Pulsed-release drug delivery

As circadian rhythms are being implicated in more and more diseases, pulsed release drug formulations offer the possibility to release a dose of active drug at exactly the right time.

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Oral pulsed-release formulations are ideal delivery systems for diseases involving circadian rhythms. Up to now, however, it has not been possible to manufacture systems cost-effectively and also provide reliable results. Röhm Pharma Polymers is now in a position to present a technology that encompasses both properties. Owing to its multiparticulate form and pH-independent release, this system offers a number of advantages.

The more physicians learn about the various circadian rhythms that diseases follow, the clearer it becomes that treatment with conventional sustained-release formulations has reached its limits. Doctors looking for successful ways to prevent asthma attacks in the morning, heart attacks in the middle of the night or the morning stiffness typical of people suffering from arthritis, are in need of drug delivery systems that release the entire active dose at exactly the desired time. The problem at the present time is to find precisely such a system. Instead, patients must get up in the middle of the night to take a tablet which ensures that their therapeutically effective plasma level is reached at the right time – usually in the morning. Pulsed-release formulations are much more patient-friendly because, thanks to their programmed drug release, a capsule containing the requisite dose can be swallowed at bedtime. Current developments, however, represent mere academic approaches that have not yet been put to the test in practice.

Polymethacrylate polymers

More recently, studies conducted by Röhm Pharma Polymers seem to have opened up a new and highly effective route to pulsed-release formulations: the coating of multiparticulate active ingredients with polymethacrylate polymers. The company has been successfully operating in the field of methacrylate chemistry for forty years, and has further developed its range of EUDRAGIT® polymeric coating materials. These products are not only suited to a variety of controlled-release formulations, but also find application in taste-masking. The functionality of such coatings is determined by their individual content in terms of anionic and cationic functional groups – a fact which enables the chemist to develop release and transportation systems tailored to the nature of the active ingredient. Thus, pH dependence can be “built in” by means of acidic or basic groups, and the site of drug release in the gastrointestinal tract can be accurately controlled. Quaternary ammonium groups like...
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those contained in EUDRAGIT® RS and RL, on the other hand, permit pure controlled time-release independent of pH. Moreover, as opposed to cellulose-based coating materials for controlled release, particularly ethylcellulose, synthetic polymethacrlylates provide more reliable film formation.

The first pulsed delivery formulations which released the active to the organism at a precisely defined point in time were developed in the early 1990s. In this context, researchers were looking for a formulation with a so-called sigmoidal release profile. The characteristic feature of this formulation was to be a defined lag time followed by a drug pulse, with the enclosed active quantity being released in a kind of “big bang”. The predestined means of obtaining this mode of behaviour were multi-units – that is, active pellets or microparticles coated with a polymer film that were subsequently filled into hard gelatin capsules and, upon ingestion, disintegrated into innumerable mini-depots in the stomach.

Röhm Pharma Polymers has strengthened its own patent position by acquiring a patent (Yoshino et al.) owned by the Japanese pharmaceutical company, Tanabe, and is now able to offer state-of-the-art technology for the manufacture of dosage forms with pulsed drug delivery. Owing to two key properties, EUDRAGIT® RS 30 D – a time-tested excipient for sustained-release coating of microparticles – is an ideal candidate for pulsed release. What makes EUDRAGIT® grades RS and RL ideally suited for the purpose is the fact that they typically contain positively polarised, quaternary ammonium groups in the polymer side chains, which in turn are always accompanied by negative hydrochloride counter-ions. Thanks to the hydrophilicity of the ammonium groups, the polymer intercalates water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time.

As current investigations by the company have shown, the time span to drug release according to Fick's first law is fairly easy to control via the thickness of the film. For the studies, the researchers first produced pellet cores with theophylline as the model drug plus a 21 per cent and 43 per cent proportion of sodium acetate on core weight, respectively. Subsequently, these pellets were coated in a top-spray fluid bed with films of EUDRAGIT® RS 30 D (10–40% polymer weight gain) in four different layer thicknesses. (The structure of a pellet is shown in Figure 1.) Tests revealed a clear correlation between film thickness and lag time (Figure 2). In-vivo studies in beagles confirmed the observed release profile.

Pulsed release

No less important for the new function is the fact that EUDRAGIT® RS 30 D – thanks to the ammonium groups present in hydrochloride form – possesses anionic ion exchanger capacities. The studies mentioned above furnished some rather surprising proof in this respect: even small amounts of sodium acetate in the pellet core have a dramatic effect on the drug permeability of the EUDRAGIT® film. After the lag time, interaction between the acetate and the polymer increases the permeability of the polymer coating so very drastically that the entire active dose is liberated within only a few minutes.

The first indication of this physicochemical property essential for pulsed release formulations emerged during earlier studies by Yoshino et al. Very early on in the 1990s, they postulated a change in the permeability of the EUDRAGIT® film caused by electrostatic interaction between the ammonium ions and the anions of dissociated organic acids. In order to find out which acids were the strongest inducers of the desired pulse effect, they performed comparative tests with different organic acids, and finally assigned the most significant pulse to acetic acid.

The studies conducted at Röhm Pharma Polymers expanded on these results. The authors were able to show that the acids could easily be replaced with sodium acetate, and that it took only a small proportion of sodium salt in the pellet core to trigger a major drug pulse. Their investigations also
revealed the effect of the sodium acetate content on the release time, as the steep slope of the curve obtained in release testing indicated that the rate of drug release depended mainly on the amount of salt contained in the core. The steepest slope was determined for a 32 per cent proportion of Na acetate in core weight (Figure 3).

Benefits
The great benefit of pulsed-release formulations with EUDRAGIT® RS 30 D is without doubt that their functionality can be influenced via two independent variables: the lag time via the film thickness, and the release time via the salt content of the active core. This enables the user to adjust these two factors separately, thereby tailoring the formulation to the given active ingredient.

EUDRAGIT® RS 30 D also offers cost advantages. The manufacture of solid dosage forms is the most economical process and therefore still the one preferred by the pharmaceutical industry – and methacrylic polymers, in particular, have long been used for this purpose. As a result, tremendous technical expertise has been accumulated over the years, and today’s manufacturers of pulsed-release formulations can avail themselves of existing equipment – that is, fluid beds and coaters – to envelop microparticles without the use of solvents, which can then be filled into capsules or compressed into tablets.

The future
Experts forecast a continuously rising demand for dosage forms with pulsatile drug release, since circadian rhythms have been extensively described for many diseases. Thus, more and more attempts are being made to adjust drug delivery systems accurately to patient requirements, both in terms of therapeutic efficacy and compliance. Pulsed-release formulations are specially suited to satisfying these needs, and novel formulations may offer interesting options for intelligent life-cycle management. From now on, a technology based on the time-tested polymer, EUDRAGIT® RS 30 D, is available for licensing: this not only permits the user to custom-tailor release profiles according to his own ideas, but also enables the desired dosage form to be manufactured in a cost-effective manner.