The Nifedipine Gastrointestinal Therapeutic System (GITS)
Evaluation of Pharmaceutical, Pharmacokinetic and Pharmacological Properties

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Summary
Nifedipine is a short-acting calcium antagonist formulated into several different oral preparations, each of which offers a distinct drug release profile. Of these, the nifedipine gastrointestinal therapeutic system (GITS) affords (rate)-controlled-release (CR) and once-daily administration. Although it is recognised that CR drug formulations may enhance the treatment compliance of patients by reducing the number of daily doses, there are several pharmaceutical, pharmacokinetic and pharmacological considerations which may influence the ultimate selection of a particular dosage form.

The formulation design of the nifedipine GITS involves an osmotic pump process which provides approximately zero-order delivery of the drug. This
mechanism serves to prevent the possibility of dose dumping, but more importantly allows for maintenance of the relatively constant plasma drug concentrations assumed necessary to maintain smooth control of blood pressure. The pharmacokinetic characteristics of the nifedipine GITS have been evaluated in both single- and multiple-dose studies. The GITS formulation provides drug concentrations which reach a plateau within 6 hours after administration of a single dose, and continue at that concentration until at least 24 hours after administration. In this way large fluctuations in plasma drug concentrations are avoided, which may improve the efficacy and tolerability of the drug. Although a trend showing a small increase in the 24-hour plasma nifedipine concentrations has been observed by our group from some single-dose studies, it does not appear to be clinically relevant. One potentially important disadvantage of the GITS compared with 'naturally' long-acting agents is that the 'intrinsic' pharmacokinetic properties of nifedipine may be exposed in poorly compliant patients, leading to extended periods of subtherapeutic drug concentrations.

Drug delivery by the nifedipine GITS is unaffected by changes in pH and gastrointestinal (GI) motility, but the rate of drug release can increase slightly with food intake (although absolute bioavailability remains unchanged). No studies have been conducted to determine the average GI transit time of this particular dosage form, but it is possible that inadequate retention may occur in some patients, perhaps leading to less optimal clinical outcomes. For example, the median GI transit time for both oxprenolol and metoprolol Oros drug delivery systems has been reported as 27.4 hours, with individual times ranging from 5.1 to 58.3 hours. The possibility of inadequate GI retention of the nifedipine GITS is perhaps more likely in patients who have pre-existing GI motility disorders or who are taking other medications that enhance GI motility.

The interaction between grapefruit juice and nifedipine is interesting, considering that the exact mechanism involved has yet to be determined. Nonetheless, inhibition of presystemic metabolic processes (probably involving liver enzymes but possibly also enzymes contained within the wall of the small intestine) is likely to be a factor in the increased bioavailability of nifedipine observed in individuals coingesting grapefruit juice. Thus, potential nifedipine formulation differences with respect to the degree of interaction with grapefruit juice may occur if a significant degree of extrahepatic metabolism is involved.

The majority of clinical trials with the nifedipine GITS have assessed its efficacy in patients with mild-to-moderate essential hypertension, and have found it to be at least equivalent to other dosage forms of the drug. Since there is limited information available directly comparing the efficacy and adverse effects of the different types of nifedipine formulation, little attention has been focused on this subject. However, modifying the rate and duration of nifedipine release may profoundly affect the clinical performance of this drug. A slower rate of intravenous nifedipine infusion has been shown to reduce the incidence of vasodilator-related adverse effects and to improve blood pressure control. Therefore, these advantages may also apply to reduced rates of oral nifedipine absorption. Another important advantage of the nifedipine GITS is that the trough/peak effect ratio following once-daily administration is maintained above a value of 0.5 to 0.66, as is now typically suggested for antihypertensive therapy.