 h at pH 7.4, and 58% at pH 5.0 over the same period.

Aside from the advantageous chemical control gained through use of covalent drug entrapment, the benefits of these drug-lipid conjugate particles are, as for the non-conjugated SLN/NLC morphology lipid-based vehicles described earlier, their ability to protect drug molecules from hydrolytic and oxidative degradation by entrapment in a water-insoluble, gas-impermeable structure [112,123]. Relatively little research has been published specifically on the shelf life and sterilizability of these conjugate structures, though one can expect that the properties would be largely similar to those of the SLN/NLCs described here previously. Their predictable size, structure and biological compatibility, in comparison to other nano/microparticle types, may grant them favourable properties toward the post-clinical trial stages of commercialisation, i.e. in regulation. However, to date, few to no drug-conjugate lipid particles are currently marketed in the pharmaceutical sector.

5.2. Polymer conjugates & their self-assembling particles

Polymer conjugates of various compositions and structural conformations have been employed as drug releasing agents for many years [196,197]. For example, linear conjugates of drug-terminated poly (ethylene glycol) have been employed in the drug delivery literature for many years, providing improvements in solubility and biological compatibility of drugs [205]. The drug-pendant polymer conformation (the Ringsdorf model) has been associated with high drug loading, good transport properties and improved solubility properties of drugs [198]. These formulations contain a polymer backbone chemically conjugated to the drug, and optionally one or both of a solubilising agent and a transport or targeting agent. They may be biologically degradable, stable, or targetable with respect to time in circulation, depending on the nature of the polymer backbone and the bonds used to link the drug to the backbone [196–198].

The advantages of these systems are a high degree of structural control, a high concentration of inactivated, labile, drug-containing groups in a small volume, and a drug release mechanism controlled by hydrolysis or disease-specific lysis of these bonds rather than displacement of weaker, secondary interactions [196,198,206]. Formation of covalently drug-conjugated, cross-linked or self-assembled nanoparticles has emerged as a leading trend in the drug delivery literature in recent years [206]. In these models, drug release is controlled by the solubilities of the polymer and drug, and also the distance between the drug and the polymer backbone (i.e. the presence/number of linking units), the charge and charge density of the prodrug system (particularly pertinent to weakly basic or acidic drugs/polymers), and biodegradation *in-vivo* by enzyme action [196]. The lattermost of these effects is seldom investigated in the literature, with articles tending to test drug release systems in saline solution, though it provides key insight into the real-world application of these systems. A selection of recent articles detailing sustained or targeted delivery of hydrophilic drugs *via* polymer conjugates is given in Table 10.

The comparative stability of covalent drug-polymer conjugates was exemplified by Danafar et al., in a study in which lisinopril, a water-soluble drug used to lower blood pressure, was conjugated to amphiphilic block copolymers of PLA-PEG-PLA [212]. Carbodiimide coupling was used to conjugate the carboxylic acid groups of lisinopril to the terminal hydroxyl groups of the PLA-PEG-PLA chain. The degradation of the ester bond, releasing the drug, occurred only under acidic conditions; at a pH of 7.4, no free lisinopril was detected over 144 h from the drug-conjugated polymer micelles, whereas over 70% of the physically entrapped drug was released. At pH 4.0, slow release of the drug from the drug-conjugate micelles over a period of 120 h was observed (*ca.* 50%), with more rapid release from non-aggregated polymer over the same period (>80% release).

Jantas and co-workers published a series of papers detailing the delivery of the water-soluble analgesic and anti-inflammatory, sodium salicylate, from hydrophilic polymers including poly(vinyl alcohol) [213], PVA, poly(2-hydroxyethyl methacrylate) [214], pHEMA, and starch [215]. In each case, the hydroxyl polymer was modified with chloroacetyl chloride, acting as an acetyl linking group between the polymer backbone and drug. The *in-vitro* release of the drug in all cases was shown to be dependent on both pH and % conversion of the hydroxyl groups to salicylate ester groups, and in each case was shown to sustain the release of the drug for over 25 days. For each of the three polymer conjugate prodrugs studied by Jantas' group, the rate of hydrolysis increased with the increasing pH of the release medium. Release was also most rapid with a lower degree of substitution, facilitated by an increase in hydrophilicity of the polymer, reduced steric hindrance, and a more efficient penetration of OH^- ions [213–215].

Haam and co-authors [207] patented a dual polymer-prodrug conjugate system in which a hydrophilic drug was conjugated to an anionic polymer, and a hydrophobic drug was conjugated to a cationic polymer. Thus, both polymer conjugates formed a polyelectrolyte complex together. The dual release of drugs in treatment of cancers is currently of great interest in the literature; thus, the hydrophilic drugs tested included gemcitabine, and the hydrophobic drug was paclitaxel. The

Table 10
Recent publications detailing polymer drug-conjugate vehicles used in the sustained and targeted delivery of hydrophilic drugs.

Ref	Drug compound	Description of conjugate system	Release characteristic
[207]	Gemcitabine	Hyaluronic acid polymer ester conjugate	Sustained release for <100 h, but with burst release of 50% within initial 4 h
[208]		Redox-responsive nanoparticles of drug-conjugated disulfide-containing vinyl copolymer	Inhibited in-vivo tumour growth for at least 55 days after injection
[209]		Brush copolymer based on PEG and PLA-drug conjugate	<25% release in 120 h at pH 5.5; 90% release in 72 h at pH 7.4.
[210]	Doxurubicin HCl	Alginate microbeads templated with internal drug conjugate voids	Sustained release of ≤15% in initial 24 h, *vs* 99% over 24 h for non-encapsulated drug
[148]		Dual-functionalised core/shell nanoparticles of chitosan-graft-polyacrylic acid-conjugated drug, coated in dual-functionalised chitosan-glycyrrhiznic acid/lactobionic acid	Biphasic; negligible release for initial 5 h, followed by near-linear release for 11 days (>80%) for the dual-ligand particle. Single and no-ligand particles ≤20% release over same period.
[211]		Reduction-sensitive disulfide-crosslinked polymer prodrug micelles of PEG-*b*-poly(2-methacryloyloxyethyl phosphorylcholine)	Reducing agent-dependent release; 90% in 10 h in presence of DTT[a], 100% at 48 h. In absence of DTT, maximal release of 30% at 12 h–48 h.
[212]	Lisinopril	Drug-conjugated amphiphilic block copolymer micelles (PLA-PEG-PLA[a])	Sustained release from the polymer conjugate up to 120 h; micelles formed from the polymer conjugate further slow the rate of release. Micelles which physically entrap the polymer (rather than chemical conjugates) leach drug at pH 7.4; conjugates are stable infinitely at neutral pH.

anionic and cationic polymers were hyaluronic acid, and chitosan, respectively. The polymer-drug conjugate was synthesised by esterifying the hydroxyl group of gemcitabine with the carboxylate of hyaluronic acid. Release studies showed that the lifetime of gemcitabine was greater than 100 h at pH 5.5, though up to 50% of the drug was released within the first 3 h. The release was less rapid at pH 7.4, indicating slight selectivity toward the lower-pH environment of tumour cells.

Paclitaxel/gemcitabine dual-drug delivery systems were also studied by Sun and co-workers in nanoparticles sensitive to reduction [208] and pH [209]. Sensitivity towards the reductive environment of a cancerous cell was achieved by conjugation of vinyl benzene chloride with a dithiodicarboxylic acid, which was block copolymerised with oligo-ethylene glycol methacrylate *via* RAFT. These block copolymers self-assembled into hydrophobic drug-core hydrophilic drug-surface nanoparticles of size 13 nm, which enhanced the penetration of the particles into the tumours. Surface –OH groups enhanced the stability of the micelles in aqueous surroundings by hydrogen bonding. *In-vivo* studies in mice inoculated with pancreatic tumours demonstrated a 79.5% reduction in tumour weight over 25 days for the hollow, gemcitabine-only micelles, and 84.6% for the combined gemcitabine/-paclitaxel micelles. Sensitivity to reducing agents was assessed by monitoring drug release in the presence and absence of 10 mM of a reducing agent, glutathione, over 24 h. Drug release was significantly greater (*ca.* 20–25%) than in its absence (*ca.* 0–4%). For the pH-sensitive micelles, a brush copolymer was synthesised from PLA, allyl-PLA and acetylenyl-PLA. Click chemistry was used to incorporate PEG to the alkyne-modified PLA, while the thiol-ene reactions allowed conjugation of thiolated esters and amides of gemcitabine and paclitaxel, respectively, to the alkene-midified PLA. Self-assembled micelles of these amphiphilic block copolymer drug conjugates were sized at 45.1 nm on average. A rapid release of gemcitabine of 75% was observed over 72 h at pH 7.4; at pH 5.5, a maximum of 20% of drug was released in 48 h.

Ionic complexes, while less chemically stable than covalently conjugated drug/polymer systems, are also effective in sustaining the release of drug molecules from particulate systems. For example, an ionic complex of doxorubicin and polyacrylate were encapsulated in hydrophilic-core nanocapsules in Ref. [148]. A graft co-polymer of *O*-carboxymethyl chitosan and poly(acrylic acid) was first synthesised, and the mixing of positively charged doxorubicin and negatively charged poly(acrylate) formed the hydrophilic nanoparticle core. A core-shell structure was formulated through the addition of hydrophilic drug complex suspension to a solution of a dual-ligand functionalised chitosan. These ligands are liver-specific targeting moieties, 18β-glycyrrhetinic acid (hydrophobic) and lactobionic acid (hydrophilic), the ratios of which control the solubility properties of the nanoparticles. Targeted and sustained release of these particles (274 nm in size) was observed over the course of 10 days for the dual-ligand particles.

Other polymer conjugates of doxorubicin have included poly(glutamic acid) as a hydrolysable drug-releasing polypeptide [216], synthesised from polyglutamate either directly conjugated to the drug, or with various short-chains of glycine and other amino acids in a brush-copolymer configuration. These were prepared using typical carbodiimide peptide synthetic pathways. In each case, drug release was sustained for up to 100 h – though a maximum of <15% of the bound drug was released. This low figure is presumably due to the relative stability of amide bonds compared to the more labile ester or carbonate bonds more common in this type of drug carrier.

The recently published drug-polymer conjugates and complexes have been shown to provide excellent drug stability and sustained release characteristics. Overall, the main advantages of polymer prodrugs include their ease of synthesis, high drug loading, and versatility with respect to conjugation of numerous species to the same backbone. Therefore, modification of the polymer systems with ligands and environment-specific linkers has realised potential for disease-specific targeting conferring enhanced stability during circulation following administration. Furthermore, micellar stability granted to the head-tail polymer prodrug type configuration has been somewhat useful in conferring favourable stability in comparison to the Ringsdorf model-type polymer prodrugs [200]. However, for drug-polymer conjugates and nanoparticles of the same to become clinically relevant, a number of regulatory considerations must be satisfied, including development of validated methods for polymer-specific properties such as molecular weight, degree of substitution, shelf-life/stability and viscosity/osmolarity of the dissolved formulation once in the body [217].

5.3. Amphiphilic drug-drug conjugates (ADDCs)

Small molecular conjugates of hydrophilic and hydrophobic drugs have recently come to the forefront of the drug delivery literature, especially in chemotherapeutics. The obvious benefit of these vehicles is in the simultaneous delivery of multiple drugs, but also in the enhanced solubility and bioavailability/biodistribution properties of both drugs. Rarely, the drugs are conjugated to one another directly through compatible reactive moieties present natively in the structures of both drugs [218]. More commonly, the drugs are linked through a short, labile linking chain, which may confer an ability for environment-specific targeting – for example, a reduction-sensitive disulfide bridge or a pH-sensitive carbonate linkage, for example. Table 11 details findings of recent published articles in which ADDCs were used in drug delivery.

Disulfide-linked ADDCs were the subject of recent articles from Hou and co-workers [219,220]. In these papers, the hydrophilic drugs gemcitabine and methotrexate were linked to the hydrophobic drugs camptothecin and podophyllotoxin, respectively. In both studies, the drugs were sequentially joined to a symmetrical dihydroxyethyldisulfide *via* linkage of the –OH groups to a triphosgene-induced carbonate bond, or direct esterification with a carboxylic acid group of the drug. The ADDCs self-assembled into nanoparticles sized at 16 nm [220] and 60 nm [219]. The trigger mechanism was assessed both by measuring release of drugs in absence and presence of the reducing agent glutathione, and by repeating these tests with a non-disulfide linked version of the ADDCs synthesised from 1,6-hexanediol. These tests showed that drug release was exclusively triggered by the cleavage of the disulfide linkage in the presence of glutathione, as far less drug release was observed in the absence of either glutathione or the disulfide bridge.

ADDCs of the hydrophilic drug, Irinotecan, with the hydrophobic drug, melampomaglonide B, were linked by a hydrolysable carbonate

Table 11
Recent publications detailing amphiphilic drug-drug-conjugate vehicles used in the sustained and targeted delivery of hydrophilic drugs.

[219]	Methotrexate	Amphiphilic drug-drug conjugate of Methotrexate with podophyllotoxin *via* disulfide bridge	Reduction-responsive release of both drugs triggered by glutathione. Sustained release over 10 h (80%) *vs.* max <20% in absence of glutathione.
[220]	Gemcitabine	Disulfide prodrug conjugate with another, hydrophobic, anti-cancer drug, camptothecin	Reduction-dependent delivery triggered only in presence of DTT; sustained delivery for <48 h (80%); 50% release in first 6 h.
[221]	Irinotecan	Self-assembled particles of carbonate-linked, dual-drug conjugate of hydrophilic irinotecan with melampomaglonide B	In vitro release of nearly 50% after pH 5.0 in presence of esterase enzyme, down to 15% at pH 7.4 with no enzyme
[218]	Floxuridine	Ester-linked amphiphilic drug-drug conjugate with antiangiogenic pseudolaric acid	<20% release at pH 7.4 with no esterase over 24 h; >65% release at pH 5.0 with esterase

linker by Qu et al. [221]. The ADDCs were prepared by introduction of a carbonate linkage between melampomaglonide and irinotecan *via* reaction with carbonyl di-(1,2,3-triazole). Stable, spherical, self-assembled particles of these drugs were sized at 122.1 nm, with drug release found to be sensitive both to acid and esterase enzyme degradation. Decreasing pH from 7.4 to 5.0 increases rate of drug release from 15% in 48 h to 40%. Addition of esterase increases maximal drug release to 50% over the same period. Another ADDC, of hydrophilic floxuridine and hydrophobic pseudolaric acid was investigated as a novel anti-cancer treatment which combined an antiangiogenic and a chemotherapeutic in a single system [218]. The one step Steglich esterification of the psuedolaric acid carboxyl group with the hydroxyethyl moiety of floxuridine led to the synthesis of amphiphilic prodrugs which self-assembled into spherical nanoparticles, of 150 nm in size. The acid and enzyme-sensitivity were both investigated, producing similar results to the Qu's earlier work [221]. Drug release was more rapid in acidic media, or media containing 30 U mL^{-1} esterase. At a buffer pH of 7.4, a maximum of 20% release was detected over 48 h. Over the same period at pH 5.0 with esterase, drug release reached 60%. *In vitro* cell studies confirmed the desired dual effect of high cytotoxicity to tumour cells and inhibition of new blood vessel growth.

Evidently, ADDC synthesis represents an efficient and effective route to novel therapeutics comprising two drugs with relatively opposing, undesirable solution properties, to give a drug delivery vehicle with desirable solution properties and specific targeting, and with inherently high encapsulation efficiency. In the recent literature, there have been ADDCs with enzyme sensitive, pH-sensitive, and reduction-sensitive functionality. Relatively little investigative work has been undertaken into the translation of these novel devices from bench to bedside; however, interestingly, research comparing different bonding types and divalent linker unit chain lengths showed that the presence of the disulfide bond offered some protection against hydrolysis of these groups in acidic conditions [201], suggesting improved stability in aqueous storage. Nonetheless, ADDCs are readily synthesised, with predictable, reproducible properties, and thus represent an interesting and novel route for the effective delivery of multiple drugs to tissues otherwise inaccessible to two drugs of such opposing nature simultaneously.

5.4. Dendrimer-drug conjugates

Dendrimers are nano-sized, symmetrical, star-shaped polymers which are highly ordered, highly branched, and uniformly distributed in structure and size. Dendrimers have a high number of functionalised terminal groups and internal groups, enabling efficient encapsulation of drugs through ad(b)sorption in internal nanocavities, and/or through chemical conjugation with reactive terminal groups [222,223]. Their small size enables dendrimers to interact with cellular components, and therefore they have been identified as excellent candidates for intracellular drug and gene delivery [224,225].

Early dendrimers were commonly based on a poly(aminoamine), PAMAM, core, generated by successive, exhaustive *aza*-Michael addition of ethylenediamine to methacrylate [226], and more recently have been synthesised using efficient click chemistry reactions [227–229] with multifunctional centres such as hyperbranched polyglycerols [230] and pentaerythritol [225,231–233]. The PAMAM family of dendrimer has been associated with toxic effects, due to their small size and cationic nature leading to interactions with cell membranes eventually leading to cell lysis [234,235]. Nowadays, toxicity has been reduced by conjugating dendrimers to biocompatible groups (e.g. PEG [236] or carboxybetaines [237]), or by using alternative starting materials to synthesise degradable polyester dendrimers [234,235] or peptide dendrimers [238]. In recent work [239], a peptide dendrimer was synthesised from a tris(triethylamine)-core with poly(lysine) branching units. The hydrophilic drug gemcitabine was conjugated to the terminal groups of the dendrimer *via* an enzyme-cleavable short peptide chain. These particles, of 80 nm in size, released the drug rapidly only in the presence of the cysteine protease enzyme, cathepsin B; in its absence, a maximum of <10% was released over 24 h, whereas in its presence, 60% was released within 30 min, and a maximum of 90% reached after 24 h. This triggered release mechanism is useful in ensuring the drug is released only when in the environment of a tumour lysosome, in which production of cathepsin B is upregulated [239].

Drug-conjugated lysine dendrimers were also the focus of Ryan et al.'s 2017 paper [240], in which methotrexate was conjugated to the dendrimer *via* either short peptide linkages or an oligoethylene glycol linker. Methotrexate was also optionally modified with a *tert*-butanol capping unit to increase its lipophilicity. In these experiments, the additional hydrophobic modification was found to increase the stability of the peptide linked dendrimer conjugates in human plasma; the non-capped dendrimers were eliminated in under 24 h, while with capping, they were still detectable after 120 h. The delivery profile of the free drug from the dendrimers was not explicit in this study, although previous work by the same group [241] has shown that methotrexate-conjugated lysine dendrimers increase the lifetime of the free drug from 3 h to >120 h in plasma.

Methotrexate has also been conjugated to dendrimers to construct controlled release anti-cancer drug formulations [242]. In this study by Torres-Pérez et al., sixth generation PAMAM dendrimers were conjugated with the drug directly, using carbodiimide chemistry. Synthesised dendrimers of an average diameter 8.5 nm were found to reduce cancerous cell viability by 50% over a period of 4 h, while healthy cell viability remained <80%. The kinetics of methotrexate release were not explicitly studied in this work.

Hydrophilic drug-dendrimer conjugates are encountered relatively infrequently in the recent literature, despite offering high drug loading capacity per unit volume and typically excellent stability in the body, with biological compatibility easily demonstrated and tuneable through material optimisation and/or surface conjugation as described in recent publications [234,235]. Furthermore, few existing dendrimer formulations have entered clinical trials [243] until very recently [244], and fewer still approved by the world's major regulatory bodies [245], due to the complexities associated with synthesis and scale-up. There also remain concerns and obstacles towards commercial viability and bench-to-bedside transition which include the reproducibility of products with predictable pharmacology and pharmacokinetics [222]. Nonetheless, dendrimers remain an innovative, interesting approach to sustained and controlled drug delivery, with unique biochemical and cellular interaction properties amongst the existing materials currently used in drug delivery science.

On the whole, prodrug-conjugate delivery vehicles are relatively rarely seen in the contemporary drug delivery literature, which more commonly encompasses drugs physically entrapped in polymeric matrix or capsule nanoparticles, fibres, or hydrogels. However, the clinical proof of concept of such devices (especially polymer and dendrimer conjugates) has been established over the last 40 years, with many linear drug-polymer conjugates entering the clinical trial phase throughout the early 1990s–2000s [217,243], with favourable properties in drug lifetime, stability, immunogenicity and targeting specificity [246]. For bench to bedside translation, the importance of extensive physicochemical characterisation has been emphasised due to the potential variances of macromolecules in structure, degree of substitution, arrangement of substituents, molecular weight and uniformity of molecular weight distribution, morphology, size, and that any biological interactions are fully characterised and predicted [243]. ADDCs, which have only recently begun to gain significant interest in the drug delivery field, have nonetheless been subjected to similar scrutiny in research papers and review articles, which identify the need for long-term clinical studies monitoring the effects of these systems on non-cancerous tissues, and the fate of the ADDC particles in the body in terms of transport and excretion [247]. They are, however, regarded as powerful systems with capability for dual drug delivery at fixed ratio and with remarkably high drug loading.

6. Conclusion

The development of hydrophilic drug delivery systems is progressing at a rapid and impressive rate, complemented by an ever-increasing advancement in understanding of polymer chemistry, pharmacokinetics, and cell biology. In this review of the recent literature, the dominant trends have been in improving hydrophilic drug encapsulation in lipid and hydrophobic polymer matrices, as well as the conjugation of hydrophilic drugs into novel, drug-only, self-delivering vehicles such as ADDCs and their self-assembling particles. These types of conjugates, along with polymer conjugates and lipid conjugate nanoparticles, have been associated with improved targeting and drug lifetime in the human body. Other developments have included advances in electrospinning and MSN technologies which have allowed the facile synthesis of nanomaterials with controlled release properties vastly exceeding what would previously have been expected for strongly water-soluble drugs in previous years.

As is a common trend throughout drug delivery (not just limited to that of specifically hydrophilic drugs), targeting and biodistribution has been another challenge which has been approached and met with ingenuity in numerous recent works. Not only have new generations of disease-specific targeting devices been developed, but we are also seeing advances in on-demand delivery technologies, and self-healing technologies now eliminating many of the mechanical frailty problems of traditional hydrogel materials. Finally, devices with predictable drug release properties and desirable near-zero order release profiles are becoming increasingly available.

In this analysis of bench-to-bedside transition of novel investigational drug delivery systems, we found that many of the barriers to clinical and commercial acceptance are in manufacturing, upscaling, and regulatory standardisation, rather than physicochemical parameters. Lab-based studies at the small scale can be constructed to demonstrate key factors such as efficacy, safety, shelf-life, biodegradability, biocompatibility, and sterilizability. However, material properties are controlled very much by the manufacturing conditions, which inherently change during the scale-up for the output volume required for clinical trials and cGMP-compliant production – this is particularly true for nanomaterials, which constitute the majority of the novel drug delivery vehicles we have reviewed here. So far, relatively few organisations have developed compliant facilities for the production of nanomaterials at a large scale; this obstacle alone is enough to prevent many of these new systems from entering clinical trials.

This lack of infrastructure applies not only to manufacture, but also to testing and quality assurance; many of these novel technologies simply have not existed for long enough for sufficient data to be generated to satisfy regulatory requirements. Even regulatory bodies themselves are still anticipating the full list of criteria required to licence facilities for novel drug delivery product manufacture, especially in the case of nanomaterials [189]. Significant investments of time and money must therefore be made into not just manufacture, but also developing analytical techniques and standards for the characterisation of these materials, in a cGMP-compliant manner.

The small-scale manufacturers of these drug products must secure investments from financiers against a back-drop of competition that includes tried and true drug delivery systems, which might appear as lower risk investments. It is likely that these novel drug delivery systems will be studied in the proving grounds of the laboratory for years to come before the scientific evidence deems them a worthy investment. Nonetheless, illness, injury, and the humanitarian desire to develop technologies to heal, will continue for as long as humanity itself. Thus, drug discovery, drug formulation, drug delivery, and biomaterials will remain a major focus in the scientific and clinical world for the foreseeable future, and it seems highly unlikely that these barriers will remain unbroken for novel medical devices and formulations in the near future.

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Data availability

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

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