

# 1 Drug delivery across length scales

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## 22 **Drug delivery across length scales**

23 Over the last century there has been a dramatic change in the nature of  
24 therapeutic, biologically active molecules available to treat disease. Therapies  
25 have evolved from extracted natural products towards rationally designed  
26 biomolecules, including small molecules, engineered proteins, and nucleic acids.  
27 The use of potent drugs which target specific organs, cells, or biochemical  
28 pathways, necessitates new tools which can enable controlled delivery and dosing  
29 of these therapeutics to their biological targets. Here, we review the  
30 miniaturisation of drug delivery systems from the macro- to nano- scale, focusing  
31 on controlled dosing and controlled targeting as two key parameters in drug  
32 delivery device design. We describe how the miniaturisation of these devices  
33 enables the move from repeated, systemic dosing, to on demand, targeted  
34 delivery of therapeutic drugs, and highlight areas of focus for the future.

35 **Keywords:** drug delivery; length scale; targeting; macro; micro; nano

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## 38 INTRODUCTION

39 Over the last century there has been a dramatic change in the nature of therapeutic,  
40 biologically active molecules available to treat disease. This is represented by the move  
41 from extracted natural products and synthesised natural product mimics<sup>1</sup>, towards  
42 rationally designed biomolecules including small molecules, engineered proteins, and  
43 nucleic acids<sup>2-4</sup>. The evolution of potent drugs which target specific organs, cells, or  
44 biochemical pathways, necessitates new tools which can enable controlled delivery and  
45 dosing of these therapeutics to their biological targets. Therapies which can be  
46 administered as a single procedure, either through the delivery of a single dose of a  
47 potent curative therapeutic, or through the implantation of a device that can maintain a  
48 precise, long term drug dosing regime, are highly desired.

49 Macro-scale drug delivery devices have been widely adopted since the 1970s,  
50 when long-acting intra-uterine contraceptive implants were offered as an alternative to  
51 daily repeated oral administration of systemically released hormones<sup>5</sup>. These implants  
52 could be inserted during a single procedure, and remained effective for several years  
53 through localised and controlled release of contraceptive hormones. Since then, a wide  
54 range of systems for therapeutic drug delivery have been developed, broadly focused on  
55 systems which can help to regulate drug dosing<sup>6</sup>, and those which aid targeted delivery  
56 for site-specific therapeutic action<sup>7-10</sup>. Drug delivery devices are in widespread clinical  
57 use, however, many of these systems are limited in their ability to deliver therapeutics  
58 to smaller biological structures with control over both drug dosing and therapeutic  
59 targeting.

60 For certain drugs, failure to adhere to a specific dosing schedule can  
61 dramatically impact therapeutic efficacy. In vaccination, the timing of drug dosing (e.g.

62 the dosing regimen as well as the time of day) is an important parameter in the  
63 development of robust immunity<sup>11</sup>. Drug dosing is therefore a crucial consideration in  
64 drug delivery device design, and many strategies have been explored to regulate dosing;  
65 including continuous, controlled release systems<sup>7, 12-15</sup>, enhanced therapeutic circulation  
66 time<sup>16, 17</sup> and stimuli responsive drug administration<sup>7, 18-22</sup>. Separately, as therapeutic  
67 targets become increasingly specific, and therapies become increasingly potent,  
68 delivering site specific therapeutic action becomes a more critical design feature.  
69 Control over both of these aspects can improve patient safety, quality of life and  
70 compliance by lessening the stringent requirements of strict medication schedules and  
71 reducing off-target effects.

72 Here, we review drug delivery systems across the macro- to nano- scale,  
73 highlighting systems which enable controlled dosing, and those which aid drug  
74 targeting. We explore the role of length scale in the function of these systems,  
75 considering macro-, micro- and nano- systems which are capable of delivery to organs,  
76 cells and cellular substructures of interest (Figure 1). We describe how the  
77 miniaturisation of these devices enables the move from repeated, systemic dosing, to on  
78 demand, targeted delivery of therapeutic drugs, and consider areas of future interest.

## 79 **MACRO SCALE DELIVERY SYSTEMS**

80 Macro scale delivery systems, measuring from 1 mm upwards in size, are particularly  
81 suited for long-term drug delivery. Their scale allows a single device to contain a  
82 considerable therapeutic reservoir, and enables precise engineering of accompanying  
83 parts required for more complex controlled drug administration, such as pumps,  
84 batteries, catheters and sensors<sup>23, 24</sup>. For effective systemic drug delivery, drugs must  
85 first traverse the body's natural physical barriers and reach the systemic circulation,

86 which can prove challenging for macro scale devices<sup>25</sup>. A number of approaches have  
87 been used to address this challenge, with examples including ingestible devices<sup>26-28</sup>,  
88 topical delivery through transdermal systems<sup>29-32</sup>, controlled release implants inserted  
89 close to vasculature<sup>6</sup>, and infusion pump systems which are connected to the systemic  
90 circulatory system via cannula or catheter<sup>23</sup>. Here, we review a range of macro scale  
91 drug delivery devices, and discuss how their scale impacts their ability to deliver  
92 therapeutics.

### 93 *Systemic delivery systems*

#### 94 *Ingestible devices*

95 Ingestion is one of the most convenient administration routes for devices small enough to  
96 pass through the oesophagus<sup>25</sup>. Although a widely used drug delivery route, ingestion  
97 based delivery mechanisms have typically had limited usefulness in long term and  
98 controlled delivery systems, due to frequent gastric emptying times of between 2-3  
99 hours<sup>33</sup>. To combat this, several approaches have been developed to improve gastric  
100 retention times for macro devices small enough to swallow. These approaches focus on  
101 retaining devices within the stomach to provide continuous, systemic drug release,  
102 through adhesion to the stomach wall or changes in device geometry. In one example,  
103 macro devices composed of drug eluting polymers can be folded into a capsule small  
104 enough to swallow, which then expands in the stomach. These low density, floating  
105 devices are buoyant, and cannot pass through the pyloric sphincter and into the intestines  
106 intact<sup>28, 33-35</sup>. Inclusion of a biodegradable moiety allows the devices to slowly degrade *in*  
107 *vivo*, and subsequently passage through the gastro intestinal tract post drug delivery.  
108 Advances in device design will enable systems to be retained beyond the current limit of  
109 a few months, potentially allowing longer term macro scale delivery systems which can

110 be administered without surgical intervention. Although ingestible devices offer a robust  
111 controlled delivery system that can passage through the gastro intestinal (GI) system,  
112 orally delivered drugs must first be absorbed through the gut to become bioavailable. The  
113 GI tract consists of the stomach, small intestine (duodenum, jejunum and ileum), the large  
114 intestine (colon), and the rectum; drug absorption can occur across the entire GI tract. The  
115 majority of drug absorption is occurs via the highly adapted microvilli in the small  
116 intestine, however class III/IV drugs have been shown to preferentially absorb across the  
117 colon<sup>36</sup>. Several drug delivery systems utilise the distinct chemical environments present  
118 in specific regions of the gastrointestinal tract to facilitate a more targeted drug delivery  
119 approach, discussed in detail in the targeted delivery section below. Regardless of  
120 absorption site, orally administered drugs are subject to first-pass metabolism and hepatic  
121 clearance, and so systemic bioavailability of a therapeutic drug concentration may be  
122 lower when compared to intravenous administration.

### 123 *Transdermal delivery*

124 In contrast to ingestible devices, transdermal drug delivery methods offer many benefits  
125 over the more traditionally administered oral route<sup>37</sup>. Firstly, compared to orally  
126 delivered pharmacologics of the same dose, they can provide increased levels of  
127 circulating, bioavailable drugs. This leads to a reduction in the drug dose needed to  
128 elicit a specific pharmacological effect<sup>38-40</sup>, and can therefore reduce side effects.  
129 Transdermal patches provide a controlled release system which is well suited to the  
130 delivery of small molecules, though dermal penetration and delivery efficacy is affected  
131 by both the molecular size and hydrophilicity of the therapeutic being administered.  
132 Transdermal patches have been widely used to deliver small molecules such as nicotine  
133 in smoking cessation therapies<sup>41</sup>, and contraceptive/postmenopausal hormones such as  
134 estradiol and estrone<sup>38</sup>. Drug delivery patches are well suited for the continuous,

135 systemic delivery of low dose therapeutics. Drug delivery profiles range from a few  
136 days to a few weeks due to limitations in drug loading capacity, and patches must  
137 remain attached to the skin for the duration of delivery.

### 138 *Polymer implants*

139 Implantable polymer devices have been in use since the 1970's for longer term systemic  
140 drug delivery. Early examples included the Norplant® and Jadelle® non-degradable  
141 subcutaneous contraceptive implants, which provided controlled release of  
142 contraceptive hormones over 5 years. Early devices were composed of an implanted  
143 polymer-drug composite coated with a porous ethyl vinyl acetate membrane<sup>42-44</sup>. This  
144 membrane facilitated controlled kinetic release of the hormones, and similar devices  
145 have been used to systemically deliver a range of pharmaceuticals including anti-  
146 inflammatory drugs and antibiotics<sup>45-48</sup>. As with the early Norplant® devices, many of  
147 these systems are based on non-degradable polymers with a fixed-rate delivery profile,  
148 controlled by drug diffusion from within the device. Devices are usually implanted, and  
149 removed, via a minor surgical procedure at the end of their delivery lifetimes. To  
150 minimise surgical intervention required in the removal of these devices, longer-acting,  
151 degradable subcutaneous rod implants are currently in development<sup>49</sup>.

152 In a similar approach, polymer hydrogel systems can be used for kinetically  
153 controlled systemic drug release<sup>7, 13, 50</sup>. Hydrogels have the potential to deliver virtually  
154 any therapeutic<sup>13, 51</sup>; controlled release parameters are widely tuneable, with the nature  
155 of the hydrogel crosslinking determining the kinetics of controlled release and the  
156 biodegradability of the system. Both chemical (covalent) and physical (electrostatic  
157 assembly, stereo-complexation, supramolecular host-guest inclusion) crosslinking can  
158 be used to form hydrogel structures, however care must be taken to ensure the  
159 crosslinking agent does not impact drug potency. The wide range of cross-linking

160 chemistries and polymer compositions provides tuneable delivery profiles that can last  
161 from several days up to several years, making polymer implants a versatile class of  
162 materials for drug delivery.

### 163 *Pump systems*

164 A number of implantable infusion pump systems have been developed for long-term  
165 delivery of therapeutics with metered dosing<sup>23</sup>. These devices can measure up to 10 cm  
166 in diameter, and are often surgically implanted into patients. They generally consist of a  
167 reservoir-pump system which offers dosing schedules based on continuous fixed rate  
168 delivery, timed dose delivery, or on-demand delivery in response to specific stimuli.  
169 Dosing is usually controlled by an integrated pump system, which can be driven  
170 through mechanical, peristaltic means<sup>52-55</sup>, propellant systems<sup>56-59</sup>, or is driven by  
171 osmosis/diffusion<sup>60</sup>. Due to the invasive surgical nature of implantation, these devices  
172 are primarily used for continuous therapeutic release in chronic medical conditions<sup>54, 56,</sup>  
173 <sup>57</sup>. Examples include intrathecal delivery of opioid based analgesic therapies, or delivery  
174 of muscle relaxants such as baclofen in patients with severe contractions. This  
175 continuous, metered dosing is particularly useful for analgesics in long term and  
176 palliative care, where the risk of misadministration and accidental overdose, a current  
177 concern with prescribed opioid tablets, can be reduced.

178         For metered and on-demand dosing, stimuli responsive pumps can be used.  
179 These have proven particularly useful in diabetes, where sensors implanted under the  
180 skin can monitor and respond to glucose levels (MiniMed, Paradigm® Revel™)<sup>61</sup>. In  
181 these systems, reservoirs containing insulin, or twin reservoirs containing insulin and  
182 glucagon, are connected to sensors and facilitate metered drug delivery in response to  
183 hypo- or hyper-glycaemic events. Recently, wireless, smartphone connected sensors



184 have been developed which allow patients and healthcare professionals to manage  
185 glucose levels in real time<sup>62, 63</sup>. These devices enable a truly patient specific, on-demand  
186 therapy, and are now clinically used in systemic applications<sup>60, 62, 64</sup>. However, the  
187 reservoir-based systems described limits the drug formulations to liquid systems, and  
188 device lifetimes are limited by the reservoir loading capacity. Additionally, the use of a  
189 power source to run the pumps in peristaltic devices limits the usefulness of these  
190 devices due to short battery lifetimes (usually limited to 4-7 years)<sup>65</sup>. Finally, due to  
191 their scale these more complex systems currently remain unsuitable for targeted or  
192 localised delivery approaches, which require smaller scale devices.

### 193 *Localised delivery systems*

#### 194 *Proximal polymer implants*

195 Many smaller macro scale devices can be surgically implanted within target organs to  
196 allow for proximal drug release, enabling therapeutic efficacy using lower doses than  
197 required in systemic delivery systems. A widespread example are contraceptive devices  
198 introduced into the body via the vaginal tract. Contraceptive devices, briefly discussed  
199 earlier, are widely adopted clinically, and intra uterine devices (IUDs)<sup>5</sup> have been in  
200 widespread use since the 1970s. IUDs and contraceptive vaginal rings can both be  
201 applied via a minor surgical procedure, and systems such as the NuvaRing® and  
202 Nestorone® offer controlled release on the order of 1 month to 3 years<sup>66, 67</sup> before  
203 removal. For increased efficacy and reduced side effects, new progestin-infused rings  
204 or combination drug devices that include both progesterone and estrogenic steroids are  
205 in development<sup>66</sup>. Future developments are focused on combining localised  
206 contraceptive drug release with systemic drug release, providing a multiplexed system  
207 to reduce the risk of sexually transmitted infections<sup>67, 68</sup> in a vaginal ring device.

208           To reach less accessible target organs, surgical intervention is often required to  
209 position macro devices correctly. A number of polymer-based macro devices are  
210 indicated for controlled drug delivery to target organs, exemplified by stent-based<sup>69</sup>  
211 drug delivery. Stents are used for drug delivery in coronary interventions, and  
212 additionally in non-vascular target organs including the oesophagus, biliary duct,  
213 trachea, bronchi, sinus cavities, ureters, and urethra<sup>70, 71</sup>. First-generation vascular stents  
214 were approved by the FDA in 1994, and were manufactured from bare metal alloys or  
215 ceramic composites. However, these stents caused complications including hyperplastic  
216 growth and restenosis. Next generation stents therefore included novel metallic and  
217 polymeric stent materials with more open mesh-like frameworks, and simultaneously  
218 eluted anti-inflammatory drugs<sup>71, 72</sup> to reduce restenosis. Stents often provide a physical  
219 support coupled with drug eluting capabilities. The continued optimisation of stent  
220 structures to reduce plaque prolapse (through increased radial strength) and increase  
221 biocompatibility (using fluoropolymer materials) renders these devices as versatile tools  
222 for the delivery of a diverse class of drugs. Many systems have been developed for the  
223 controlled delivery of anti-inflammatory, antimicrobial, and analgesic drugs<sup>70, 71</sup> using  
224 diffusion based release profiles.

225           In contrast, less rigid polymer systems, have been used for non-structural drug  
226 delivery. Both biodegradable polymer stents, and implantable hydrogel systems can be  
227 used for localised therapeutic delivery. Biodegradable polymer systems are particularly  
228 useful for non-structural drug delivery systems<sup>70</sup>, as they can be packed into surgical  
229 sites and release drugs during healing before being resorbed into the body. These  
230 polymer systems have been used in applications ranging from advanced wound healing  
231 to the delivery of chemotherapeutics<sup>73, 74</sup>. In contrast, macro scale polymer-based  
232 hydrogel systems are useful for both surgical and non-surgical drug administration. A

233 widespread example is hydrogel contact lenses used for ocular drug delivery. These  
234 devices can increase the bioavailability of drugs otherwise limited by burdensome  
235 ocular administration dosing regimens<sup>48, 75</sup>. They have proven particularly useful for  
236 delivery of medications for eye diseases including glaucoma, and delivery of  
237 antibacterial agents to the eye<sup>76-78</sup>. In general, hydrogel thickness can be used to control  
238 drug loading, and delivery profiles can be tuned to offer zero-order release kinetics.  
239 Many hydrogel systems are unsuitable for localised ocular delivery applications due to  
240 their limited transparency, stability, and the use of non-biocompatible crosslinking  
241 agents during formation. Drug delivery contact lenses must be designed to possess  
242 luminous transmittance, oxygen permeability, mechanical stability, and  
243 biocompatibility<sup>76-79</sup> in addition to their drug loading capacity. These stringent material  
244 requirements highlight the complexities in designing drug delivery systems which  
245 match localised tissue requirements. Next, we discuss advances in macro scale drug  
246 delivery systems which enable a more targeted delivery approach.

#### 247 ***Targeted delivery systems***

248 Targeted delivery systems, where a device enables the delivery of a therapeutic to a  
249 target organ or cell based in a different location to the administration site, are relatively  
250 limited in macro scale devices. Due to their scale, macro devices are often too large to  
251 engage with many biological structures and target cells. A notable exception to this is  
252 the use of stimuli responsive macro scale devices for delivery to chemically distinct  
253 regions of the gastrointestinal tract<sup>34, 80-82</sup>. The chemical environment of the stomach  
254 often poses a challenge to pH sensitive and enzymatically degraded protein and peptide  
255 therapeutics. Drug delivery devices frequently utilise local variations in target tissue pH  
256 to control drug release, with hydrogels sensitive to alkali pH and enteric tablet coatings  
257 facilitating delivery to the intestines.

258 For many other target tissues, macro scale devices are too large to travel through the  
259 vasculature or lymphatic system and move towards target organs. In an alternative  
260 approach, macro devices which can recruit a target cell towards the device to selectively  
261 deliver a therapeutic drug to a target cell type have been developed. These devices have  
262 been trialled in vaccination systems, where chemokines (CXCL12) have been  
263 incorporated into a polymer material to encourage the recruitment of immune cells.  
264 Once the immune cells reach the macro device, they “collect” the drug. In this way, the  
265 macro device can overcome the transport limitation imposed due to its size, and  
266 provides a targeted delivery system to specific cells by recruiting the cell of interest<sup>83-85</sup>  
267 to the device location. This relatively new concept offers promise for the design of a  
268 range of macro devices which can act in a targeted manner

### 269 *Summary*

270 Macro scale devices and their component parts can be precisely engineered to allow fine  
271 control over drug dosing schedules, and in some cases, can be coupled with sensor  
272 technology to enable patient specific systemic drug release. The dimensions of most  
273 macro scale devices and their capacity to hold large therapeutic reservoirs renders them  
274 suitable to long term drug delivery. However, these dimensions also limit their  
275 usefulness in targeting smaller biological structures. Although some smaller macro  
276 devices can be surgically inserted into larger target organs (i.e. uterus, large arteries) to  
277 facilitate proximal or localised drug release, devices cannot migrate through the body,  
278 limiting their ability to deliver drugs in a targeted fashion. The advent of new polymer  
279 implants which can directly recruit target cells offers the potential to combine the  
280 intrinsic advantages of macro devices (drug loading capacity, precision engineering,  
281 patient specific stimuli responsive systems) with the targeting advantages usually found

282 in smaller scale systems, and is an exciting future direction for macroscale device  
283 development.

## 284 **MICRO SCALE DELIVERY SYSTEMS**

285 Devices at the micron scale range from 1-1000 $\mu\text{m}$ , allowing them to be introduced  
286 within the body without the need for a major surgical procedure through ingestion  
287 (orally administered osmotic pumps)<sup>24, 86, 87</sup>, inhalation, and inoculation (microparticles,  
288 microneedles)<sup>88-92</sup>. Many key biological structures are organised on the micron length  
289 scale, with cells themselves measuring from 5-20 microns in diameter and possessing  
290 cellular substructures on the order of nano- to micro-meters. Several biological transport  
291 networks are also organised on the micro-scale; lymphatic capillaries<sup>93, 94</sup> have a  
292 diameter of ~10-60  $\mu\text{m}$ , whilst circulatory vasculature<sup>95</sup> measures on the order of 10  
293 mm in arteries and veins to around 1  $\mu\text{m}$  in capillaries. Micro-scale drug delivery  
294 devices therefore offer the unique advantage of being able to interface with organoid,  
295 cellular, and subcellular structures on a comparable length scale to their biological  
296 targets. In addition, they may be able to navigate through the body's transport networks,  
297 rendering them particularly suitable for localised and targeted delivery systems. Here,  
298 we review a range of micro scale delivery systems with increasing target specificity.

### 299 *Systemic delivery systems*

#### 300 *Microfabricated electromechanical systems (MEMS)*

301 Microfabrication techniques and advances in pump technology have allowed injection  
302 and infusion devices (described earlier in the macro section) to be created on smaller  
303 and smaller length scales. Micro fabricated electromechanical systems (MEMS) offer a  
304 micron sized infusion device that can provide localised fixed rate or variable dose

305 delivery, and recently further miniaturisation of fabrication technologies has encouraged  
306 development of nanoelectromechanical systems<sup>96</sup> (NEMS). MEMS systems can deliver  
307 both liquid and solid-phase drug formulations<sup>97-104</sup> in a manner analogous to macro  
308 scale infusion pumps. The delivery dose is controlled by an infusion system, which is  
309 either fixed rate (i.e. diffusion-based) or active (i.e. pumped)<sup>9,97</sup>. In pumped systems,  
310 devices can be either non-mechanical (i.e. electrophoresis, electro osmosis) or  
311 mechanical in nature (piezoelectric, electromagnetic, shape memory alloy), with the  
312 choice of pump system impacting both the delivery dosage schedule and device life  
313 time<sup>101-103, 105, 106</sup>. For example, non-mechanical pumps usually have a limited flow rate  
314 compared to variable piezoelectric pumps<sup>101, 104, 105, 107-110</sup> yet piezoelectric pump  
315 systems often require higher voltage systems and increased operating power, reducing  
316 battery and device lifetime. Although these devices are small enough to be implanted  
317 within the body, they have a reduced reservoir capacity compared to their macro scale  
318 counterparts. To combat the low loading capacity, refillable devices<sup>99</sup> are being  
319 developed which enable reservoir replenishment and dose manipulation post-  
320 implantation. Due to the placement of these devices within the body, refilling these  
321 systems will likely require an additional surgical procedure, rendering these devices  
322 unsuitable for non-surgical applications.

### 323 *Microneedles*

324 Microneedle patches have been developed which facilitate drug delivery without  
325 surgical intervention. These consist of an array of high aspect ratio needles<sup>90,91</sup> on the  
326 order of 500-1000  $\mu\text{m}$  in length, which can penetrate the epidermis and reach the  
327 underlying dermal layer. Once they are in contact with this layer, they can be used to  
328 deliver small molecules, proteins, or nucleic acids via hollow, solid, or biodegradable  
329 needles<sup>30</sup>. The needles are usually made of metal, silica, or polymer composites, and are

330 fabricated through microlithography<sup>29, 88-91, 111</sup> using etching, casting, or printing  
331 methods. The simplest of these systems use solid and porous non-degradable needles  
332 coated with a drug, or biodegradable drug-polymer composite that can dissolve into the  
333 tissue once the microneedles contact the dermal layer. Alternatively, the microneedles  
334 can be uncoated, and removed once they have penetrated the epidermal barrier,  
335 allowing topical application of therapeutics to the area. An alternative system uses  
336 hollow needles coupled to a liquid reservoir, using capillary action to inject liquid into  
337 the dermal layer in an analogous manner to traditional macro needles. In contrast,  
338 biodegradable needle systems can be applied directly to the skin and used to deliver  
339 drugs with a more continuous release profile. By carefully tuning polymer  
340 compositions, these systems can controllably deliver drugs in a single administration  
341 lasting a few seconds, or with a longer kinetic release profile of a few weeks<sup>30, 90</sup>.

#### 342 *Polymer implants*

343 A range of injectable administration methods have been developed to implant polymer  
344 based micro scaled drug delivery systems. The simplest of these involve micro scaled  
345 polymer masses which are administered using a clinical gauge needle to directly  
346 penetrate the skin barrier, and deposited subcutaneously. A wide range of injectable  
347 polymer compositions have been explored, from early studies using polylactic acid and  
348 biodegradable polylactide-co-glycolide acid polymer systems, to newer stimuli  
349 responsive copolymer systems, and novel hydrogel systems<sup>112</sup>.

350         Micro scale injectable hydrogels with controlled release properties<sup>83, 113-115</sup> have  
351 emerged as promising polymer delivery systems for clinical applications. For example,  
352 shear-thinning hydrogels are particularly well suited to subcutaneous systemic delivery  
353 devices<sup>115-117</sup>, as they remain liquid during application and solidify on placement post-

354 injection. This renders shear thinning hydrogel systems suitable for delivery to a wide  
355 range of target locations, however for longer term release profiles (over 6 months)  
356 multiple hydrogel injections would likely be required in a clinical setting. To prevent  
357 overloading the subcutaneous space with polymer materials, hydrogels with tuneable  
358 degradation rates (matched to the rate of drug release) can ensure polymer residue does  
359 not remain in the body after the therapeutic has been delivered. As an alternative,  
360 refillable drug delivery depots have recently been developed, which aim to overcome  
361 the drug loading limitations inherent in microscopic drug delivery depots. These  
362 systems use “tagged” drugs which can be administered intravenously and migrate  
363 towards the polymer depot<sup>118, 119</sup>, providing a refillable controlled release depot.

#### 364 *Microparticles*

365 Microparticles typically consist of a degradable, drug loaded microparticle that acts as a  
366 drug delivery depot. These particles can be suspended in saline, and injected  
367 intravenously where, if appropriately sized, they circulate systemically. Microparticles  
368 are typically formed by emulsion or solvent evaporation techniques<sup>15, 32, 120-125</sup>,  
369 potentially resulting in a loss of potency for sensitive therapeutics after exposure to  
370 organic solvents during the fabrication method. In an alternative approach, ultra-  
371 sonication and freezing can be used to generate microparticles with control over  
372 polydispersity[11], reducing the need for organic solvents and maintaining drug  
373 potency. A variety of polymers have been used to fabricate microparticles, and the  
374 choice of polymer directly impacts both the microparticle targeting ability and the  
375 specific release kinetics. For example, PLGA microparticles are FDA approved for  
376 clinical use in a range of applications, including chemotherapeutic drug delivery and  
377 hormone release. Their release profiles can be tuned to continuously deliver therapeutic  
378 load over the course of two days, or for up to eight weeks, depending on the lactide to



379 glycolide ratio<sup>126-128</sup> within the polymer. Recently, more advanced microparticles have  
380 been developed which offer a more complex kinetic release profile. These materials  
381 combine several different polymer architectures to offer a single particle that can release  
382 therapeutic load in 2-3 distinct bursts. These systems are likely to prove extremely  
383 useful in vaccine development, where an entire multi-dose vaccination schedule could  
384 be administered systemically in one injection<sup>11, 129</sup>.

### 385 *Localised delivery systems*

#### 386 *Implantable microchips*

387 As infusion pump and microchip devices have been miniaturised, they have become  
388 increasingly suitable for localised drug delivery applications. Recently, new MEMS  
389 devices have been developed which offer an implantable “pharmacy-on-a-chip” design,  
390 allowing the delivery of multiple therapeutics, each at a specified time. These devices  
391 can provide precise dosing control through as many as 100 unique reservoirs opened on  
392 the order of microseconds. The first “pharmacy-on-a-chip” devices successfully  
393 completed phase one human clinical trials in 2012, and were used to deliver human  
394 parathyroid hormone fragment<sup>86, 130</sup> to eight osteoporotic patients. Taking this  
395 technology further, micron-sized reservoir-based devices holding up to 100 drugs and  
396 drug combinations in a small microchip have been implanted into tumour sites. Due to  
397 their high aspect ratio and small scale, implants can be extracted using a conventional  
398 biopsy needle, and the tissue can be examined to determine tumour regression in  
399 response to each of the therapeutic drugs and drug combinations tested. In this way,  
400 surgeons and oncologists can develop a personalised drug treatment plan for cancer  
401 patients based on positive responses to specific drug combination therapies<sup>131, 132</sup>, tested  
402 using the microchip.

### 403 *Controlled polymer architecture*

404 Polymers can be modified to display controlled topographical and physical features,  
405 enabling delivery of therapeutics to a specific biological target organ. For example, the  
406 Nektar aerosolised inhaler based systems deliver microparticles containing a range of  
407 therapeutics, and uses microparticles with a reduced density to aid pulmonary particle  
408 delivery<sup>133</sup>. Microparticle geometry has also been shown to directly impact cellular  
409 uptake, with both particle size and shape<sup>134-138</sup> playing an important role in the response  
410 of specific tissues and cells. Given the importance of the three dimensional structure to  
411 cellular interactions, shape memory polymers are being developed that can be injected  
412 into a target organ using a syringe, and then resume a specific 2D or 3D shape on  
413 reaching 37°C in the body. One example of these systems involves bio-adhesive shape  
414 memory hydrogel sheets, which provide an easily applied, injectable patch drug  
415 delivery device for local drug administration<sup>72, 139-142</sup>.

### 416 *Targeted delivery systems*

#### 417 *Ligand targeting*

418 The identification of organ and cell specific ligands has facilitated targeted delivery of  
419 micro scale systems. This is often accomplished using conjugation strategies which link  
420 targeting ligands onto polymers. Ligand conjugated polymers can be used to form drug  
421 delivery microparticles, which can be formulated to encapsulate a range of therapeutic  
422 cargo including proteins, small molecules, and cytokines within a ligand decorated  
423 polymer shell<sup>17, 143</sup>. Conjugation of specific ligands can also alter the systemic  
424 circulation time; for example the inclusion of a polyethylene glycol (PEG) moiety is  
425 thought to prevent binding and uptake of microparticles by non-targeted cell types. The  
426 inclusion of specific ligands facilitates microparticle binding to specific cells and tissues

427 presenting the receptor for the attached ligand. These systems have proven particularly  
428 useful for targeting the liver through the ASGPR1 receptor<sup>144, 145</sup>, or targeting  
429 systemically circulating dendritic cells<sup>146, 147</sup>. As ligands of other target organs are  
430 identified, this method will enable more specific targeting.

#### 431 *Microbubbles*

432 In an alternative approach, smaller, drug loaded microbubbles have been injected  
433 systemically. The application of ultrasound (which bursts these bubbles) can be used to  
434 target drug release to a specific therapeutic area. This emerging technology makes use  
435 of clinically available imaging facilities located in hospitals and clinics to induce  
436 controlled release in target biological structures. The technique has proven popular in  
437 delivering drugs to larger target organs, such as the kidney<sup>148-150</sup>. The development of  
438 ultrasound mediated drug delivery follows previous discoveries that traditional delivery  
439 through topical administration to the skin, gastrointestinal tract and mucus membranes  
440 is enhanced with simultaneous application of an ultrasound probe<sup>151, 152</sup>.

#### 441 *Summary*

442 Micro scale systems offer a robust tool to facilitate drug delivery in systemic, localised,  
443 and targeted fashions. Whilst macro scale devices can offer controlled release for  
444 durations of months to years, micro systems have limited reservoir and loading  
445 capacity, usually limiting drug delivery to weeks and months. There are also limited  
446 examples of systems with programmed release profiles, as the majority of the drug  
447 delivery systems rely on diffusion and biodegradation to provide a continuous and fixed  
448 rate delivery. Recently, pulsatile hydrogel release systems, pulsatile microparticles, and  
449 stimuli responsive drug delivery approaches have been developed which offer the  
450 promise of greater control over complex dosing schedules. Although micro systems are

451 limited by therapeutic reservoir and release profiles, they excel in providing localised  
452 and targeted drug delivery. Their small scale enables implantation into key organs, and  
453 microparticles and microbubbles can travel through the vasculature to enable both  
454 systemic and more targeted delivery. Poorly vascularised tissues, and those isolated by  
455 complex physiological barriers such as the blood-brain barrier, remain difficult to target.  
456 As new approaches to crossing physiological barriers are identified, micro scale systems  
457 will play an increasingly important role in targeted delivery.

## 458 **NANO SCALE DELIVERY SYSTEMS**

459         Nanoscale systems are generally defined as being of the order of between 1 to  
460 100 nm (ISO/TS 80004-1:2015), however in practice can range from 1 to 1000 nm<sup>153</sup>.  
461 Nanotechnology can be used to improve the pharmacokinetic properties of traditional  
462 pharmaceuticals, increase circulation time, solubility, and enhance delivery into  
463 difficult-to-access tissues. In addition, nanostructures below 200 nm can undergo  
464 uptake in various cell types and avoid clearance by phagocytosis<sup>154</sup>, making nanoscale  
465 systems particularly promising for targeted intra-cellular delivery of a variety of  
466 therapeutic cargo. This section will provide an overview of recent advances in  
467 nanotechnology for drug delivery, and identify remaining challenges.

### 468 *Systemic delivery systems*

#### 469 *Nanoparticles*

470 Nanoparticle systems enable the systemic delivery of sensitive or unstable therapeutics  
471 by protecting them against degradation, extending circulation time, and facilitating  
472 delivery across biological barriers that would normally be prevented due to  
473 hydrophilicity, size or charge [9, 10]. Re-formulating existing drugs into nanoparticle

474 delivery systems can reduce toxicity, and nanoparticles can be formulated using a  
475 variety of materials including lipids, polymers and peptides. Nanoparticle formulations  
476 can also be used to deliver sensitive cargo at risk of degradation from ubiquitous  
477 nucleases *in vivo*, such as nucleic acids. Systemic nanoparticle mediated delivery has  
478 been demonstrated for mRNA<sup>155</sup>, and localized delivery of DNA has been demonstrated  
479 following topical application of DNA nanoparticles to the skin<sup>156</sup> in patients with  
480 epidermolysis bullosa.

481 To improve solubility, drugs are often encapsulated inside micelle carriers, or  
482 conjugated to water soluble polymers. Liposome-based carriers were first described in  
483 the 1960s and are amongst the most well established nano-carriers for systemic delivery  
484 <sup>157</sup>. They have been widely used to improve aqueous solubility of hydrophobic drugs,  
485 illustrated by the antifungal amphotericin B, which is insoluble at physiological pH and  
486 also highly toxic. The liposomal formulation of this drug, AmBisome®, can be  
487 administered systemically with dramatically reduced toxicity<sup>158-160</sup>.

488 Synthetic conjugates have also been used to formulate drug delivery nanoparticles, and  
489 inclusion of water soluble polymers, such as polyethylene glycol, can aid systemic  
490 solubility without the inclusion of dose-limiting solvents. Paclitaxel is an example of a  
491 poorly water-soluble drug that has been formulated within degradable polylactide-  
492 polyethylene glycol block co-polymers, allowing better delivery through nanoscale drug  
493 delivery micelles (Genexol-PM). These micellar nanoparticle formulations can also  
494 enhance transdermal drug delivery<sup>161-163</sup>, and have been used to deliver hormones such  
495 as estradiol via topical application. The incorporation of polyethylene glycol (PEG) into  
496 these nanoparticle systems can increase particle stability<sup>164-166</sup>, reduce protein  
497 adsorption (opsonization), and prevent subsequent phagocytic clearance. For example,  
498 PEGylated liposomal doxorubicin formulations have been shown to extend circulation

499 times<sup>164, 167</sup> when compared to uncoated liposomes, or free doxorubicin. However,  
500 studies have indicated that repeated administration of PEGylated formulations can lead  
501 to an increased clearance rate of subsequent doses of PEGylated liposomes. This is  
502 likely due to IgM antibodies raised after first exposure<sup>164</sup> or pre-existing IgG antibodies  
503 to PEG.<sup>168</sup>

#### 504 *Nanowires, nanoneedles and nanotubes*

505 High-aspect-ratio nanoscale systems<sup>169-171</sup> such as nanowires, nanoneedles and  
506 nanotubes have been used to deliver a wide variety of biomolecules, and can be  
507 combined with macro and micro systems to enhance drug delivery technologies. For  
508 example, micron scaled drug delivery particles have been coated with nanowires which  
509 enhance retention in the mucosal tract. This strategy enables prolonged retention to  
510 mucosal epithelial tissue<sup>172</sup>, facilitating enhanced drug delivery and limiting clearance.  
511 In addition, nano scale needles (nanoneedles), wires, and tubes can be loaded directly  
512 with drugs for intracellular drug delivery. Biodegradable silicon nanoneedles grafted  
513 onto micron sized patches have been used for the intra-cellular delivery of VEGF DNA  
514 to localised regions of skin and exposed muscle<sup>169</sup>, where they are able to enhance  
515 neovascularization compared to delivery of naked DNA. Recently, more sophisticated  
516 systems have been developed which can release cargo in response to specific stimuli<sup>29</sup>.  
517<sup>92</sup>, including changes in pH and temperature, and the presence of specific enzymes.  
518 High-aspect delivery systems are typically silicon-based, however alternative materials  
519 (such as carbon nanotube based drug reservoirs<sup>173-176</sup>) are currently being developed.  
520 These material systems will need to meet stringent nano scale safety and toxicity  
521 requirements before widespread clinical use.

## 522 *Nanogels*

523 Nanoscale hydrogels (nanogels) broadly consist of crosslinked polymeric particles  
524 which can be synthesized using a range of synthetic and naturally derived materials  
525 including polyacrylamides, polydimethylsiloxane, and chitosan<sup>166, 177-180</sup>. Nanogels offer  
526 a large surface area for bioconjugation, and as for the microgel systems described  
527 earlier, cross-linking can be used to fine tune drug delivery release kinetics for the  
528 delivery of hydrophobic, hydrophilic and charged solutes. Nanogels have been used for  
529 both targeted intracellular delivery and systemic delivery. These systems have recently  
530 been applied to intra-nasal vaccine delivery, where they can be retained in nasal mucosa  
531 to generate systemic immunity as well as local mucosal immunity<sup>181, 182</sup>.

## 532 *Localised delivery systems*

### 533 *Stimuli responsive nanosystems*

534 In an effort to move towards systems with spatio-temporal control of drug delivery, a  
535 number of nanosystems have been developed which can be triggered to release cargo by  
536 exposure to external stimuli such as heat, light and ultrasound. Ultrasound has been  
537 utilized to increase transdermal delivery of a variety of nanoparticles through the skin<sup>29,</sup>  
538 <sup>149, 150</sup>, whilst heat and light sensitive nanosystems have enabled delivery to deeper  
539 tissues. For example, thermosensitive lipids that have transition temperatures between  
540 40-45°C can be used to formulate liposomes that become unstable and release cargo  
541 once exposed to this temperature. ThermoDox® is a temperature-sensitive doxorubicin-  
542 PEGylated liposome that is systemically delivered but releases cargo in regions where  
543 local temperatures are elevated to 40 °C by application of radiofrequency. The thermo-  
544 responsive formulation was shown to increase local concentration of the drug several  
545 folds higher in the radiofrequency treatment area compared to intravenously

546 administered doxorubicin, and compared to non-thermosensitive liposomal formulations  
547 of doxorubicin<sup>183</sup>.

548           Alternatively, light has been used as an external stimulus for photodynamic  
549 therapies. Visudyne® is a liposomal formulation of verteporfin<sup>184, 185</sup> used to treat  
550 ocular conditions. It is systemically administered but only exerts its toxic effects when  
551 exposed to light. When light is applied to the eye, this formulation can be used to treat  
552 ocular neovascularization due to diseases such as age-related macular degeneration. For  
553 these treatments to be successful, stimuli must be able to penetrate to the target tissue to  
554 facilitate drug release. This renders tissues closer to the surface more amenable to these  
555 therapies; for deeper structures alternative targeted delivery systems are required.

## 556 ***Targeted delivery systems***

### 557 *Site-specific accumulation*

558 Systemically delivered nanoparticle systems may accumulate in organs such as the  
559 liver, lung and in tumors. This site-specific accumulation after systemic administration  
560 has been observed using nanocarriers where there is no specific targeting moiety.

561 Nanoparticles that tend to accumulate at tumor sites are thought to be subject to the  
562 enhanced permeability and retention<sup>186</sup> (EPR) effect. Nanoparticles are small enough to  
563 traverse through the leaky blood-tumor barrier resulting in accumulation and therefore  
564 enhanced drug delivery to the tumor site. Lung accumulation is thought to be due to the  
565 cationic nature of nanoparticles leading blood component aggregation and accumulation  
566 in pulmonary vasculature.<sup>187, 188</sup>

567 Selective biodistribution has also been attributed to *in vivo* post-modification of  
568 nanoparticles, where particular apolipoproteins are preferentially adsorbed onto the  
569 nanoparticle, and can facilitate trafficking to, and enhance retention in, the



570 corresponding organ. In one example, polysorbate 80 modified polybutylcyanoacrylate  
571 nanoparticles were used to deliver doxorubicin to the brain. Doxorubicin does not cross  
572 the blood brain barrier alone, but when delivered as a nanoparticle formulation, delivery  
573 to the brain was achieved<sup>189</sup> and found to be due to adsorption of apolipoprotein onto  
574 the polymer nanoparticles. Similarly, lipid nanoparticles carrying nucleic acids were  
575 shown to accumulate in the liver after adsorption of apolipoprotein E<sup>190, 191</sup>. These  
576 examples demonstrate that nanoparticle design must consider factors such as particle  
577 size, charge and shape<sup>170, 192</sup>, which can influence tissue accumulation and therefore  
578 targeting efficacy.

#### 579 *Receptor-mediated targeting*

580 In a similar manner to microparticle based delivery, nanoparticles can be formulated  
581 with protein and ligand tags to enable selective delivery. Identifying specific receptor  
582 ligand pairs which enable cell selective delivery is a topic of great interest. To reduce  
583 phagocytosis and enhance therapeutic efficacy, nanosystems can be conjugated with  
584 “self” peptides such as CD47<sup>193</sup> which act as a “don’t eat me” marker. For tumor  
585 targeting, nanoparticles can be decorated with ligands that target receptors that are  
586 overexpressed in cancer cells, such as the transferrin receptor<sup>194</sup>. Protein and antibody  
587 tagging can also facilitate organ and cellular targeting; HER2 antibodies have been  
588 conjugated to liposomal doxorubicin<sup>165</sup> to mediate targeted binding in breast cancer.  
589 Antibody presentation on nanoparticles can also increase cellular particle uptake; when  
590 trastuzumab and rituximab were bound to PLA particles, particle uptake was increased  
591 six-fold compared with PLA particles lacking targeting molecules<sup>195</sup>. In an alternative  
592 strategy, Abraxane, an albumin bound nanoparticle formulation of paclitaxel, is thought  
593 to undergo an albumin-receptor (gp60) mediated endothelial transcytosis<sup>196-198</sup>, enabling  
594 the drug to pass through endothelial cell walls in tumor micro vessels to achieve

595 enhanced intra-tumoral concentrations and anti-tumor activity.

596 In addition to targeting specific cells, nanocarriers that contain cargo must also  
597 efficiently enter cells to deliver the therapeutic component. Particle shape, size, and  
598 composition can all affect penetration efficacy, and coating the nanoparticle with cell  
599 penetrating peptides is proving a promising strategy. By screening a library of cell  
600 penetrating peptides (CPP) using a high throughput strategy, three human peptides were  
601 identified which improved *in vivo* delivery when conjugated to lipid-like  
602 nanoparticles<sup>199</sup>. As the mechanism for cellular entry and endosomal escape become  
603 better understood, new ligands will be identified to enhance these processes and  
604 enhance intracellular targeting with increased specificity and efficiency.

## 605 ***Summary***

606 Nano based systems are an enabling technology for the delivery of traditional drugs and  
607 novel therapies such as nucleic acid based drugs. Nanoparticles can be used to optimize  
608 the pharmacokinetics of conventional therapeutics, and offer a promising platform for  
609 targeting specific cells and organelles by manipulating biological pathways such as  
610 endocytosis and ligand targeting to gain cellular entry. Due to their small scale, drug  
611 loading and precision engineering is challenging, rendering current nanoscale systems  
612 less suited for the continued or controlled release of therapeutic loads. Additionally, the  
613 development of safe and effective nanoscale materials presents a significant hurdle for  
614 clinical translation.

## 615 **CONCLUSIONS**

616 Modern drug therapies include small molecules, proteins, and genetic  
617 engineering based strategies. These therapies often have precise biological therapeutic  
618 targets, and are most effective when delivered with specific dosing regimens. The need

619 to combine targeted delivery and dosing in smaller and smaller scale systems has driven  
620 the miniaturisation of drug delivery devices from the macro to micro to the nano scale.  
621 We have reviewed a range of devices and described their ability to controllably deliver  
622 biomolecules, summarised in Table 1 and Figure 4. In general, macro devices offer  
623 precisely engineered systems which can provide systemic and localised drug delivery  
624 over a period of several years. Devices have a defined lifetime, usually limited by  
625 battery power and reservoir capacity, before they need to be surgically replaced. In  
626 some cases, precision engineering and the incorporation of wireless sensors for on-  
627 demand sensing has enabled patient specific drug delivery, most commonly applied to  
628 insulin therapies. As the length scale of these devices is reduced to smaller macro  
629 devices, they can be surgically implanted into additional target organs to enable  
630 localised therapeutic delivery, however their scale limits their ability to target smaller  
631 biological structures. In a smart workaround, cell specific delivery can be achieved  
632 using macro scale polymer implants that recruit desired cells for targeted delivery, and  
633 when coupled with refillable drug depots this will provide an exciting future direction  
634 for cell specific delivery.

635 In contrast, micro and nano systems can often be coupled with targeting ligands and can  
636 travel through the vasculature and lymphatic systems to reach specific cell targets.  
637 Several of these systems can undergo burst release in response to external stimuli such  
638 as light, heat, or ultrasound. However, there are limited examples of these systems being  
639 able to intrinsically facilitate controlled dosing schedules. Notable exceptions are burst  
640 release polymer particles which offer a single administration of an entire dosing  
641 schedule, and stimuli responsive nanoneedle delivery systems which use cleavable  
642 linkers to deliver therapeutics in response to target enzyme expression. These systems  
643 straddle the boundary between sensing and drug delivery and offer an exciting direction

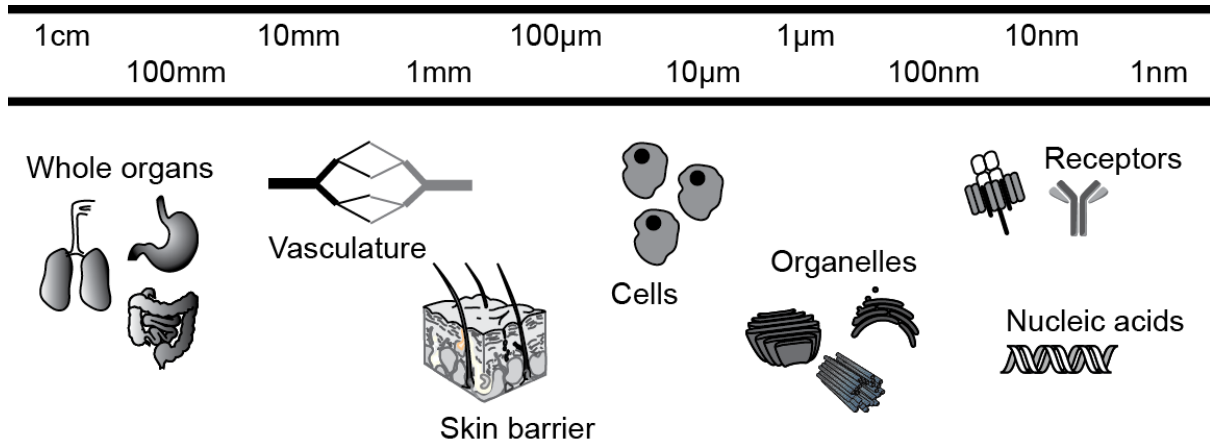
644 for responsive drug delivery therapies. A major limitation to micro and nano scale  
645 systems is the limited therapeutic load these systems can carry, limiting the duration of  
646 controlled release to between hours and, at most, a few months. This suggests micro-  
647 and nano- scale systems are best suited to short term delivery of up to 3 months, or the  
648 targeted delivery of curative and preventative therapeutics that can be administered with  
649 a single application.

650 Moving forwards, next generation devices will focus on increasing the efficacy of  
651 therapeutic delivery at smaller and smaller length scales. As mechanisms of  
652 nanoparticle cellular entry and endosomal escape are elucidated, nanoscale systems with  
653 greater delivery efficacy and therapeutic effect will be developed. Additionally, the  
654 development of stimuli responsive polymer systems will enable on-demand and patient-  
655 specific delivery systems to be developed in response to specific cues. Future devices  
656 will combine the advantages of macro scale delivery systems with the precise targeting  
657 capabilities of devices on the nano scale.

658

659 **FIGURES AND TABLES:**

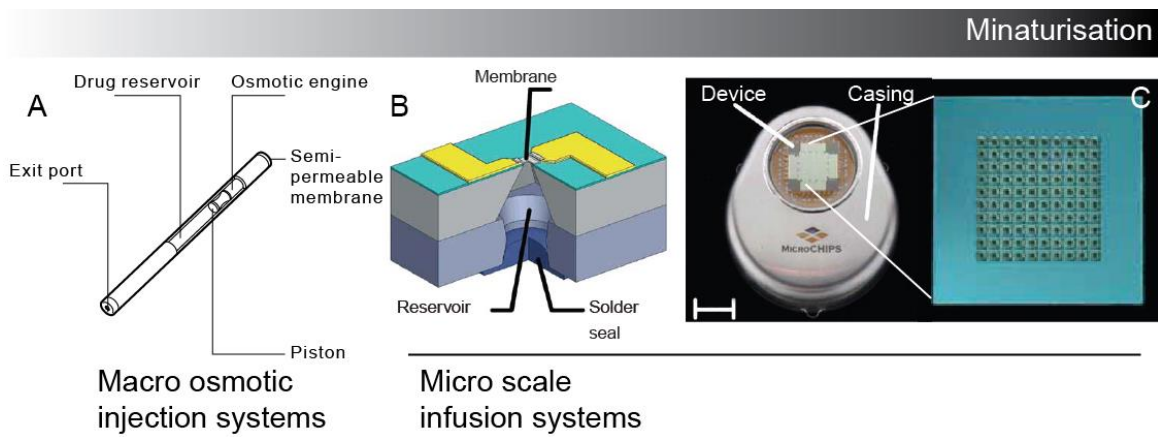
660 **FIGURE 1: Length scales in drug delivery** An overview of the biological length  
661 scales important in drug delivery, including target organs, biological barriers and sub-  
662 cellular structure of interest.



663

664

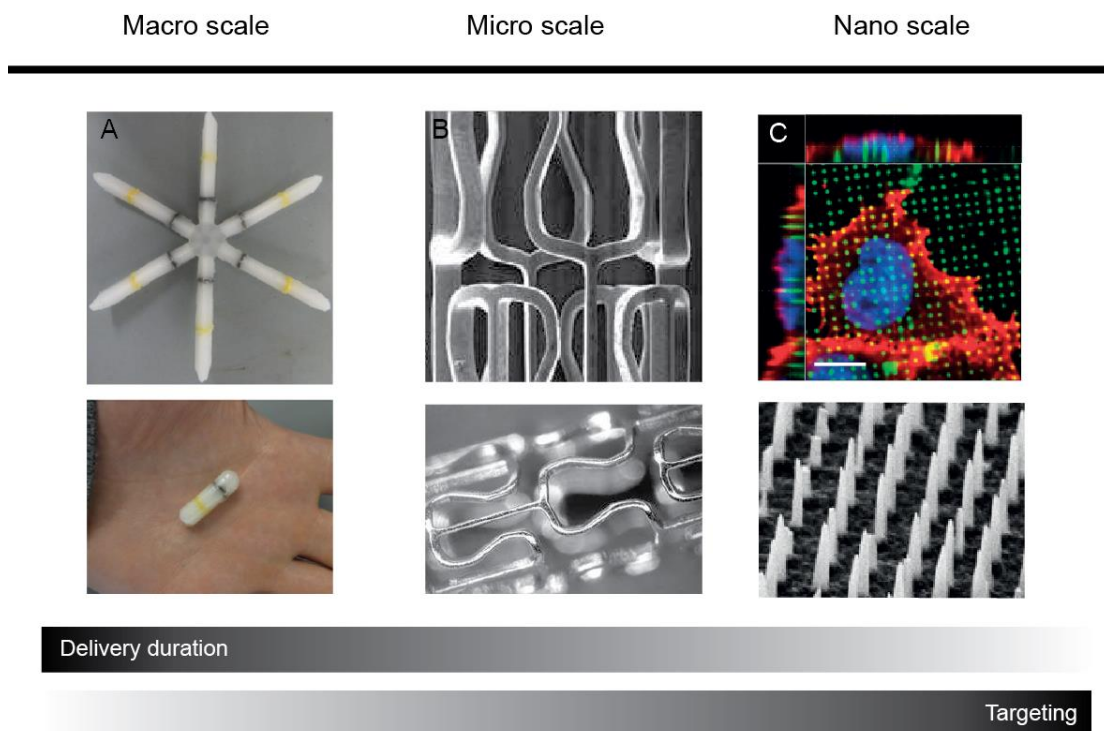
665 **FIGURE 2: Miniaturisation of controlled dosing pump systems** Infusion based  
666 devices have progressed rapidly from macroscale implantable pump systems able to  
667 deliver single therapeutics (A) to micro scaled pumps capable of delivering over 100  
668 individual doses (B). Figures were adapted from the following references with  
669 permission: A- Adapted with permission from Nature Biotechnology<sup>200</sup> © 2003; B-  
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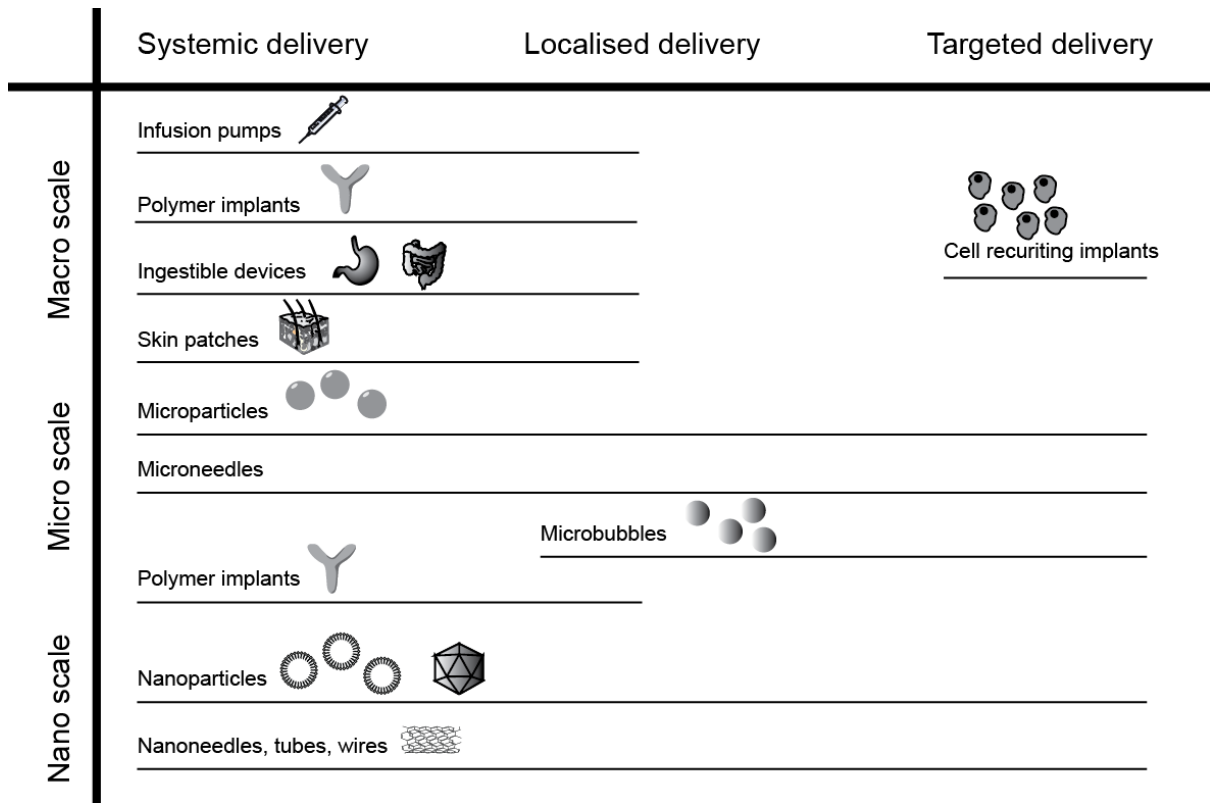
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672

673 **FIGURE 3: Polymer based drug delivery systems across length scales** Polymer  
674 based drug delivery systems offer extremely versatile morphologies for drug delivery  
675 applications across several orders of magnitude. On the macro scale, flexible polymers  
676 have been folded into capsules small enough to swallow. (A) Precision engineering has  
677 enabled macro scale stents which possess micron scale features. These features are often  
678 made of, or coated in, biodegradable polymer substrates (B) providing both rigidity and  
679 drug eluting capabilities. (C) Polymer nanoneedles can be fabricated with a variety of  
680 aspect ratios to penetrate cells for nucleic acid drug delivery. Figures were adapted  
681 from the following references with permission: A- Reprinted with permission from  
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687 **FIGURE 4: Overview of drug delivery systems by length scale** A comparison  
 688 between drug delivery strategies across length scales, illustrated by material delivery  
 689 class, scale and the targeting ability to each therapy. Due to their scale, there are few  
 690 examples of targeted macro scale drug delivery systems.



691



692 **TABLE 1: Considerations in drug delivery device design** The table provides an  
 693 extension to Figure 4, and overview of the main considerations in drug delivery device  
 694 design according to device scale. Types of device, typical therapeutics, targeting ability  
 695 and typical delivery profiles are indicated for highlighted delivery systems.

Scale	Device (administration route)	Types of therapeutic typically delivered	Targeting			Delivery Duration					
			Systemic	Localised	Targeted	Hours	Days	Weeks	Months	6 months+	Years +
<b>Macro</b>	Ingestible devices (ingestion)	Peptides, Proteins, Small molecules									
	Skin patches	Peptides, Proteins, small molecules									
	Polymer implants	Peptides, Proteins, Small Molecules									
	Pumps	Proteins, Small Molecules									
<b>Micro</b>	Microneedles	Peptides, Proteins, Small Molecules, nucleic acids									
	Microparticles	Proteins, Small Molecules									
	Polymer implants	Proteins, Small Molecules									
	Microbubbles	Proteins									
<b>Nano</b>	Nanoneedles, tubes and wires	Peptides, Proteins, nucleic acids, small molecules									
	Nanogels	Peptides, proteins, small molecules									
	Nanoparticles	Peptides, Proteins, nucleic acids, small molecules, nucleic acids									

696

697

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702

703 **DECLARATIONS OF INTEREST**

704 R.L. is co-inventor on multiple patents and patent applications describing drug delivery  
705 systems, and has a financial interest in Lyndra Inc., a biotechnology company focused  
706 on the development of oral drug delivery for long drug release. The rest of the authors  
707 declare no competing financial interests.

708

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