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TIMERx®: novel polysaccharide composites for controlled/ programmed release of drugs in the gastrointestinal tract

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Over the last 100 years tablets have grown from first invention to becoming the world's leading medicinal form, by any measure. This article considers some of the reasons for the pre-eminence of pharmaceutical tablets. Particular attention has been given to the role of controlled-release tablets and to a very versatile hydrogel-based controlled-release technology, called TIMERx®. The unique nature of TIMERx intermolecular physical chemistry is described in relation to the technology's potential to provide any one of a number of different release profiles, ranging from zero order to chronotherapeutic release. The unusual nature of TIMERx technology lies in its ability to provide different release kinetics by the manipulation of molecular interactions. This 'molecular engine' replaces the need for complex processing or novel excipients and allows desired drug release profiles to be 'factory set' following a simple formulation development process. The article describes the physicochemical interactions of TIMERx technology at a molecular level and how they can be manipulated by formulation considerations. The article describes how TIMERx technology has been developed to the point where today it underpins a number of marketed pharmaceutical CR products as well as products under development by Penwest Pharmaceuticals.

Keywords: controlled release, tablet, TIMERx technology

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1. Overview of the market

For most of the last five millennia, medicines have evolved very slowly in different countries to meet the gradually changing needs of people and their societies. However, over the last century the pace of change has quickened to match the increasing technical demands placed on medicines both to deliver ever more potent drugs safely and enable optimum therapeutic performance of the drug in the patient's body. In particular, the last 100 years has seen the burgeoning growth of the compressed tablet into the present day's predominant dosage form. Tablets occupy the position they do today because they effectively optimise the needs and requirements of the various interested groups in healthcare: patients, prescribers, providers, pharmaceutical companies and regulators.

The needs of the first and second groups, patients and prescribers, can be considered together, as both are joined in a desire to have an effective medicine. In the case of the patient, the fastest possible return to health is axiomatic, and in the case of the prescriber there is the added desire to avoid the requirement to see even the most congenial patient back in the consulting room the following week. We will assume that the prescriber has accepted that the drug will do what he has read in the medical and scientific literature and that the patient believes the prescriber along with various internet sites they may have also consulted. In that case, all that is left is for

them to select the best way of getting that drug into the patient's body. In an increasingly mobile society, tablets are a very attractive choice for many adults, allowing the medicine to be taken easily and conveniently with a minimum of fuss: no measuring out, painless, inconspicuous and, hopefully, not unpleasant, so the patient is ready and willing to take the next dose in a few hours time if necessary. Even in cases where either the prescriber or their patient may have a preference for the use of a skin patch or an aerosol over taking a tablet, this may not necessarily mean that the tablet form is not prescribed. Because the point has been reached where someone has to pay for the medicine and if it's not the patient themselves, then both the prescribers' and patients' medicine preference will be influenced by the willingness of their healthcare provider, which could be a national health service or a medical insurer, to 'pay up'. Today, tablets are generally the most cost-effective way of putting a unit dose of medicine into the patients' hands.

The next interested parties in the chain are the pharmaceutical companies who produce the medicines that the healthcare providers make available to the prescribers and patients. It was the newly emerging pharmaceutical companies that stimulated the introduction of the tablet from the beginning of the twentieth century and have encouraged its exponential growth since that time. Their reasons are partly financial: tablets are a highly cost-effective means of producing medicines. However, tablets also provide an excellent means of achieving good technical performance, like high dose uniformity, safety and drug stability. Drug stability relates, eventually, to shelf life and in a worldwide market, the ability to manufacture tablets in one place and ship them around the world for eventual consumption up to 2 or more years later, is a valuable asset. Tablets have one other big shot in their locker for the pharmaceutical companies who research new drugs. To bring a new molecular entity to most major markets today takes the lion's share of the patent life granted by national governments to give the innovators protection from competition and allow them some reward for making the discovery. For pharmaceuticals, this protected period from competition is the part of the new drug-product's life that allows the innovator company to make a return on its investment. And this period is disappearing fast as the world's regulators demand lengthier evaluation of safety and efficacy before approving a new product for sale. In recent years, pharmaceutical companies have seen their reward period shrink further and further, and have turned to tablets to help them out of the fix. Henry Wellcome, one of the commercial pioneers of the original compressed tablet, would have approved of their solution. It starts with a novel technical solution to a problem that can create new protectable intellectual property.

Many medicines, including tablets, still require patients to take three or four doses each day in order to maintain therapeutically effective blood levels of the drug in the body. However, for many patients, taking tablets so frequently is a big disadvantage and compromises therapy: when was the last time you woke up to take your very early morning penicillin tablet at the correct 6-h interval? Good for you, if you did, but when you join the over eighties, taking 12 different tablets a day, you'll definitely be glad to know that help is at hand. The pharmaceutical companies have come up with all sorts of new types of tablets that solve the problem of multiple dosing so that patients only need to take one, or at most, two tablets daily of each of the drugs they have been prescribed. These so-called 'sustained' or 'controlled-release (CR)' tablets also have other benefits for the patient, such as reducing side effects and further improving the effectiveness of the original drug. The technical advantages of CR tablets bring potential market advantages [1].

The final link in the chain confirming the tablets position as the most widely used medicinal form is made up of governmental agencies. The government regulators are medicines regulatory agencies, like the FDA in the US, the European Agency for the Evaluation of Medicinal Products (EMEA) in Europe and others around the globe, that ensure that all new medicines are safe to use and an effective treatment for the purpose claimed. Because tablets provide all the necessary safety requirements, such as dose weight and drug content uniformity, together with locking the drug in a stable unreactive chemical environment, tablets get off to a good start with the medicines regulatory agencies. There are no other medicinal forms in use today that have proved as capable of satisfying the requirements of all interested parties, from patients to regulators and pharmaceutical companies, and for the range of drugs and therapeutic indications as tablets.

2. How the technology works: the molecular engine powering a TIMERx® tablet

CR tablets that prolong drug delivery have one particular technical feature in common: they all have a barrier zone that restricts the free movement of drug into the lumen of the gastrointestinal (GI) tract. In many cases the barrier zone is provided by a tablet coating or core matrix that remains in place and through which the drug moves; for example, due to differences in a diffusion concentration gradient or osmotic potential. Less commonly, the barrier does not remain in place but is 'lifted' with time by the actions of dissolution or diffusion. In this case, the drug can be released into the GI tract in either particulate or molecular form. Recent reviews of the different types of drug delivery technologies include those by Kim [2], Mathiowitz [3] and Farrell *et al.* [4].

Most non-swelling matrices, as well as some conventional hydrogel matrix tablets, control release as a result of providing a constricted and tortuous pathway, which remains relatively unchanged over time and acts to restrict solvent diffusion into the core and counter-diffusion of the drug solution from the tablet. This type of diffusion restriction constitutes a 'fixed barrier' type of release control and most commonly results in first-order release kinetics. Alternatively, some matrices erode

or dissolve over time so that the diffusion path length and structure changes, to the extent that some drug release may also occur by a free surface dissolution mechanism. This type of changing diffusion/dissolution release mechanism constitutes a 'lifting barrier' type of release control that can generate exponential drug release kinetics. Unlike most other CR technologies, TIMERx® tablet technology (Pestwest Pharmaceuticals), is capable of achieving both fixed and lifting barrier-type release control, depending on the formulation characteristics and the manipulation of the molecular interactions between the hetero- and homopolysaccharide components. It is this 'dual-release mechanism' characteristic that allows near zero-order kinetics to be achieved using a TIMERx hydrogel system. In addition to allowing 'fixed', 'lifting' and 'fixed-lifting' control systems, TIMERx is also uniquely capable of a third type of release control. In this case, the barrier zone can be lifted and then replaced, to be lifted again at a later time. The barrier to diffusion in this type of release profile is provided by a tortuous pathway created between interacting polysaccharide chains. As the chains become more crosslinked, the molecular chains are pulled into a smaller space occupancy within the tablet envelope. This in turn opens up larger diffusion channels and speeds up release. However, as time goes on, the intermolecular forces become weakened and the polymer chains tend to drift apart, relaxing into the diffusion channels, increasing tortuosity and reducing the rate of drug diffusion. This secondary mechanism that can be achieved with certain TIMERx formulations constitutes a 'replaceable' barrier. The choice of fixed, lifting or replaceable barrier for a particular therapy or product development is governed by the type of CR profile required: single-order kinetics (zero or first order) or multi-phasic and chronotherapeutic release. TIMERx and its associated technologies, Geminex® and SyncroDose™, are capable of achieving many different CR delivery profiles, enough to meet the needs of even the most demanding new molecular entities and product requirements. TIMERx technology achieves this great flexibility of drug delivery profiles as a result of the use of a molecular-level physicochemical release-controlling mechanism. Details of the molecular mechanism governing release control, as well as the chemical structures of the heterodisperse polysaccharides, xanthan (X) and locust bean gum (LBG), can be found in previous publications [5,6]. Earlier sustained-release tablet technologies commonly relied on a barrier to delay drug release that was typically composed of a single insoluble or poorly soluble polymer that restricted diffusion. However, these systems are usually only capable of first-order release because the rate of diffusion slowed down with time as the concentration of drug in the tablet is depleted and increases the diffusive path length [7]. Alza, which is now part of Johnson & Johnson, invented and developed an ingenious CR tablet technology called Oros®. An Oros tablet, which possesses a semipermeable polymer coat with a laser-drilled hole, is an 'osmotic pump', which can release drug solution continuously and steadily for half a day or longer in a near zero-order rate profile [8]. However, the technology required to achieve zero-order release was more complex than that used for standard production and the tablets themselves tended to be significantly larger than non-osmotic CR tablets due to the need to include additional osmagent ingredients.

The challenge for newer CR systems, such as TIMERx technology, was to enable either conventional first- or zero-order release profiles to be achieved efficiently so that smaller tablets could be produced using ingredients and processes that were economically attractive. A further challenge for the technology was to do all of the above and, in addition, to provide an even more flexible drug delivery platform capable of achieving phased, pulsed or chronotherapeutic release profiles required for a new generation of product developments. TIMERx technology is able to achieve this flexibility by shifting from a 'factory-fixed' delivery platform to a physicochemical control system powered by polymeric molecules that self-assemble and whose interactions are themselves time-dependent and can be varied to suit specific product development requirements.

At its heart, the TIMERx molecular engine has two heterodisperse polysaccharides that self-assemble into a complex three-dimensional structure. The interactions between the two polymer molecules can be engineered to allow them to become entwined, disentangled, more entangled or dissolved with time depending on requirements or in response to physiological conditions. The keys that switch the molecular engine on and off are the London–van der Waals, hydrogen and/or ionic bonds between the two heterodisperse polysaccharides [6].

The two heterodisperse polysaccharides commonly used in TIMERx CR technology are both safe, naturally occurring vegetable materials: X and LBG. These two TIMERx polysaccharides and their physicochemical interactions have been the subject of extensive international research over a number of years. In the course of this work, the time-dependent polysaccharide structures have been elucidated using a variety of spectroscopic methods, including attenuated total reflectance infrared, Raman and electron spin resonance. Micro-magnetic resonance imaging has also been used as a non-invasive method for following the changes in gel structuralisation with time. Dynamic gel rheometry methods have also been used to quantify structural gel strengths at different times [9].

X is a heterpolysaccharide, which dissolves in water to form viscolysed or thickened solutions. This thickening property of X is made use of in other pharmaceutical products to prepare sugar-free syrups and results from a reversible dimerisation of X molecules, shown schematically in **Figure 1**. In solution, one X molecules associates with a second molecule by hydrogen bonding to produce a helical structure. These X helices are dispersed through the solution and act to create sufficient inhibition of free movement of water molecules to produce the thickening observed. As there is no interlinking of separate helixes, X does not produce a true gel on its own and this is a weakness that restricts its value as a CR material when used alone.

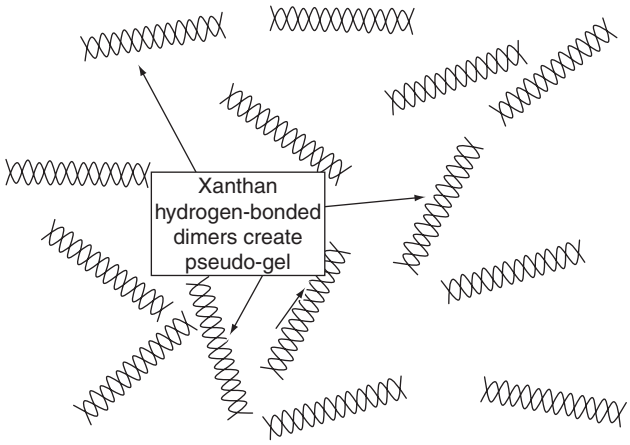

Figure 1. Schematic representation of the arrangement of xanthan molecules in water.

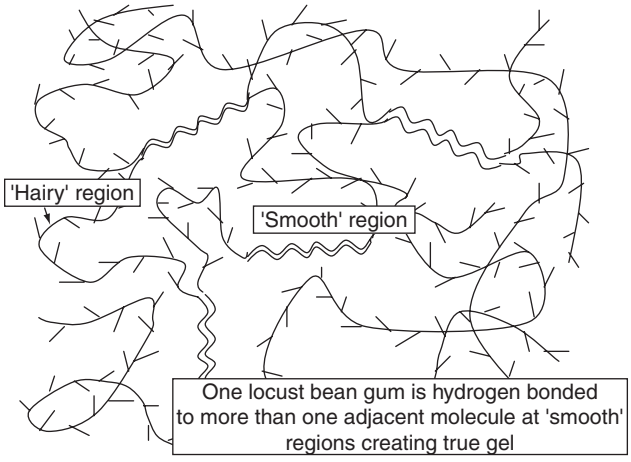

Figure 2. Schematic representation of locust bean gum molecules in an aqueous gel.

LBG is a long-chain homopolysaccharide that is physicochemically more complex than X. The LBG molecule has two distinct regions, which alternate along the mannose polymer backbone. During biosynthesis, galactose residues periodically become attached roughly once in every four mannose units. The regions of LBG where successions of galactose molecules stick out from the mannose backbone are known as 'hairy' regions. Regions of the LBG molecule that are free of galactose residues are known as 'smooth' regions. The absence of galactose in the smooth regions allows two LBG molecules to become hydrogen bonded, and the existence of more than one smooth region on every LBG molecule allows several different LBG molecules to become entangled by hydrogen bonding. This produces a three-dimensional interlocking network of LBG molecules in water, shown schematically in **Figure 2** [6]. However, this true gel structure requires energy and in the case of pure LBG only occurs when it is dispersed in water at > ~ 60°C. For

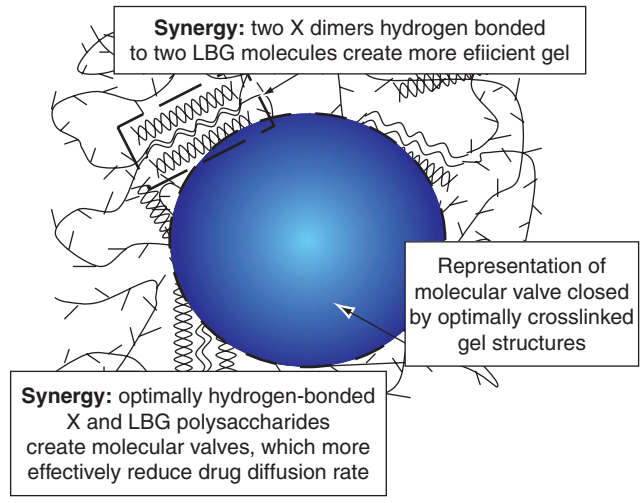

Figure 3. Schematic representation of optimal synergistic interaction of LBG molecules with X in an aqueous gel.
LGB: Locust bean gum; X: Xanthan.

this reason, LBG is unsuitable as a material for producing CR tablets when used alone. Furthermore, something quite unusual occurs when LBG is mixed with X. First, a synergistic interaction occurs, which results in the rigid helices of X in solution becoming incorporated into the true gel structure of the LBG molecules. The interaction can be considered synergistic because the viscosity build that occurs when both polysaccharides are used is significantly greater weight for weight than either material used alone. This is due to the X helices forming molecularly rigid 'pillars' within the LBG matrix, further stiffening the three-dimensional structure of the true gel, shown schematically in **Figure 3**. In addition, something else that is crucial to the use of X/LBG as a composite CR system occurs when the two polysaccharides are mixed: gel formation develops at ambient temperature.

The behaviour of X and LBG when mixed together in the solid state is different than when the two materials are blended in low concentrations in the liquid state, as occurs when X/LBG is used as a viscolyser in foods such as low-fat ice cream or mayonnaise. In these examples the total synergistic viscolysing effect is measurable from time zero, whereas in the use of X/LBG in the solid state in CR tablets, the effect is time dependent. The reason for the time-dependency is that X and LBG, when beginning in the solid state, must first become hydrated or solubilised, which takes time. Second, the hydrated molecules must find each other before they can become intermolecularly bonded and this, too, takes time as X and LBG are large molecules, which concentration have limited freedom of movement in high solids .

These and other effects, such as hydrogen-bonding modifiers (e.g., some sugars), and ionic crosslinking promoters, such as some salts discussed below, each have different rate constants that can be manipulated during formulation. For such reasons, X/LBG makes a very efficient and effective starting point for producing CR tablet products with a

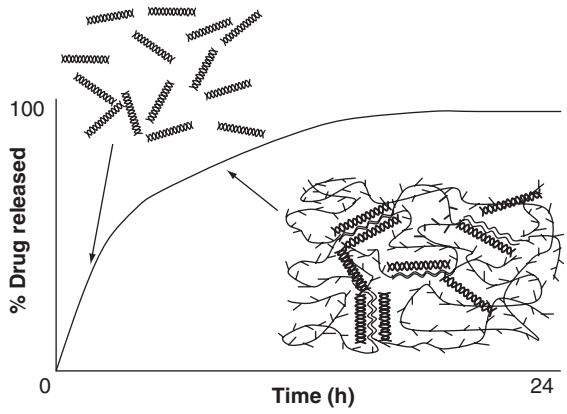

Figure 4. Example of TIMERx® structures developed at different times and providing a first-order release profile.

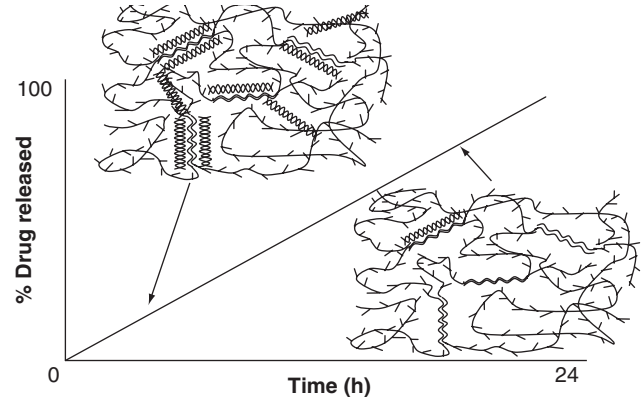

Figure 5. Example of TIMERx® structures developed at different times and providing a zero-order release profile.

variety of different release profiles. Not only can the concentrations and ratios of the two polysaccharides be varied to provide a more efficient weight-basis formulation for a required signature release profile for a particular product, but even more flexible and efficient systems are possible by incorporating simple third or fourth components that further modulate drug release. For example, the basic hydrogen-bonding interaction between the two polysaccharides can be further enhanced by stimulating ionic interactions through the incorporation of cations, especially divalent cations, into the formulation. Another third component additive, dextrose, has the effect of stimulating gel formation in some formulations.

Manipulations of the basic X/LBG synergistic interaction using third or fourth component materials are used to provide specific single-order release profiles, as well as multi-order drug-release profiles.

Different release profiles, whether single or multi-order, are achievable because the barrier to drug release provided by the synergistic interaction between X and LBG polysaccharides can be lowered, as well as subsequently raised or even re-lowered. A convenient way of envisioning the events that occur at a molecular level is to consider the physicochemical interaction between the two polysaccharides as a macromolecular valve. The pore-valve model is effectively the equivalent of the 'spring and dashpot model' used to explain rheological behaviour. In the pore-valve model of CR, each diffusion pathway is represented by a pore. Each pore is either open or closed for diffusion at a given time, depending on a variety of factors, including tortuosity, diameter, concentration gradient and viscosity. When one or more of these factors causes diffusion to close down, they are behaving like valves closing. At a later time when a change in these factors allows diffusion to re-start, they are behaving like valves opening. Each pore in a hydrogel can, therefore, be envisaged as having one or more valves along its length that act to control diffusion and counter-diffusive movement of the drug. Just as with the rheological 'springs' of a Hookean fluid, these pore valves result from molecular interactions and can, therefore, be regarded as 'molecular valves'. The unusual aspect of TIMERx hydrogels is that they are true gels, not simply viscolysed solutions, such as the hydrogels produced by hydroxypropyl methylcellulose and other cellulosics. Nor do TIMERx gels depend on changes in pH, such as those required to produce the alginate egg-box gels. The pore-valve model is particularly useful in describing TIMERx gel behaviour because these gels are uniquely capable of both opening, closing and re-opening. Most other hydrogels have insufficient complex molecular interactions to allow this degree of flexibility of drug-release control.

In TIMERx tablets, when a molecular valve is open, the drug can pass out of that part of the gel; but when a valve is closed, drug diffusion is stopped. A valve can be considered to be open when the intermolecular bonding between X and LBG is either at a minimum or a maximum. Molecular valve opening and closing in TIMERx gels is controlled by the degree of crosslinking 'allowed' at a given point in time. For example, a low degree of crosslinking between the polymer chains is likely to cause valves to be open, as there will be a large number of less tortuous channels in the gel. As the polymer chains crosslink the pores become more tortuous and constricted, leading to valve closure. At later stages, pore-valves can be made to re-open, either by allowing the X component to become dissolved and, therefore, causing un-crosslinking, or alternatively by encouraging over crosslinking. In this case, formulations are produced that add an ionic crosslinking component to the already-present hydrogen-bonding crosslinking component. These over-crosslinked gels drag the solid content into a smaller volume occupancy, thereby opening up pores for diffusion. The molecular interactions that cause a particular degree of crosslinking and hence pore-valve opening or closing at a particular time can, therefore, be manipulated by formulation characteristics. These include the ratio of the two heterodisperse polysaccharides, the drug:polysaccharide ratio, the channelling agent (e.g., dextrates) concentration, and the presence or absence of mono- or di-valent cations (e.g., calcium

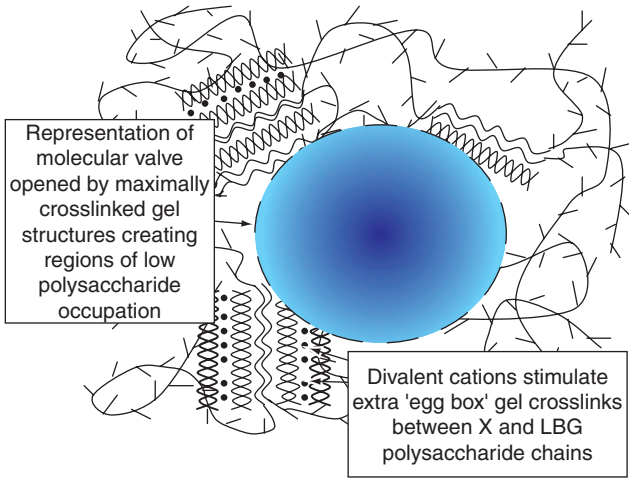

Figure 6. Schematic representation of over crosslinked interaction of LBG molecules with X in an aqueous gel.
LBG: Locust bean gum; X: Xanthan.

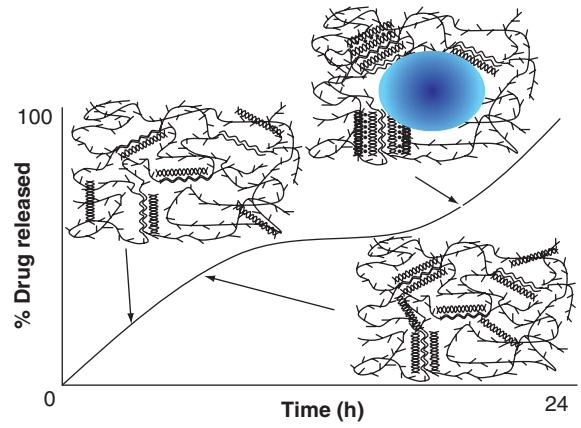

Figure 7. Example of TIMERx® structures developed at different times and providing bi-modal release profile.

phosphate). The TIMERx molecular engine can be manipulated by formulation to provide the different interaction rate processes required for different CR profiles. In contrast, a valve can be considered to be closed when the intermolecular bonding between the two polysaccharides is at an optimum, below maximal as shown schematically in **Figure 3**. The more molecular valves that are open, the faster the drug diffusion rate is at that time point. Conversely, the fewer molecular valves that are open at any particular time, the slower the release rate. Examples of the changes in gel structures that can be manipulated to provide different single-order CR profiles are shown schematically in **Figures 4** and **5**.

In order to achieve multi-order release, the molecular valves that provide the barrier to drug release described above must first be put in place as for single-order release, by designing the formulation to allow a significant degree of hydrogen-bonding between the heterodisperse polysaccharides. However, for multi-order or exponential drug release, the molecular valves must subsequently be raised. This can be achieved, for example, by allowing the X component to be eluted from the LBG gel. In passing into solution the X opens molecular valves in the gel matrix and thereby effectively raises the barrier to drug release. In cases where multi-order or biphasic release profiles are required the barrier to drug release must once again be replaced at a later time by closing molecular valves. The X/LBG molecular engine can be tuned to allow this to happen. For example, the two polysaccharides are allowed to synergistically interact to close a significant proportion of molecular valves in the initial hours, providing the first, slower, drug release rate. The use of cations in the formulation allows the inter-molecular interactions to be overstimulated so that the limited solid content becomes pulled into a smaller volume. This in turn opens a proportion of the molecular valves in the gel, raising the drug-release rate. This over-crosslinked gel structure, which re-opens the molecular valves in the X/LBG hydrogel is shown in **Figure 6**. The X/LBG extra crosslinking in TIMERx gels differs from that in other gels as it is additive over a pre-existing hydrogen-bonding level of crosslinking. The underlying hydrogen-bonding crosslinking mechanism also provides a safety mechanism against dose dumping that purely ionic crosslinked gels, such as those containing alginates, lack. The changes in gel structure that occur in generating this type of biphasic release profile are shown in **Figure 7**. In yet other cases, where required, the formulation can be designed to allow cations to become washed out of the gel, which on relaxation re-closes some of the molecular valves and once again restricts drug diffusion and slows the release rate.

With these brief examples, it is hoped that the flexibility, efficiency and effectiveness of using two synergistically interacting materials as a molecular engine to control drug release will have become apparent.

The advantage of using a molecular engine to control drug release is that smaller tablets can be produced that have a more precisely tailoured delivery profile using a conveniently flexible system that does not require specialist manufacturing hardware or demand that processes or materials be changed to accommodate different product developments.

3. Product developments and clinical studies

TIMERx and the related Geminex and SynchroDose technologies (discussed below) have been used in a number of successful product developments. Some of these developments have already resulted in marketed products containing TIMERx CR technologies. A number of other CR product developments using TIMERx technologies are either at the pre-clinical stage or are progressing through clinical studies. Of the products using TIMERx technologies that are currently under development, Penwest has two products awaiting new drug application approval, one with Endo Pharmaceuticals and

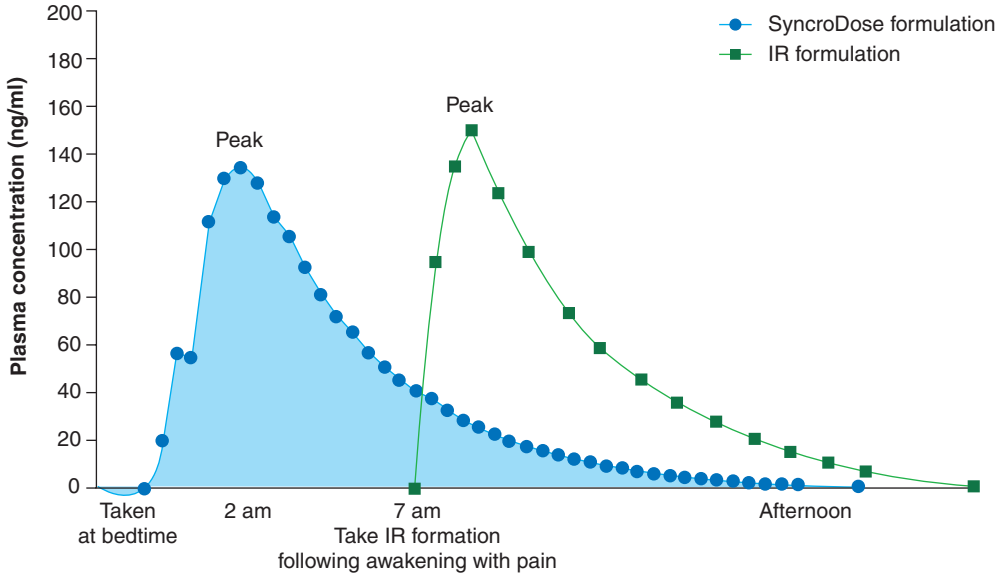

Figure 8. Plasma concentration of drug active from SyncroDose formulation versus IR formulation.
IR: Immediate release.

Table 1. Approved drugs using TIMERx® technology.

Brand name	Generic name	Indication	Collaborative partner	Territory
Procardia®XL	Nifedipine	Hypertension, angina	Mylan Pharmaceuticals	USA
Slofedepine®XL	Nifedipine	Hypertension, angina	Sanofi-Synthelabo	UK and Italy
Cronodipin	Nifedipine	Hypertension	E Merck	Brazil
Cystin®CR	Oxybutynin	Urinary incontinence	Leiras OY	Finland

CR: Controlled release.

another with IVAX Corporation, and another two products in Phase III trials that are available for partnering. Penwest has a further five product developments that are currently in Phase II clinical studies. A summary of the stage of various product and clinical developments using TIMERx technology is shown in **Table 1**.

3.1 TIMERx®

TIMERx technology, utilising X/LBG polysaccharides, has been used in a large number of single-order CR product developments and some marketed products around the world. A TIMERx system designed to match the zero-order release kinetics of the Oros technology was the basis of the first competitor product development for Procardia®XL, in collaboration with Mylan, to receive approval by the FDA.

The first marketed product using TIMERx technology was Cystrin®CR, a CR form of oxybutynin. Since then other products have been launched using TIMERx, including Slofedipine®XL, a CR tablet form of nifedipine marketed by Sanofi-Synthelabo in Europe. TIMERx technology has also been used as the basis of a number of product development alliances with companies in the US and Europe. For example, TIMERx has been used in the recent oxymorphone CR tablet product co-development with Endo, which is currently awaiting NDA approval.

3.2 Geminex®

Geminex is a CR TIMERx technology that allows biphasic delivery of the same drug. Alternatively, two different drugs can be delivered from the same tablet at either the same or different rates. Geminex technology utilises X/LBG as the release-controlling modality, but uses two different formulations in the same tablet to achieve the required bi-modal performance. The Geminex CR technology was first used in a collaboration with the UK-based Celltech group to work on developing a centrally-acting analgesic designed to reduce dosing frequency and side effects by delivering two different isomers of the same drug at different release rates [5].

3.3 SyncroDose™

SyncroDose is a chronotherapeutic release TIMERx technology that allows a lag time to be built into a CR tablet system after which complete drug release is triggered. This is especially useful in cases where early morning, pre-waking dosing of drug into the bloodstream is desirable. An example of the potentially beneficial use of this type of

chronotherapeutic delivery is in the treatment of rheumatoid arthritis, where early morning stiffness can be reduced or eliminated by bed-time administration of a SyncroDose tablet containing an anti-inflammatory drug. The heterodisperse polysaccharide content of a SyncroDose tablet is located separately from the drug, in a shell that completely blocks diffusion until the desired time delay for triggered drug release has been reached. SyncroDose formulations can be produced, which accurately delay drug release over a trigger time period ranging ~ 2 – 12 h as shown in **Figure 8**. The data shown in **Figure 8** relate to chronotherapeutic delivery of an experimental drug, AD-121 [6].

4. Expert opinion

Ask a pharmaceutical scientist what the main job of a medicine is and the reply will often be "to deliver the correct dose of drug to the body safely and effectively". However, this reply perhaps overlooks or underestimates the value of a medicine for its ability to simply have the patient want to keep taking it. "Keep taking the tablets" is a phrase we hear so often, but that is precisely what a patient must do to retain their health. If a patient is suffering from a physiological disease, such as high blood pressure, the chances are that they are going to be taking their medicine several times a day for a long time. Even when the drug is the very best that is currently available, if the patient does not want to, or worse still, can not take the tablet or capsule, their therapy may be compromised.

The reduction of dose frequency that is possible using CR tablets is very beneficial. It has been found that reducing the need for a patient to take multiple daily doses of tablets significantly improves the possibility that the patient will take the medicine as required for effective treatment. However, there are other benefits of using CR medicines, which, as we have seen, are more technical, but also improve the way the body uses the drug being delivered. Amongst other effects, CR delivery can improve the way the target tissues react to the drug as well as reducing side effects. All of these factors mean that CR medicines can significantly improve on the clinical benefits of the drug itself. These are valuable benefits and have resulted in specialty pharmaceutical companies, such as Alza, Penwest Pharmaceuticals and SkyePharma, inventing and commercialising a variety of oral CR medicines in tablet form. Alza's Oros CR tablet technology powered the world's first billion dollar medicine. During the 1980's, the first billion dollar drugs, such as Zantac® were created. These drugs were delivered inside tablets, but it was the drug molecule not the tablet medicine that created most of the value. The Pfizer product Procardia XL was a CR form of nifedipine that used Oros osmotic pump technology to create a tablet that only needed to be taken twice daily. Procardia XL became the first billion dollar medicine based on a CR tablet technology.

The original technology behind Oros was invented > 20 years ago and since that time less complex, less mechanical and less process-intensive ways of achieving oral CR have been discovered. There are now oral CR tablet technologies where smaller tablets can be produced using simple, standard manufacturing processes that can achieve the same results as those using laser beams and complex mechanics. The new simpler processes for making smaller tablets with more flexible drug delivery profiles are possible as a result of making specialised drug delivery molecules in the formulation that do the work. In these newer technologies, such as Penwest Pharmaceutical's TIMERx hydrogel tablets, complex time-dependent physical chemical interactions between pharmacologically inert excipient molecules are used to control drug release. These specialised drug delivery ingredients form the molecular engines that power a new generation of CR tablets capable of more flexible drug delivery, such as biphasic or chronotherapeutic release, as well as straight line, zero-order profiles, to get the best drug performance to the patient in a form that promotes treatment adherence. That means making CR tablets that patients are willing to take not just once a day, but once every day for the treatment period. The TIMERx molecular engine is a very effective way of meeting the challenge and driving the change.

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