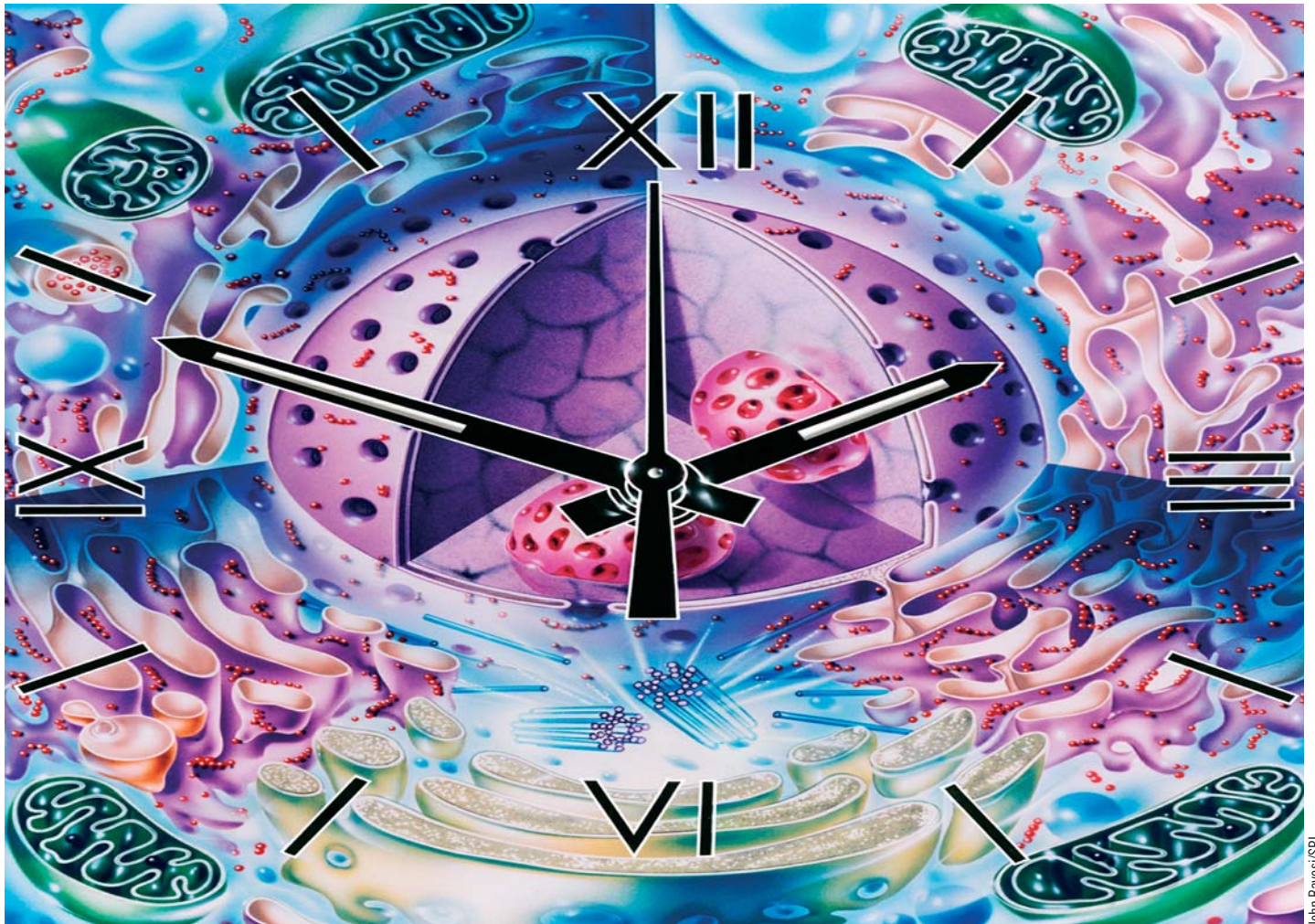


# Development of drug delivery systems that match the circadian rhythm

In the sixth article in our series looking at developments in drug technologies, **Jenny Bryan** describes why emphasis should now be placed on the development of drug delivery systems that take account of variations in bodily functions, such as blood pressure, during the day and night



John Bavosi/SPL

Targeting drug release to specific times of day when there is maximal clinical manifestation of disease has obvious advantages

**M**atching drug release to the body's circadian rhythms has been the elusive goal of a select band of drug delivery companies for at least two decades. But the hazards of the gastrointestinal tract have meant that only a handful of truly chronopharmaceutical products have reached the market, and few are in development. Researchers such as Howard Stevens, head of exploratory drug delivery at the University of Strathclyde, recognise the value of a chronopharmaceutical approach, but differ in their level of optimism about what can be achieved.

"The idea of targeting release to the specific time of day when there is maximal clinical

manifestation of a disease has obvious advantages, and there is no shortage of ingenuity in designing formulations for time-delayed drug release. But the difficulty lies in designing products that are resistant to breakdown by the fluids in the GI tract," explains Professor Stevens.

In 2000, his group reported the successful pulsatile release over a two- to 12-hour period of propranolol sealed inside an insoluble capsule by an erodible tablet, the release time being controlled by the amounts of insoluble and gel-forming excipients in the tablet.<sup>1</sup> But Professor Stevens remains pessimistic about the large-scale development of timed-release formulations of commonly used drugs, not least because of the need to show practical, and not just theoret-

ical, advantages of a chronopharmaceutical approach.

However, in a recent major review of chronopharmaceutical applications, Bi-Botti Youan, from the department of pharmaceutical sciences, at the Texas Tech University Health Sciences Centre School of Pharmacy, Amarillo, Texas, argues that, in addition to their scientific advantages, such approaches have commercial benefits for pharmaceutical companies seeking to prolong the patent life of expiring products.<sup>2</sup> "Until now, the emphasis has been on formulations that maintain constant drug levels throughout the day. But we now need to develop more biologically appropriate formulations that take account of variations in bodily functions, such as blood pressure, during the day," says Dr Youan.

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As well as in hypertension and other cardiovascular disease, Dr Youan offers good theoretical reasons for carefully timed drug delivery in the treatment of asthma, arthritis, duodenal ulcer, cancer, diabetes, hypercholesterolaemia and some neurological disorders. In cancer, for example, he argues that chemotherapy could be more effective and less toxic if drugs could be administered at times that take more advantage of tumour cell cycles. In asthma, a drug that could address the progressive increase in airway resistance during the night could offer better symptom control in the early morning hours.

A number of systems have been developed for timed release of commonly used medicines. Most established is probably the OROS technology marketed by Alza and used, among other products, for a controlled onset extended release formulation of verapamil.

The drug is released overnight, four to five hours after the tablet is ingested, to provide optimal blood pressure control in the early hours of the day, with the aim of addressing the peak morning risk of cardiac events.

OROS uses osmosis to release the drug contained within a semi-permeable membrane. As water from the GI tract enters the tablet, a layer of osmotically active agents expands and pushes on the drug core, so that the drug is released through laser-drilled holes in the outer membrane. An additional layer between the active drug core and the semi-permeable membrane enables release to be delayed.

An alternative approach, used by Elan in its chronotherapeutic oral drug absorption system (CODAS), relies on a combination of water soluble and water insoluble polymers, coated on to drug-loaded beads to delay release by four to five hours after ingestion. The

polymer coat is gradually dissolved by water from the GI tract, and the drug diffuses through the resulting pores in the coating.

The Italian drug delivery company, Eurand, also uses a polymer layer for timed release from drug-containing particles in its Diffucaps technology. By incorporating beads with differing drug release profiles, the company offers capsules with both immediate and delayed release components.

In contrast, US-based drug delivery company, Penwest, uses a gum matrix for its TIMERx controlled release technology. On exposure to GI fluids, the combination of xanthan and locus bean gels becomes hydrated and the drug core is gradually released. The TIMERx system is being adapted for chronopharmaceutical applications, with lag-time controlled by variations in the gum matrix.

Demonstrating that chronopharmaceutical technologies can deliver active drug, when and where they say they will, is difficult enough. But before cost-conscious purchasers are prepared to pay for what will inevitably be premium-priced brands, they will want clear evidence of beneficial effects on clinical outcomes and, as Professor Stevens points out, such data are sadly lacking.

One aim of the controlled onset verapamil investigation of cardiovascular endpoints (CONVINCE) trial was to find out if the OROS-based system of verapamil delivery could reduce morning cardiac events, compared with a standard beta blocker or diuretic. But the study was halted two years early, and there were too few events to show whether there was any real value of the chronopharmaceutical approach to blood pressure control.<sup>3</sup>

Both Professor Stevens and Dr Youan agree that outcomes trials like CONVINCE

are needed if chronopharmaceutical products are to compete with conventional formulations. But the cost of such large studies may be prohibitive.

Dr Youan believes that future chronopharmaceuticals will also have to be "smarter" than current systems.

"Most people are using polymers to control release, but they are not smart enough to think about when a drug should be released. Nanomedicine and microchips may improve control, but we will need to balance that against the invasiveness of the system," he says.

As Dr Youan points out, external and internal infusion pumps have been delivering timed doses of insulin and analgesics for many years. But their invasive nature continues to limit their wider use for common chronic conditions. Even so, he remains optimistic: "We have focused on the physics and chemistry of drug delivery for long enough, now it is really is time for us to think more about what the body needs. Chronopharmaceutics is not just a gimmick, it has clinical relevance, but we need doctors, pharmacists, chemists and others to work together to assess its real benefits."

## References

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