

Extended release drug delivery technology

By providing smooth plasma levels of drug over longer periods of time, extended release drug delivery technology can minimise side effects, improve efficacy and – by enabling once-daily dosing – maximise patient compliance.

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Extended release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance. By incorporating the dose for 24 hours into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented. This helps avoid the side effects associated with high concentrations and the lack of activity associated with low concentrations – giving better overall therapy. In addition, in the treatment of diseases that are asymptomatic – such as hypertension – patients generally remember morning and evening medication, but tend to forget doses in between. Once- or twice-daily dosing thus improves therapy through the constant presence of the drug.

Early drug delivery systems (DDS) tended to give non-constant release rates, although this was still a large improvement over immediate release formulations. The ideal DDS should show a constant zero-order release rate, as this has the potential to create constant plasma concentrations.

A range of technologies

Many current oral extended release systems are of the matrix type, based on hydrophilic polymers. With these technologies, drug and excipients are mixed with polymers such as hydroxypropyl

methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), and then formed as a tablet by conventional compression. Release from these tablets takes place by a combination of physical phenomena. Water diffuses into the tablet, swells the polymer and dissolves the drug, whereupon the drug may diffuse out to be absorbed. If the drug diffuses out faster than the polymer dissolves, the release rate declines with time. Water penetration also depends on factors such as tablet porosity, and this makes matrix tablets inherently variable and difficult to formulate. If the medication is taken with food, the increased mechanical stress leads to an increased release rate and a higher risk of dose-dumping. In addition, these systems require a large amount of excipient, and drug loading is consequently comparatively low.

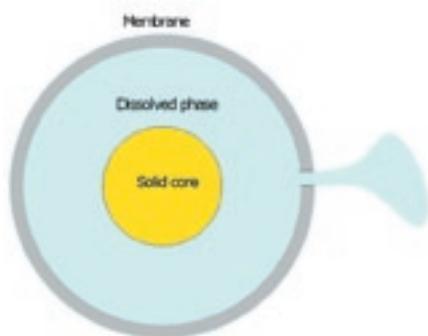
Another method of obtaining controlled release is to employ diffusion-controlling membranes. Here, a core that may be pure drug is coated with a permeable polymeric membrane (see Figure 1). Water diffuses through the membrane and dissolves the drug which then diffuses through the membrane at a rate determined by the porosity and thickness of the membrane, the solubility of the drug and the membrane area. Available membrane polymers – such as ethylcellulose – have relatively low permeability and, consequently, this technique

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Figure 1. Diffusion controlling membrane.



Figure 2. Osmotic pump.



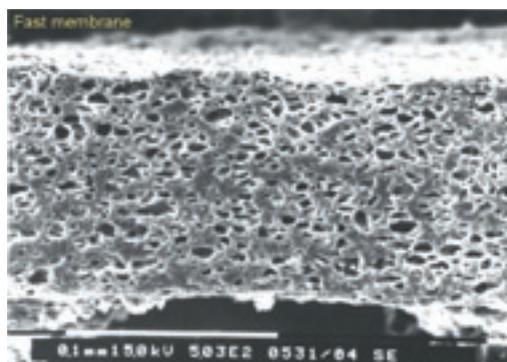
Amongst the stable of patented oral DDS is the diffusion controlled vesicle (DCV) platform which uses impenetrable water-insoluble polymers that are either dissolved in an organic solvent or used as aqueous dispersions

is mainly used on small pellets to increase the total membrane area.

A special version is the so-called osmotic pump. Here, the membrane is semi-permeable – water can diffuse in through the membrane but the drug cannot diffuse out. However, by drilling a hole in the membrane, dissolved drug may flow out (see Figure 2). Drilling the hole is, however, an expensive step; furthermore, the existence of the hole must be assured since the system may otherwise explode – leading to complete dose-dumping.

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Figure 3. Macroporous membrane that controls drug diffusion.



polymers that are either dissolved in an organic solvent or used as aqueous dispersions. A water-soluble pore former is suspended in the polymer solution/dispersion, and this coating mix is then spray-coated onto drug-containing cores by conventional coating techniques. This process creates a macroporous membrane that controls the diffusion of the drug (see Figure 3). Compared with the osmotic pump, the membrane contains about one million holes. These are created by a stochastic process during coating, and consequently dose-dumping cannot take place by osmotic rupture of the membrane. Furthermore, the drug is released over the entire membrane surface, as compared with a single spot with the osmotic pump. This reduces the risk of side effects due to high drug concentrations close to gastric and intestinal mucosa.

Mathematical models

The release of drug from the DCV system is described by a well-established mathematical model. The processes that may control the release include:

- Dissolution of the drug at the surface of the solid depot,
- Mixing of the drug into the dissolved phase inside the membrane,
- Diffusion of the drug through the membrane, and
- Mixing of the drug into the fluid outside the membrane.

It can be assumed that the first two processes and the last process are much faster than diffusion through the membrane. Consequently, the release rate is given by Fick's first equation of diffusion:

$$J = -D_d \frac{dc_d}{dx}$$

Where J is the rate of mass transport (mg/time), D_d is the diffusion coefficient of the drug, and dc_d/dx is the diffusion gradient. The gradient can be approximated with the concentration difference (C_s) across the membrane and the thickness of the membrane (h). The tortuous porous membrane reduces diffusion of the drug and D_d is replaced by $D_d(P)$, the diffusion coefficient as a function of membrane porosity. Finally, we have to multiply with the membrane area A, which gives the release rate:

$$\frac{dQ}{dt} = A D_d(P) \frac{C_s}{h}$$

After integration, we obtain the cumulated release:

$$Q(t) = \frac{A D_d(P) C_s}{h} t$$

While there is a solid depot of the drug present inside the membrane, all parameters are constant and, thus, the release rate is constant. The release rate declines exponentially when the depot is depleted:

$$\frac{dQ}{dt} = \frac{A D_d(P) C_s}{h} e^{-\frac{A D_d(P)}{Vh} t}$$

The model accurately predicts drug release from the system, and the formulation is consequently constructed by computer simulation using the following parameters:

- Drug dose,
- Drug solubility,
- Drug size (diffusion coefficient),
- Tablet size, membrane area,
- Membrane thickness, and
- Membrane porosity.

Figure 4 shows a comparison between a simulated release profile and the release profile of a formulation manufactured according to the simulation specification.

Drug solubility often depends on pH; this being the case, drug release rates *in vivo* from most drug delivery systems change as the tablet transits from the

acidic stomach to the neutral intestinal environment. In the DCV system, this can be easily adjusted for by the addition of suitable buffers to the formulation. Constant pH is thus maintained inside the membrane and a constant release rate is attained along the entire gastrointestinal canal (GIC). Given that the absorption, distribution, metabolism and elimination (ADME) of the drug is known, it is possible to predict the pharmacokinetics of the DCV formulation. The drug is released and absorbed with constant rate along the entire GIC, giving steady plasma profiles over 24 hours. Figure 5 shows a diltiazem DCV once-daily formulation, showing that absorption takes place even at times longer than 24 hours.

By using a technique called Wagner-Nelson analysis, it is possible to find the absorption rate of the DCV compared with the solution. Figure 6 shows that there is a linear relation between *in vitro* release and *in vivo* absorption. This means that the *in vivo* is entirely predictable given that the *in vitro* release is pH-independent. This is demonstrated by formulating a super-generic, which is a product that is bioequivalent to another extended release product. The appropriate DCV *in vivo* release profiles were obtained by fitting the linked DCV pharmacokinetic model for the drug to the plasma profile obtained with the original product. Two such formulations were then compared with the original in a pharmacokinetic study; Figure 7 shows a close match of both formulations which were bioequivalent to the original product.

Recently, there has been a new development that allows for the delivery of nanoparticles through the membrane; this will expand the applicable range to all bioavailable drugs.

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Figure 4. DCV mathematical modelling and experimental profile.

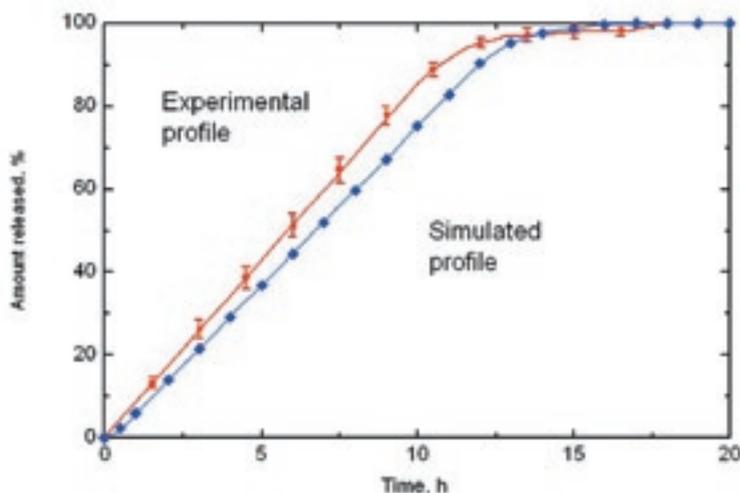
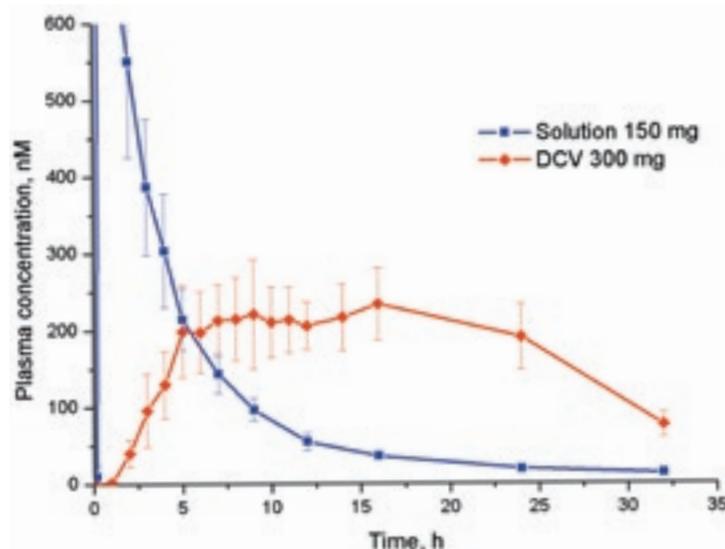


Figure 5. Diltiazem DCV once-daily formulation.



In an ageing population, it is also evident that patient compliance is seen as a significant factor in managing a disease or condition, and extended release and once-daily dosing has been shown to maximise this

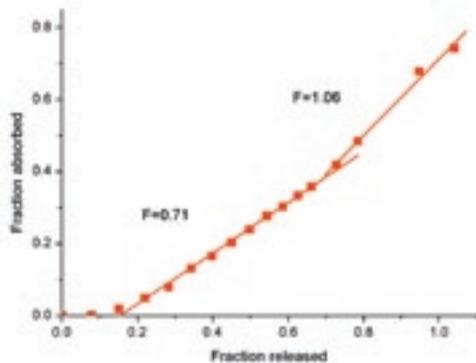


Figure 6. Absorption rate of the DCV compared with the solution.

Conclusion

It is clear that oral drug delivery has come a long way since the 1960s and, with it, major advances in the technology employed. By providing smooth plasma levels of drug over extended periods of time, side effects are minimised and efficacy improved. In an ageing population, it is also evident that patient compliance is seen as a significant factor in managing a disease or condition, and extended release and once-daily dosing has been shown to maximise this.

Today, it is estimated that around 80 per cent of all medications utilise the oral route, and tablets, capsules and granules will remain the form of choice. It is therefore not only important that oral drug delivery technology continues to advance, but as the ever-demanding patient population becomes more informed, it is in fact essential for the future drug treatment of disease.



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Figure 7. Formulation comparison.

