

# Gels for constant and smart delivery of insulin

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## Abstract

**The focus of this review is the role of gelatinous materials for oral, transdermal and peritoneal insulin platforms as alternatives to the ubiquitous subcutaneous depot approach. Hydrogels that form hydrated, cohesive materials and the topologically complex micellar types can add ligand interaction, bond vulnerability and rheological characteristics to develop reliable programmed release, including closed loop (automated basal and bolus) activity in non-oral routes. In addition, the potential protection of the protein and likely increased paracellular uptake mean that orally active insulin is feasible. While unlikely to be suitable for closed loop delivery, the driver for gut absorption is not only to increase the convenience and decrease dosage trauma, but to target the mesentery-portal vasculature rather than peripheral tissue, thus improving hepatic glycogen equilibrium and reducing the obesogenic effect and hypoglycaemic episodes.**

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**Key words:** insulin, drug delivery, polymer, gel, hydrogel, micelle, critical solution temperature, rheology, visco-elastic, closed loop, kinetic, enzyme protection, ligand, interactive, oral, subcutaneous, peritoneal

## Introduction

The discovery of insulin in 1921 and its rapid introduction as mainstream treatment for type 1 diabetes (T1D) was truly life-saving. Until then, anyone developing T1D faced practically certain death.<sup>1</sup> However, it is well recognised – almost 100 years later – that, despite many improvements in the tools for assessing blood glucose (BG) and administering insulin, those who need it for either T1D or type 2 diabetes (T2D) still run the risk of developing the complications of diabetes. Landmark randomised trials have underlined the need for a much more tailored approach to insulin therapy for both conditions,<sup>2,3</sup> with more frequent insulin doses correlated where possible to the ambient BG, the carbohydrate content of an impending intended meal and the likely forthcoming energy expenditure.

Intensive insulin therapy is demanding but has become the standard for T1D, albeit with many daily finger-sticks and the ever-present hazard of hypoglycaemia. The debate beyond T1D, in extending tight control to T2D insulin users, is interesting with many care providers advocating the upwards titration of insulin to better control BG, but a problem being that this is potentially obesogenic<sup>4,5</sup> in addition to the hypoglycaemic risk.

Parenteral insulin is not an easy regimen to manage,<sup>6</sup> whether by pen injection, patch pump or conventional pump. New insulin types, sensor technology and phone apps have improved matters, but patient acceptability, compliance and kinetic considerations are important reasons for developing the other paradigms. These are discussed here in the context of gel formulations that could be used as such by various routes or inside a device. Gels offer compatibility with insulin and tissue, enhanced uptake by tissue and protection from enzymic destruction. There is also the possibility of kinetic control to produce not only continuous dosing at a constant background rate but also combination with routes that could provide hepatocentric strategies. The latter mimic the physiological norm and would minimise the obesogenic effects of insulin. In addition, automated glucose-responsive bolus doses could be delivered by designer gels, especially where using fast administration routes would allow real-time transmission of the altered insulin dose rate, thus producing triggered and closed loop systems that could obviate hypoglycaemia. The structure and properties of gels potentially able to deliver on these ideas are discussed below.

## Suitability and biocompatibility of gel carriers

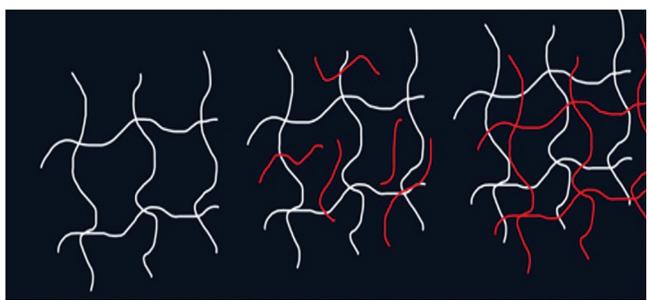
Soluble insulins, whether native or biosynthetic monomeric types, are charged polar molecules.<sup>7</sup> Consequently, they are water soluble although this is pH- and additive-dependent. Suitable candidate carriers for insulin delivery via the routes mentioned are therefore also often highly hydrophilic, arising from natural and synthetic sources. Water-soluble, dispersible or swellable gels feature strongly in the literature with impressive inventions for solving the problems of diabetes treatment, including by closed loop. Hydrophobic and dried (xero) gels exist, but this review section will focus on gelling systems with which insulin is likely to interact, using various types of carrier linking and mechanisms built in to achieve the goals of dependable but flexible dosing. Hydrophilic gel types are additionally appropriate because of biocompatibility, especially if of natural origin such as chitosan, heparin, casein, pectin, alginate, tragacanth, dextran and gelatin-based materials.<sup>8</sup> Ultimately, tissue response

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**Figure 1.** Simple gels and the incorporation of second components that bond around the original structure to form interpenetrating gels; both types are used to develop materials for drug delivery



depends, however, on many demanding factors and some synthetics provide properties that are useful (eg, cyclodextrin, acrylics, etc). Some gels are bio- and/or muco-adhesive, a property that can overlap with viscosity but differs from it and can be used to extend residence time in, for example, the gut.<sup>8</sup> Intense research has led to materials that are capable of forming safe oral, parenteral, implantable or mucous membrane delivery devices for insulin basal and bolus dosing,<sup>9</sup> although none has yet reached the clinic.

### Gel structure

A gel is typically described as a semi-solid, often with the continuous permeation of at least one three-dimensional structure (the gelator system) with a second (normally a liquid 'solvent'). Where more than one gelator is present, there may be a synthesised interlacing of solvated polymer frameworks that precludes separation unless bonds are broken; this is known as an interpenetrating network (IPN), discussed under hydrogels (Figure 1). Gels may be simple or smart with ligand interaction for differential delivery.

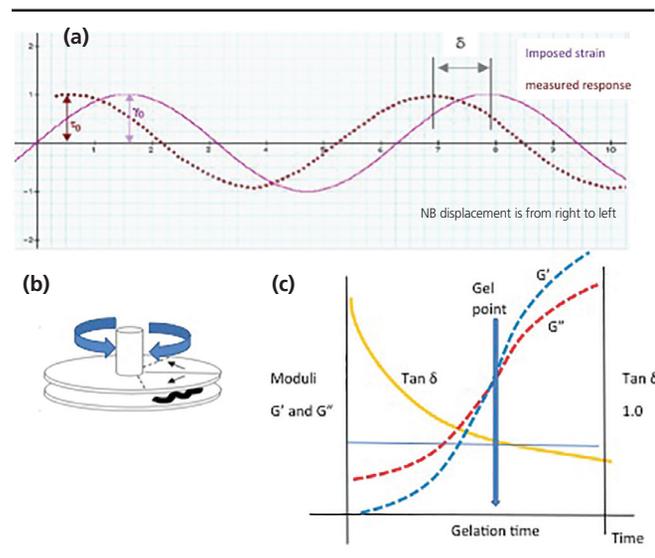
### Gels designed to deliver co-formulated peptides

The entrapping of co-formulated peptides such as insulin in the network depends on specific polymer characteristics and the gelling mechanism. The gelator may produce simple entanglements, especially if branched. Alternatively, there may be physical interlocking because of attractive forces acting between specialised regions (see Release mechanism: 2 – Bolus below) or there may be covalent bonding (see Hydrogels below).

Some gels are not homogeneous but are formed by the combination of particulates including a range of micro- and nano-structures such as minigels, micelles and liposomes (see below). Each hydrated gel type produces internal solvent-filled spaces potentially on the scale of the peptide inclusions that are present either as molecules dissolved in the solvent phase or as much larger undissolved drug particles where the displaced polymer network forms around them.

The polymeric gelators are usually in lower concentration than the solvent and can be similar to materials routinely used

**Figure 2.** (a) Parallel plates used in oscillatory mode, (b) the imposed strain and response signals, and (c) the captured parameter data translated into moduli and tan delta plots



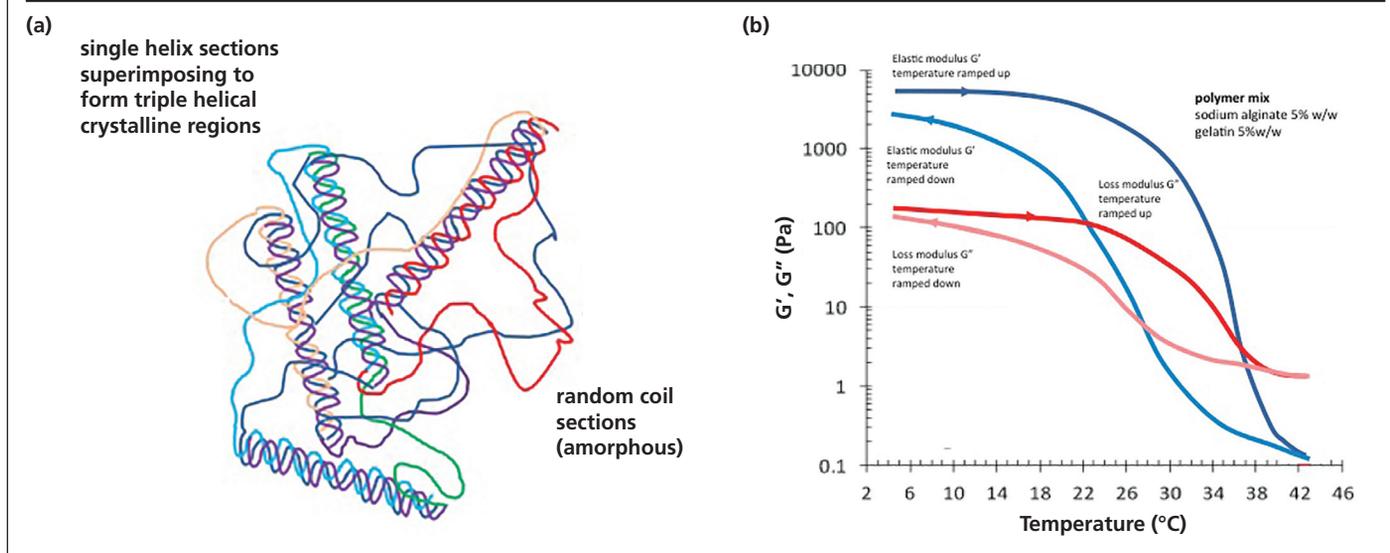
to increase the consistency of liquid pharmaceuticals and foods – for example, as suspending and emulsifying agents like polyacrylic acid. The technical specification that separates mere thickening in consistency from true gelling is revealed in viscoelasticity measurements (Figure 2), so that a gel has a value of less than unity for tan delta (or damping factor) which is the ratio of the loss modulus,  $G''$ , to the elastic modulus,  $G'$ .<sup>10</sup> In descriptive terms, this means that the loss modulus becomes less prominent than the elastic counterpart as a system gels. The perfectly elastic solid would return the imposed shear signal synchronously and thus any shift (the phase angle delta, for which the tangent is normally stated) represents the  $G''$  energy loss both as heat and viscous flow from the theoretical perfect elastic response (the elastic modulus).

Relevant properties are typically measured by oscillatory rheometry using a stress amplitude that is within the viscoelastic limit for the material concerned, so that with the almost imperceptible oscillation, the structure remains undamaged throughout the stress testing. Typical oscillation tests involve changes with time, shear rate frequency or temperature sweeps and can reveal critical tan delta values occurring as the physical chemistry changes to allow the elastic modulus to dominate or fade. Rheometry is a powerful tool to hone the gel behaviour for relevance to insulin drug delivery because the viscous component relates to the likelihood of drug diffusion, assuming the pore size is appropriate.

### Hysteresis

In some gels, such as agarose and gelatin, the physical stabilisation arises on cooling from interlocking helical segments in otherwise linear polymeric chains (Figure 3a). Repeated cycles for these often give characteristic hysteresis loops if the complex

**Figure 3.** (a) The structures formed as gelatin cools. (b) Plotted modulus graphs showing hysteresis

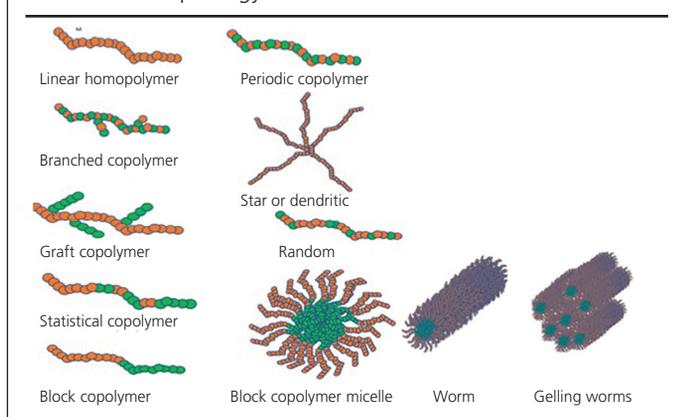


structures reform more slowly than the test cycle time (Figure 3b). Hysteresis creates uncertainty in the gel performance for drug delivery but, in any case, gel formulations that lose consistency at body heat are obviously of limited use for insulin delivery, since they are neither injectable (unless hot) nor are they gelled at body temperature. Even so, these agents are biocompatible and have often featured in more complex formulations.

### Innovative design using gelling polymers

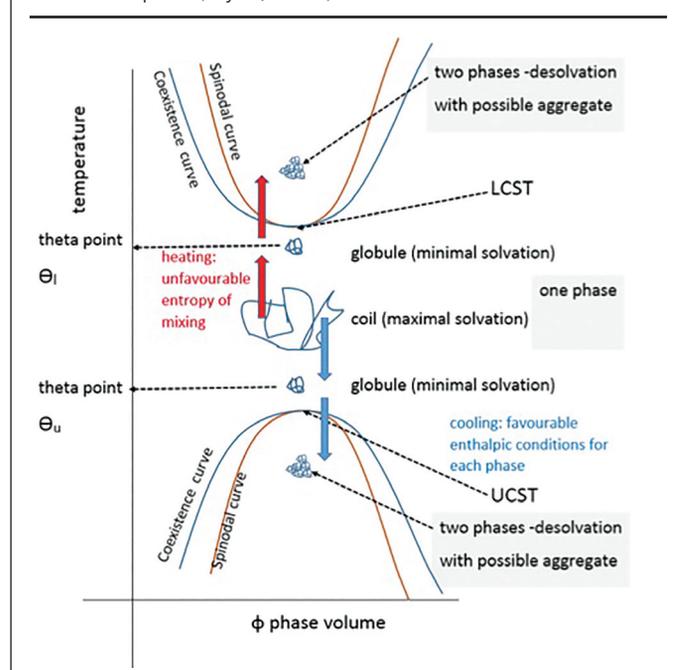
Synthetic co-polymers comprise combinations of monomers, synthetic or otherwise, that can be incorporated in linear or branched, regular or random patterns, including grafted and block types (Figure 4). These have been exploited for materials useful for convenience of administration, controlled release, specific responses and target recognition, all of which have a place in the delivery of insulin, other peptides or drug molecules in general.<sup>11,12</sup>

**Figure 4.** Various polymeric types that form gels with properties determined by monomeric inclusion and morphology



Block polymers may micellise and group to create gelling phenomena that may change with ambient conditions (Figure 4). Insulin can be carried within or between the structures. One special effect is reverse thermogelling, as with the well-known poloxamer family (eg Pluronic®). Poloxamers have polyoxyethylene (POE) and polyoxypropylene (PPO) sections as a POE-PPO-POE sandwich that, in appropriate concentration, cause gelling as the single molecules micellise in an entropically-driven self-association of hydrophobic moieties as temperature increases above a critical level.<sup>13</sup>

**Figure 5.** Upper and lower critical solution temperature plots (Taylor, 2017)



This broadly fits with the coil to globule shrinkage as the structure approaches critical solution temperatures. The lower critical solution temperature (LCST) characterises the behaviours of reverse gelling materials (ie, those that gel on heating rather than cooling) (Figure 5).<sup>14</sup>

Pluronic F-127<sup>®</sup> is liquid when refrigerated but, at suitable concentration, gels above about 20°C (depending on purity). It is therefore solidified at body temperature, making it relevant for in situ gel formation deliverable as a cold injection. Choi and Kim used a more persistent gelling polyester-POE-polyester (γPGLA-POE-γPGLA) synthetic to deliver insulin in rats,<sup>15</sup> but Chen *et al* described a similar system that may have relevance for detemir. They examined both the physicochemical characteristics and the release in mice<sup>16</sup> and confirmed the formation of core-corona micelles, but which in this case incorporated liraglutide into this structure because of its own amphiphilicity rather than randomly as a passive passenger where it might otherwise be held within or between micelles in the analogous poloxamer. This allowed lengthy sustained release and also degradation to non-toxic products.

Micelles interact with tissue features such as tight junctions in a manner crucially different from that of larger particles, but they also can transport insulin across membranes. The incorporation of recognition ligands such as transferrin, niacin, lectins and antibodies or cell-penetrating peptides such as penetratin make a variety of effects possible for the specialised delivery of insulin<sup>17</sup> (see also Figure 8).

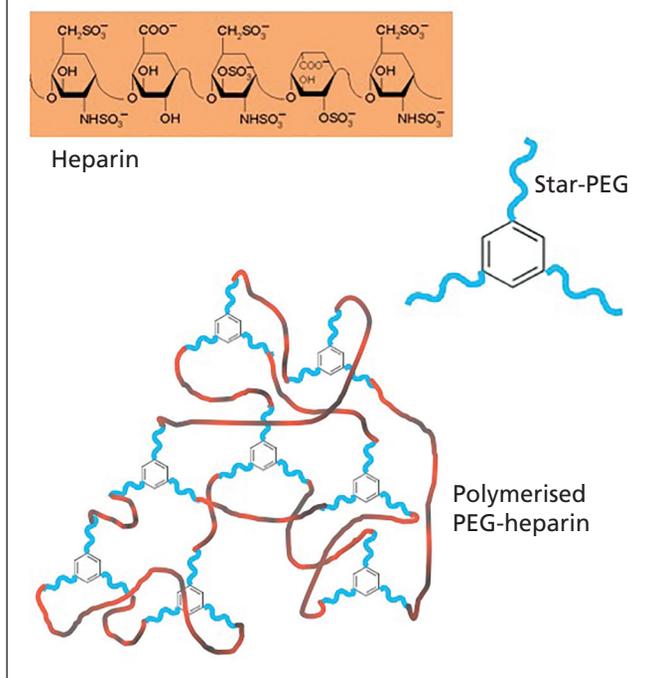
## Hydrogels

A different type of gel system occurs where stabilisation occurs between gelator linear polymers. This is mediated mainly by covalent links, but gelatin is a physically stabilised hydrogel, as discussed above. The cross linking agents can be double or multivalent in terms of the connections they make and can therefore also be defined as gelators, imposing three-dimensional structure on linear systems that might be viscous but would not otherwise technically gel. These can also be interpenetrating gelators, as discussed earlier (Figure 1). The resulting materials are hydrogels with the cross link density influencing the rigidity and the pore size either in bulk or in gelatinous particulates (see Minigels below).<sup>18,19</sup>

Hydrogels have been formed from a variety of natural and synthetic materials including the innovative star-PEG gelled heparin, as shown in Figure 6. As with micellar gels, smart ligands can be designed to create responsive materials.

Hydrogels are insoluble because of their very high molecular weight, although often soft and pliable when hydrated. In that state they have interesting condition-dependent shrink-swell and phase change characteristics where the analogous non-cross linked materials have differential solubility instead.<sup>20</sup> Some materials can be injected to form covalently stabilised hydrogels in situ by, for example, enzymatic coupling.<sup>21</sup> Nguyen *et al* have recently described the in situ hydrogel formation of novel pentablock copolymer sols, where insulin was released from co-formulated chitosan inclusions.<sup>22</sup> Photo-cross linked types have

**Figure 6.** Heparin, a polymerised aminosaccharide converted to three-dimensional gel, using star-PEG

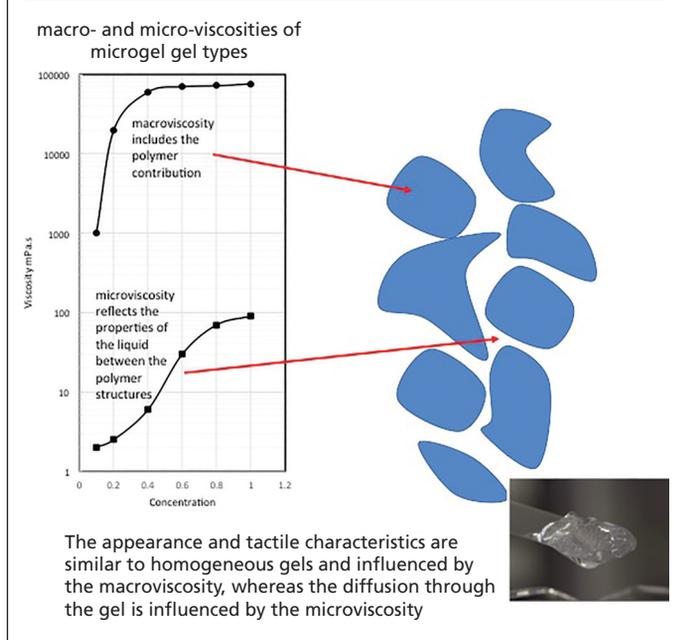


also been suggested, such as that described by Custodio *et al* for hydrogels formed from laminarin, a low molecular weight glucan.<sup>23</sup> Some can be placed subcutaneously as dried pellets to hydrate in situ and deliver peptides such as insulin long term. Disadvantages are that any implant into tissue could be immunogenic and attract fibrous growth, can contain toxic monomers, may harbour infection or invite opportunist blood-borne infection.<sup>24-26</sup> If not safely metabolised, they may also need surgical removal and thus be unsuitable for implanted insulin delivery.

However, the same types of materials can be formulated for other routes of administration such as oral, other mucous membrane or transdermal. Minigels (particulate hydrogels) present a useful vehicle in this regard. They are closely packed, globular hydrates that give the tactile and visual impression of a confluent gel. An example is polycarboxylic acid polymers of various types (carbomers, eg Carbopols<sup>®</sup>). Some versions of these are cross linked with allyl sucrose, comprising particles of about 0.2 μm diameter and a molecular weight of several billion. They flocculate to a diameter of up to 7 μm, but when hydrated may approach 70 μm.

These particles can carry molecular cargo within the aqueous pores produced by the cross links<sup>27</sup> if the drug molecule is small enough. Larger molecular weight agents can certainly be carried between the hydrated particles (minigels) and this space can also accommodate undissolved finely divided solid. For insulin, the latter could be crystalline or amorphous precipitate, provoked by high concentration or pH. The addition of protamine or excess zinc also causes loss of insulin solubility and could be accomplished in these gels. The viscosity of such a gel is compli-

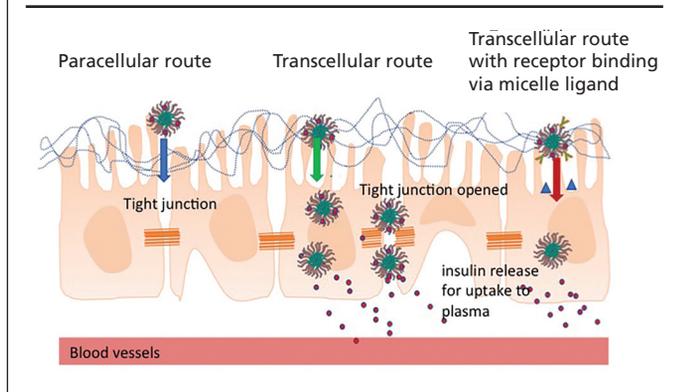
**Figure 7.** The appearance of homogeneity belies the particulate nature of minigels that contain water channels and therefore have a macro- and micro-viscosity



cated by the dual nature of the material having an overall consistency as measured by rheometry but a microviscosity of the channels between minigels, in which the drug diffusion is more likely (Figure 7). Reverse micelle imprinting can selectively trap structures such as insulin,<sup>28</sup> and interactive ligands<sup>29</sup> that respond to glucose by a rheological change are also possible.

Smaller entities such as micro- and nano-particles (1–100 nm), including nano-sized micelles with their ability to access tight junctions, have been fabricated to carry insulin (Figure 8). Nanoparticles can be gelatinous because of their polymeric form but, in any case, their surface energy density differs from that of larger entities<sup>30</sup> and they potentially overcome barriers such as hostile gut environments and apical impermeability.<sup>17,31</sup> This

**Figure 8.** Transport across membranes of simple and ligand-bearing micelles released from micelle gels

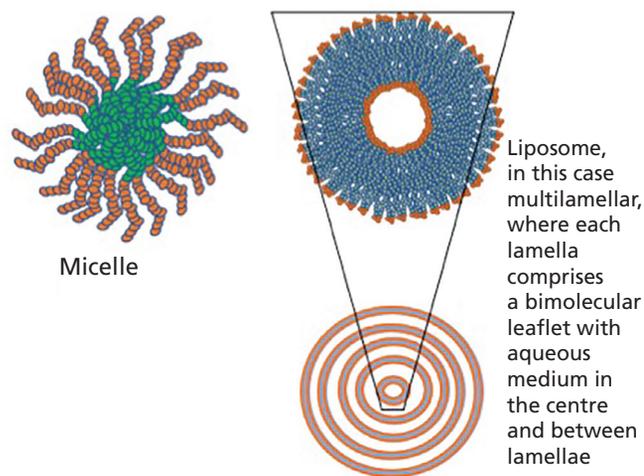


latter advantage is important because of the mesenteric drainage to the portal system. The first pass effect associated with oral delivery is doubly useful because the dose is short lived, which may mitigate hypoglycaemic threats, but also a major antihyperglycaemic effect is the polymerisation of glucose to glycogen in the liver. Subcutaneous insulin produces a non-physiological ratio of peripheral to hepatic effects by comparison that can promote the unwanted accumulation of fat.<sup>32</sup>

Nano-structures vary considerably. Unlike micelles, many are particles that are not self-assembling and, apart from size, have more in common with both minigels and microparticles. The composition varies from natural polymers such as chitosan, alginate, dextran, hyaluronic acid and other polysaccharides,<sup>33-36</sup> but also includes synthetically altered chitosan such as carboxylated, trimethylated (TMC), ethyl (DMEC), mucin-complexed,<sup>37</sup> carboxymethyl (CMCS), oleic acid-zinc insulin complexed,<sup>38</sup> thiolated chitosan<sup>39</sup> and vitamin B12-conjugated chitosan (VitB12-Chi) among many others. Chaturvedi *et al* included a complex multicomponent particle designed to optimise gut absorption.<sup>9</sup> Synthetics such as poly( $\gamma$ -glutamic acid) ( $\gamma$ -PGA), phospholipid  $\gamma$ -PGA conjugates and polyacrylics such as the various Eudragit® materials have also been used. Some of these are built layer by layer to achieve particular goals (as discussed below in the context of glucose sensitivity),<sup>40</sup> as are further micellar examples and the related liposomal structures.

Superficially similar to micelles are liposomes (Figure 9), which are uni- or multi-lamellar vesicles that self-assemble when phospholipids of various types, sometimes co-formulated with

**Figure 9.** Liposomes in context with micelles. The micelle is much smaller and formed from block polymers in this case (differing from surfactant micelles) while the liposome is formed from lipid bilayers with polar head groups (orange) on the inner and outer aspects, the lipid chains in the interior of the double layer. Liposomes can comprise one or many concentric bilayers. Both micelles and liposomes can form tubular gelling structures



cholesterol, are combined with water.<sup>40</sup> Each lamella consists of a bimolecular leaflet producing hydrophilic and lipophilic domains that can carry not only lipophilic material but hydrophilic cargo like proteins and peptides, including insulin.<sup>41</sup> Liposomes can reach 2.5  $\mu\text{m}$ , comprising single or concentric bilayers, depending on the method of preparation. In high concentration they lose the spherical shape and form an ordered gelatinous tubular mass. Zhang *et al* recently described an insulin-loaded phospholipid-based phase separation gel that appears to form vesicles, possibly liposomal, during processes releasing the insulin.<sup>42</sup>

### Protection

A gel should offer protection for the fragile insulin from hostile environments of administration sites such as extracellular matrices, gut fluids, etc, and yet foster uptake at the apical surface and be benign in terms of the biological integrity, as described above.<sup>8</sup> Covalently bonded gels can be enzyme-resistant, the water-filled pores between polymer structuring creating protection against insulin proteolysis because of differential transport for insulin egress and enzyme ingress. It has relevance, particularly for the oral route of insulin delivery, where proteolysis is the main destructive route.<sup>43-46</sup> The polymer chosen should be compatible with gut pH, but also with the insulin and its native folded state.<sup>8</sup>

Other means exist of enzyme protection by gelation such as the use of enzyme inhibitors. Those containing the  $\gamma$ PGA-DTPA conjugate are inherently protective against proteolysis as well as being a structural component,<sup>47-49</sup> and both albumin and aprotinin have been suggested as sacrificial targets for co-formulated insulin<sup>33</sup> – for example, in microspheres.<sup>50,51</sup>

### Release mechanism: 1 – Basal

The release mechanisms of dissolved insulin from the protected storage site within a gel include dissolution, diffusion control and, in addition, degradative changes in the polymer<sup>52</sup> (Figure

10). For example, a drug release at a sustained basal rate from block polymer gels, bulk gels or hydrogels might simply occur by being able to dissolve or diffuse out, depending on whether it exceeded solubility in the gel solvent when formulated. The kinetics can be zero order (ie, delivery rate is constant) in some circumstances. Alternatively (or additionally), where covalent bonds are involved, release could involve chemically or enzymatically-induced bond breakage to remove obstruction formed by polymer entanglements. While unlikely with a fragile peptide, similar mechanisms could release drug covalently bound to the polymer.<sup>53</sup>

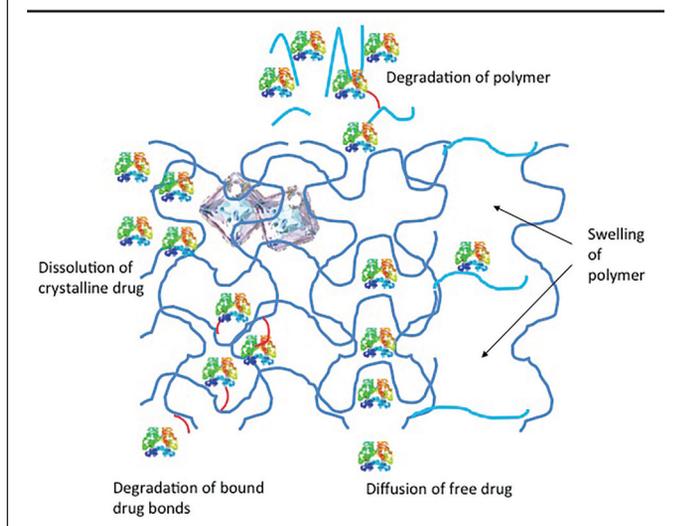
### Release mechanism: 2 – Bolus

For optimally effective diabetes control using gel-administered insulin, the basal dose rate must be supplemented by glucose-responsive bolus doses that operate automatically and preferably repeatedly to deal quickly and effectively with meal-induced glucose spikes without risk of subsequent hypoglycaemia. A limited triggered system with oral gel responding to gut glucose can hold only the dose appropriate for the daily gut transit time. It would depend on gut glucose content, absorption site and conditions, therefore delivering possibly inappropriate insulin doses for systemic circumstances. Subcutaneous tissue behaves more predictably and implantable gels could hold a larger depot. Skin-based closed loop therefore has advantages, albeit with the known differential with BG and also lacking the hepatocentric delivery of gut insulin.

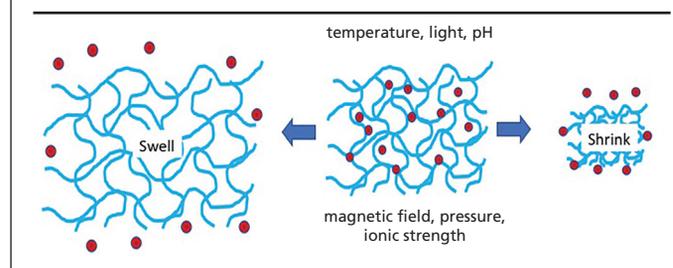
The methods for formulating insulin to act in a glucose-responsive way rely on modified or normal insulin formulated with bulk or dispersed carrier materials that interact with the environment to create a differential release rate. Specific and non-specific binding, chelation and charge-related interactions are of particular importance for designs to form the basis of insulin boost dosage in either triggered or closed loop release (in addition to a basal dose rate).<sup>54</sup> Light, magnetism, electrical signal, salts, pH and ionic strength mechanisms<sup>55-58</sup> are all capable of physicochemical stimulus-sensitive design into polymers used for gels for insulin delivery (Figure 11).

The most useful mechanisms would be more clearly glucose-specific, however, so that hyperglycaemia would trigger a prompt and appropriate dose of insulin such that the BG is kept within the target range. The three mechanisms relate to glucose

**Figure 10.** Various mechanisms of drug release identified for gels



**Figure 11.** Innovative designs using physical stresses cause either swelling or shrinking, each of which can result in release



interactions with glucose oxidase, phenylboronic acid and the lectin concanavalin A. These and others have recently been reviewed by Shen *et al.*<sup>59</sup>

### Glucose oxidase (GOD)

A common mechanism is the pH-linked change that is related to the coupled enzymatic oxidation of glucose to gluconic acid.<sup>60</sup> For GOD-related mechanisms, the insulin could be a passive passenger or may participate in the mechanism in some way, as exemplified by Fischel-Ghodsian and Newton many years ago in which the solubility of tri-lysyl insulin was manipulated by altering the net charge due to the GOD oxidation.<sup>61</sup>

However, in many cases, a proton-sensitive polymer will either be charged or neutralised as a result and expand to release insulin or contract to expel it (Figure 12a).<sup>62</sup> Li *et al.* have described a modification of this in a hydrogel made from a self-assembling peptide with alkaline amino acid side chains that are prevented from linkage when the pH drops due to the oxidation of glucose. This releases insulin from the loose structure.<sup>57</sup> A recent variation used GOD to modify the aggregation of oppositely charged chitosan-PGLA nano-complexes to release insulin responsively.<sup>49</sup>

Many variations have been devised on the basic model, including liposome types containing GOD, where the polymeric decoration is destabilised by the protons generated to form leaky micelles, thus dispensing insulin in a once-only trigger (Figure 12b). Yu *et al.* have described a sophisticated derivative mechanism of

self-assembled micelles comprising cross linked hyaluronic acid with pendant nitroimidazole groups presented in a microneedle array. These undergo a hydrophilic change during the oxygen consumption required to produce gluconic acid (ie, becomes relatively hypoxic).<sup>63</sup> Alternative nitroimidazole nanoparticulate systems with GOD are described by Jana *et al.*<sup>64</sup> and in a PEG-polyserine micellar model by Zhao *et al.*<sup>60</sup> A variation with an alginate carrier cross linked with ferric ions and containing enzyme-coated silica particles fosters the oxidation causing the irreversible degradation of the alginate releasing the insulin.<sup>65</sup>

The GOD-based systems have two serious shortcomings. First is that any local pH alteration can accomplish the same changes. In addition, the build-up of hydrogen peroxide must be addressed to prevent imposition of a suppressive equilibrium. Catalase has been incorporated to deal with this in simple and complex examples, including a microneedle version that has a conical core containing the insulin as a PVA conjugate plus the enzyme while the shell surrounding it comprises catalase to eliminate peroxide, continuously re-enabling the device but also reducing an inflammatory effect.<sup>44,66,67</sup>

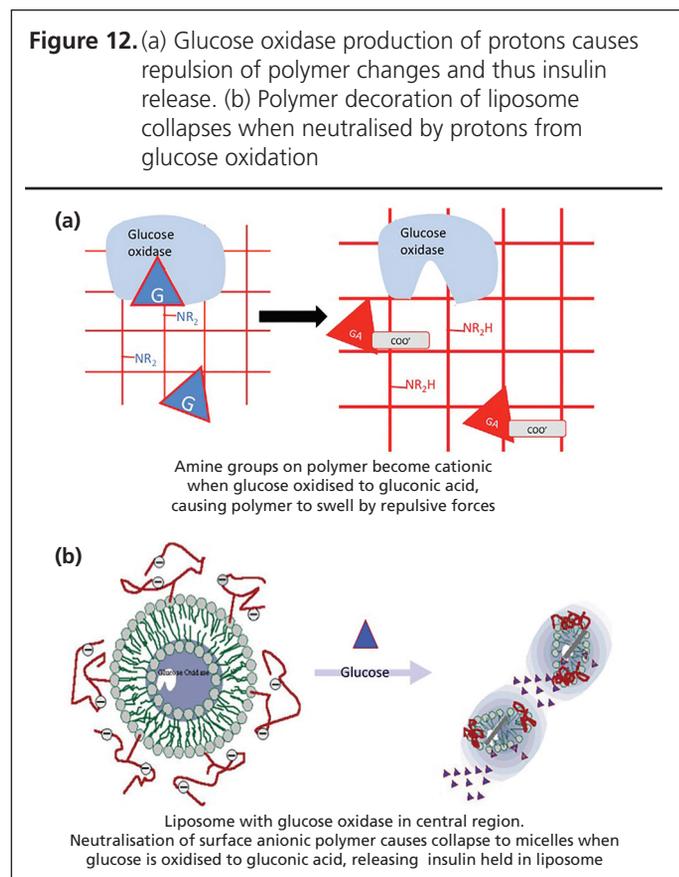
### Phenylboronic acid

Various designs are based on phenylboronic acid (PBA), which interacts by hydrogen bonding to the vicinal OH or cis-diol moieties of glucose (Figure 13) and can operate in bulk gels, gelatinous particles and vesicles.<sup>68-70</sup> This is not entirely specific but it is widely discussed for triggered dosing, sometimes by manipulation of the pI.<sup>71</sup>

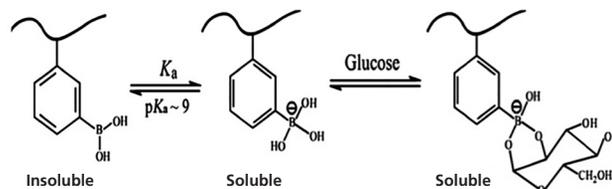
Li *et al.* describe a hyaluronic acid gel intended to deliver such particles to the enteric apical surface or to be injected subcutaneously.<sup>72,73</sup> Other nanostructures bear the glucose-sensitive gel-forming material on the exterior surface.<sup>74</sup>

Zhao *et al.* describe insulin in PGLA-PBA microparticles with cross-linking hyaluronic acid as physical bonding to the vicinal OH groups in the glucuronic acid units. As glucose enters, it displaces the link to occupy the PBA site, loosening the gel structure and allowing insulin to escape.<sup>73</sup> PBA systems are well enough developed to have been studied for the effects of gamma and neutron irradiation for sterilisation.<sup>75</sup> Masumoto *et al.* have published work in rodents using a PBA closed loop system.<sup>76</sup>

Minigels with imprinted glucose receptor sites can be formed by polymerising PBA in the presence of glucose, which acts as a template and is then washed out leaving the imprint. Materials like this can behave like lectins, the imprinted pattern imposing a multivalent affinity for glucose.<sup>77,78</sup>



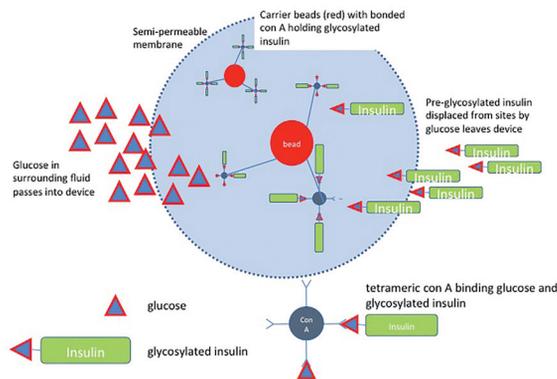
**Figure 13.** The reversible response of soluble forms of phenylboronic acid to glucose



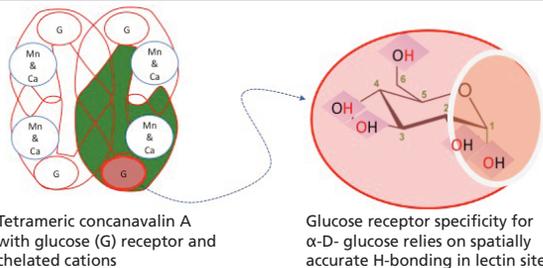
**Concanavalin A type**

The lectin con A is a tetrameric protein of MW about 110 kDa. Each monomer has a receptor for glucose and several insulin controlling mechanisms have been based on this interaction, including the original Brownlee and Cerami model that had the

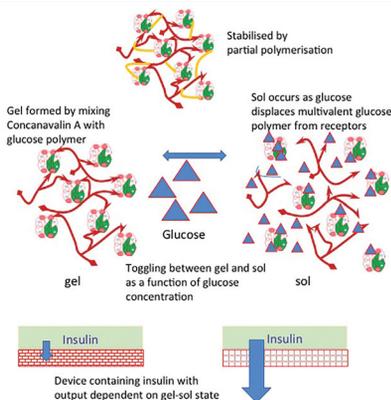
**Figure 14.** Brownlee and Cerami model for competitive displacement of glycosylated insulin by glucose from specific receptors on concanavalin A bound to beads inside a membrane permeable to insulin and glucose



**Figure 15.** Highly simplistic depictions of the receptor interactions of glucose and concanavalin A



**Figure 16.** The closed loop system based on gel formation with dextran and concanavalin A, stabilised by light polymerisation. Gel governs the output of insulin from a reservoir delivering to peritoneal tissue



immobilised lectin on beads inside a semipermeable arrangement (Figure 14).

The lectin interacted with insulin glycosylated at the B29 lysine which allowed the insulin to retain activity.<sup>79</sup> The fully assembled tetrameric protein has four receptor sites for glucose, for which it is fairly specific in terms of human physiological tissue components (Figure 15).

It can interact with glucose itself or saccharides bearing an appropriately configured glucose terminal unit forming a three-dimensional network with suitable branched glucans. Nanoparticulate gels have been made from this lectin and a glucan but also from synthetics such as glycosylated acrylate (glycosyloxyethyl methacrylate or GEMA).<sup>80</sup> Their shrink-swell activity works either as a sensor or as an insulin releasing agent.<sup>81</sup>

A polymerised lectin gel is the basis of an in vivo peritoneal system by Taylor in which insulin output is controlled by a variable viscosity gel from an implantable and refillable reservoir (Figure 16) and extends the insulin implant concept<sup>82,83</sup> to closed loop.<sup>43,84-87</sup>

**Conclusions**

Gels provide a biocompatible medium for the creative delivery of insulin. They can occur in forms such as semisolids but also as



**Key messages**

- Hydrophilic gelatinous formulations are good candidates to develop into carriers for insulin
- Gels are formed from a variety of materials including micelle agglomerates, micronised materials and interpenetrating polymer strands that may be covalently or physically cross linked to form hydrogels and minigels
- Gels can be formed from natural and synthetic polymers, are often biocompatible and frequently biodegradable
- The physicochemical properties of gels make them able to maintain solubility or accommodate depot forms of chemically divergent insulin types
- Gel formulation of insulin can provide protection from gut enzymes, providing a means for oral administration, one advantage of which would be the provision of hepatocentric delivery
- Some polymeric components of gels promote paracellular uptake of proteins by the gut apical surface
- Polymers and self-assembling particulates are modifiable in ways that confer properties useful for interactive functions, that produce potential closed loop mechanisms responding to ambient glucose levels

hydrated particulates with viscoelastic properties and a range of structure, size and function, suitable for delivery by several useful routes. This may mean that the treatment of diabetes of both main types may not, in the future, be restricted to subcutaneous injection. Insulin formulation could well comprise gelatinous forms to act as the naked substance or within devices, each creating effects such as hepatocentric, triggered and closed loop delivery. Gels can protect the peptide contents from hostile environments and those with nanostructures may gain apical access or otherwise make routes possible, such as oral. These may be more convenient, increasing compliance and therefore promoting euglycaemia. Closed loop delivery is a further worthy aim where the insulin dose is tailored closely to changes in the BG. Presently, closed loop delivery is experimental and either biologically or electronically controlled. Neither of these is in general use and both still have significant drawbacks. Development of gel systems is currently also addressing the closed loop aim and, with the polymer synthesis variety available, seems worth the effort to offer an efficient counter to the complications of diabetes.

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