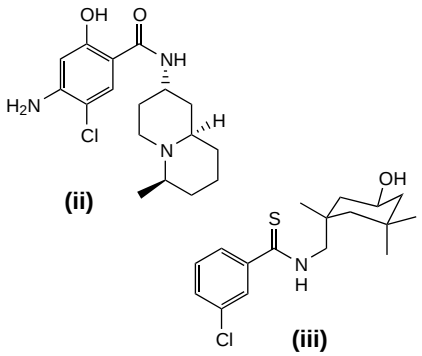

in solution. The libraries were screened for inhibition of the H1 subtype of influenza A viruses that act by preventing the pH-induced fusion process, thereby blocking viral entry into host cells. In a plaque-reduction assay, the most potent inhibitor found from both libraries synthesized was compound **(iii)**, which possessed an EC_{50} value of 0.02 μg ml^{-1}. This work has identified highly potent inhibitors of H1 influenza fusion based on the lead BMY27709 **(ii)** and could lay the foundation for further work to improve potency in this series.

2 Luo, G-X. *et al.* (1996) Characterization of a hemagglutinin-specific inhibitor of influenza A virus. *Virology* 226, 66–76

3 Deshpande, M.S. *et al.* (2001) An approach to the identification of potent inhibitors of influenza virus fusion using parallel synthesis methodology. *Bioorg. Med. Chem. Lett.* 11, 2393–2396

Paul Edwards
Lead Discovery Technologies
Pfizer Global Research and Development
Sandwich, Kent, UK
fax: +44 1304 643 555
e-mail: paul_edwards@sandwich.pfizer.com

Drug delivery

Zero-order release of nifedipine

Nifedipine is a calcium antagonist that is commonly prescribed as an antianginal and antihypertensive. Clinical studies have shown that the duration of the hypotensive effect has a direct correlation to the nifedipine plasma concentration. Nifedipine has poor aqueous solubility, rate-limiting absorption through the gastrointestinal (GI) tract and a biological half-life of ~2 h. Absorption of the drug is poor when orally administered via the currently available immediate-release dosage forms. Nifedipine is also available as an extended release formulation that consists of a tablet core surrounded by a slow-releasing layer composed of the drug and hydrophilic polymers, such as hydroxypropylcellulose and hydroxypropylmethylcellulose. The outer slow-release layer provides initial drug release followed by a rapid drug release from the tablet core. The overall drug release from such a formulation follows first-order kinetics. One of the most desirable characteristics in a controlled-release formulation of a drug such as nifedipine is to achieve zero-order kinetics, or constant drug release, thus maintaining a constant therapeutic level *in vivo*.

Mehta *et al.* have recently reported the development of a novel, multi-unit, erosion matrix-pellet system, with zero-order release *in vivo* [1]. The principal components of the formulation include nifedipine and two members of the Eudragit® (Rohm GmbH, Darmstadt, Germany) class of polymers, Eudragit L10055 and Eudragit S100. This erosion matrix formulation was extruded into small pellets, ~2mm in diameter, which were packed into capsules. The pellets erode slowly in the GI tract, thus releasing nifedipine. An *in vivo* study in beagle dogs demonstrated that the erosion matrix formulation releases nifedipine by zero-order kinetics.

The bioavailability of nifedipine from erosion matrix pellets was tested against a currently available immediate-release soft gelatin capsule formulation (Adalat®; Bayer Aktiengesellschaft, Leverkeusen–Bayerwerk, Germany) by dosing, in a randomized comparative cross-over study, the two formulations to four dogs. Capsules containing 30 mg nifedipine were dosed in each phase of the study. After a one-week washout period, dogs were dosed with the opposite formulation. Serial blood samples were drawn and the plasma analyzed by HPLC assay, the results of which were used for pharmacokinetic evaluation [C_{max}, T_{max}, $AUC_{0-24\,h}$ and mean residence time ($MRT_{0-24\,h}$)]. The mean T_{max} for nifedipine erosion matrix pellets was 15.5 h. By comparison, the T_{max} of the immediate-release formulation was 0.5 h. The $MRT_{0-24\,h}$ was 12.5 h for the erosion matrix pellets and 1.72 h for the immediate-release formulation, indicating a much longer residence time in the GI tract. The mean $AUC_{0-24\,h}$ for nifedipine from the erosion matrix pellet formulation was fourfold higher than the conventional immediate-release gelatin capsules.

Nifedipine release from the erosion matrix pellets is governed by the polymer-controlled surface erosion process. By this mechanism, drug release occurs in a constant fashion in the form of a microfine suspension in the GI tract and, thus, is readily available for a prolonged period. Overall, the release of nifedipine from the erosion matrix pellet formulation followed zero-order kinetics and a constant plasma level of nifedipine was observed. Nifedipine release from this erosion matrix formulation continued for >24 hours, at which point the observations were discontinued. It is also interesting to observe that a significant nifedipine plasma concentration was obtained 1 h after administration without any significant lag time. Thus, careful consideration of variables in a controlled-release formulation had a considerable effect on *in vivo* release parameters. In this case, it could lead to a formulation of nifedipine with therapeutic advantages over those currently available, and the same principles could potentially be applied to other poorly soluble drugs.

1 Mehta, K.A. *et al.* (2002) *In vivo* release performance of nifedipine in dogs from a novel Eudragit-based multi-unit erosion matrix. *Drug Deliv. Technol.* 2, 34–37

John Weidner
Scientist, Parallel Synthesis
Medicinal Chemistry, Emisphere Technologies
765 Old Saw Mill River Rd
Tarrytown, NY 10591, USA
tel: +1 914 785 4792
fax: +1 914 593 8250
e-mail: Jweidner@emisphere.com

  PII: S1359-6446(02)02270-5