# Felodipine: A Potent Drug for Hypertension

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**Abstract**

Felodipine belongs to the dihydropyridine class of calcium channel blockers. It works by selectively blocking L-type calcium channels in vascular smooth muscle cells, leading to vasodilation. This action results in reduced peripheral vascular resistance, decreased arterial blood pressure, and improved coronary blood flow. It is widely used for treating hypertension and cardiovascular diseases. It was developed as an extended released(ER) formulation to allow for convenient once daily dosing, improving upon earlier conventional tablet formulations that required twice daily administration.

**Discovery and further history**

Felodipine is a second-generation dihydropyridine calcium channel blocker that was developed during the late 1970s and early 1980s. It was synthesized by researchers at Hassle AB, a subsidiary of Astra AB(now AstraZeneca), in Sweden. The drug was designed as part of a broader effort to improve upon the first-generation calcium channel blockers, such as nifedipine, by offering better vascular selectivity and longer duration of action. Felodipine demonstrated strong vasodilatory effects with minimal cardiac depressant activity, making it particularly useful in the treatment of hypertension and angina pectoris. Its high lipophilicity and rapid metabolism initially posed challenges, but these were overcome by developing extended-release formulations, which provided more stable plasma concentrations and improved patient adherence. Felodipine was approved for clinical use in Sweden in 1988 and subsequently approved in other countries including the United States(FDA approved in 1991). It was marketed under brand names such as Plendil and Renedil. Since then, it has become widely used worldwide, either as monotherapy or in combination with other antihypertensive agents like beta-blockers or ACE inhibitors. Ongoing research has continued to explore novel delivery systems for felodipine to address its limited bioavailability and first-pass metabolism, including nanoparticle systems, transdermal patches, and lipid-based carriers.

**Physiochemical properties**

| **Property** | **Value/Description** |
|---|---|
| Chemical name | 3-ethyl 5methyl-2,6-dimethyl-4-(2,3-chlorophenyl)-1 ,4-dihydropyridine-3,5-dicarboxylate |
| Molecular formula | C18H19Cl2NO4 |
| Molecular weight | 384.25g/mol |
| Melting point | ~145-146 degree Celsius |
| Appearance | Yellow crystalline powder |
| Solubility | Practically insoluble in water; soluble in ethanol, methanol, and acetone |

| | |
|---|---|
| Partition coefficient | ~3.8-4.5(high lipophilicity) |
| pka | ~5.1(acidic group of dihydropyridine ring) |
| UV absorption | Max at ~360nm(used in HPLC analysis) |
| Stability | Light-sensitive; degrades under UV exposure |
| Polymorphism | Exist in multiple polymorphic form with variable solubility |

**Chemical name of felodipine**

3-methyl5-methyl2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxyla te and the molecular formula is C18H19Cl2NO4.The molecular weight is 384.25g/mol. It appears as a yellow crystalline powder. It has a melting point of nearly about 145-146 degrees Celsius. It is practically soluble in water; and soluble in methanol, acetone, and ethanol. The partition coefficient value is approximately 3.8-4.5(high lipophilicity) and the pka value is approximately 5.1(acidic group of dihydropyridine ring). The UV absorption is approximately maximum at 360nm(used in HPLC analysis). It is light sensitive; and degrades under UV exposure. Felodipine exists in multiple polymorphic forms with variable solubility.

**Pharmacokinetic properties**

| Property | Description |
|---|---|
| Absorption | rapidly absorbed |
| Bioavailability | About 15% |
| Distribution | Extensive distribution |
| Volume of distribution | Not consistently influenced by age |
| Metabolism | Extensive hepatic metabolism |
| Primary metabolite | Pyridine metabolite |
| Elimination half-life | Increases with age |
| Plasma clearance | Decreases with age; 56.1L/h in young,25.4L/h in elderly |

**Absorption**

Felodipine is rapidly absorbed through the gastrointestinal tract after oral administration. However, it undergoes extensive first-pass metabolism in the liver, resulting in low oral bioavailability(about 15+-20%). The drug is typically administered as an extended-release formulation, which helps maintain therapeutic plasma concentrations over 24 hours.

**Distribution**

Felodipine is highly protein bound (>99%) in plasma, primarily to albumin. This high protein binding contributes to its long half-life and prolonged duration of action. The volume of distribution is approximately 10L/kg, indicating extensive tissue distribution.

**Metabolism**

Felodipine undergoes extensive hepatic metabolism, primarily by the cytochrome P450 3A4(CYP3A4)enzyme system. The main metabolites are inactive pyridine derivatives. Due to its dependence on CYP3A4, felodipine is subject to drug interactions with CYP3A4 inhibitors or inducers, which can significantly affect its plasma concentrations.

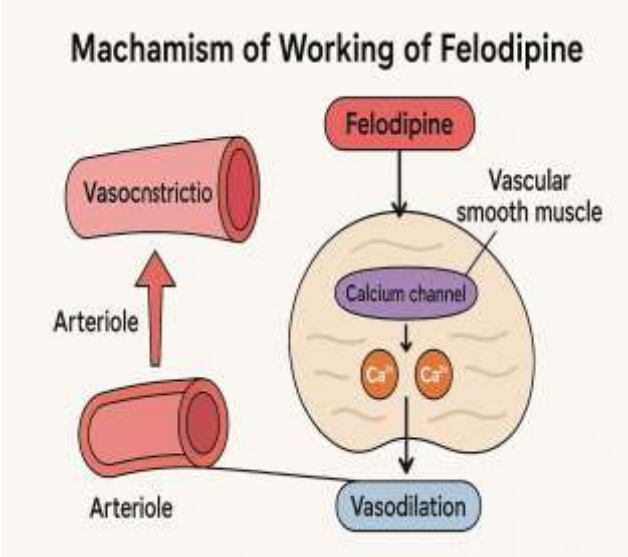
**Elimination**

The elimination of half-life felodipine is approximately 11-16 hours allowing for once daily dosing. Felodipine is primarily excreted as metabolites in urine(70%) and feces(30%). Less than 0.5% of the drug is excreted unchanged in urine.

**Mechanism of working**

Felodipine is a dihydropyridine calcium channel blocker that works by

- Blocking L-type calcium channels : Felodipine selectively binds and blocks L-type voltage-gated calcium channels in vascular smooth muscle and cardiac tissue. This action prevents the influx of extracellular calcium ions into these cells.
- Vasodilation: By reducing calcium influx into vascular smooth muscle cells, felodipine causes relaxation of arterial smooth muscle,leading to vasodilation.This effect is more pronounced in arterioles than in venules, resulting in reduced peripheral vascular resistance and decreased blood pressure.
- Coronary vasodilation: Felodipine also causes coronary vasodilation, which can improve myocardial oxygen supply in patients with angina pectoris.
- Minimal effect on cardiac contractility: Unlike some other calcium channel blockers, felodipine has minimal negative inotropic effects on the heart at therapeutic doses, making it safer for patients with compromised left ventricular function.




**Methods of synthesis**

Several methods have been developed for the synthesis of felodipine. Here are two common approaches:

1. Hantzsch Pyridine synthesis: This is a classical method for synthesizing dihydropyridines like felodipine.The process involves the condensation of an aldehyde, two equivalents of beta-ketoester and ammonia or an ammonium salt. The general steps include-

a) Reaction of 3-nitrobenzaldehyde with ethyl acetoacetate and methyl 3-amino crotonate
b) Cyclization to form the dihydropyridine ring
c) Reduction of the nitro group to an amino group

d) Chlorination of the amino group

2. Modified Hantzsch synthesis: A more recent and efficient method involves a modified Hantzsch synthesis using a microwave-assisted approach.

Key steps include:

a) Microwave-assisted reaction of 3-nitrobenzaldehyde, ethyl acetoacetate and methyl 3-aminocrotonate.

b) One-pot synthesis of the dihydropyridine ring

c) Subsequent reduction and chlorination steps

3. Asymmetric synthesis: For the production of enantiopure felodipine, asymmetric synthesis method have been developed.These often involves chiral catalysts or auxiliaries to control the stereochemistry of the reaction.

**Medicinal uses:**

1. **Hypertension-** Felodipine is primarily used as an antihypertensive agent, particularly effective in treating mild to moderate essential hypertension. It can be used as monotherapy or in combination with other antihypertensive agents.
2. **Angina pectoris-** Felodipine is also indicated for the prophylactic treatment of chronic stable angina pectoris. It reduces myocardial oxygen demand and increases coronary blood flow, thereby improving exercise tolerance in patients with angina.
3. **Reynaud's Phenomenon-** Some studies have shown that felodipine can be effective in treating Reynaud's phenomenon, a condition characterized by reduced blood flow to the extremities.
4. **Potential neuroprotective effects-** Emerging research suggests that felodipine has neuroprotective properties, potentially beneficial in neurodegenerative diseases like Parkinson's and Huntington's disease.

**Adverse effects:**

**1. Peripheral Edema -** The most common side effect of felodipine is peripheral edema, particularly in ankles and feet. This is due to the drug's vasodilatory effects.

**2. Flushing -** Facial flushing can occur due to the vasodilatory effects of felodipine.

**3. Gingival Hyperplasia -** Although rare, felodipine can cause gingival hyperplasia( overgrowth of gum tissue) in some patients,particularly with long term use.

**4. Cardiovascular effects-** In rare cases, felodipine may cause tachycardia or worsening of angina, particularly in patients with severe obstructive coronary artery disease.

**Treatment of overdose:**

Felodipine overdose treatment primarily focuses on supportive care and managing cardiovascular symptoms. As a dihydropyridine calcium channel blocker, felodipine selectively relaxes vascular smooth muscle, leading to decreased systemic vascular resistance and blood pressure. In cases of overdose, this can result in severe hypotension and bradycardia. The initial management of felodipine overdose is similar to that of other calcium channel blocker overdoses. Treatment typically includes intravenous fluids, vasopressors, and calcium administration. For cases with evident cardiotoxicity, a combination of calcium and epinephrine is considered first-line therapy. In refractory cases, high-dose insulin with supplemental dextrose and potassium therapy (HDIDK) may be employed. Interestingly, recent case reports suggest that intravenous lipid emulsion therapy may be effective in treating overdoses of lipophilic drugs, including calcium channel blockers like felodipine. This treatment creates an expanded intravascular lipid phase, potentially driving the drug from target tissues into a "lipid sink." However, optimal regimens for non-local anesthetic poisonings have not been established, and further research is needed to determine the efficacy of this approach for felodipine overdose specifically. Felodipine overdose treatment is not specifically addressed in the provided papers. However, as felodipine is a calcium channel blocker (CCB), the treatment approaches for CCB overdose can be applied.In cases of CCB overdose, conventional treatments include intravenous calcium, high doses of catecholamines, insulin, and glucagon. For evident cardiotoxicity, first-line therapy typically involves a combination of calcium and epinephrine.

Some studies have shown promising results with insulin-dextrose infusion in stabilizing hemodynamic status in patients with hyperdynamic circulatory shock from CCB overdose. Interestingly, newer approaches are being explored for

severe CCB poisoning. Levosimendan, a calcium sensitizer, has shown the potential to improve hemodynamics in cases refractory to conventional treatments. Additionally, in extreme cases of respiratory failure and refractory shock, early institution of venoarterial extracorporeal membrane oxygenation (ECMO) may be considered.

In conclusion, while specific treatment for felodipine overdose is not detailed, management typically follows CCB overdose protocols. These include conventional therapies like calcium, vasopressors, and insulin-dextrose infusion, with newer approaches like levosimendan and ECMO being considered in severe cases. It's important to note that treatment should be tailored to the individual patient's condition and response.

**Contraindications:**

Felodipine, a calcium channel blocker, is widely used for treating hypertension and cardiovascular diseases. However, there are some contraindications and precautions to consider when prescribing this medication:

1. Elderly patients: Felodipine pharmacokinetics are significantly altered in elderly patients. Studies have shown that the maximum concentration (Cmax), minimum concentration (Cmin), and area under the curve (AUC) were 3 times higher in elderly patients compared to young subjects. This increased exposure may lead to a higher risk of side effects in older patients.

2. Patients with liver dysfunction: Felodipine is primarily metabolized in the liver, and reduced hepatic blood flow or enzyme activity may affect its pharmacokinetics. Caution should be exercised when prescribing felodipine to patients with liver problems.

3. Patients with congestive heart failure or angina pectoris: While felodipine is being investigated for use in these conditions, more research is needed to establish its safety and efficacy in such patients.

4. Pregnancy: Felodipine has shown adverse effects in animal studies, including fetal toxicity. Felodipine should not be used during pregnancy unless needed.

**Interactions:**

Felodipine, a dihydropyridine calcium channel blocker, has been shown to interact with various substances and medications. Grapefruit juice can markedly augment the oral bioavailability of felodipine by reducing its presystemic metabolism through selective post-translational down-regulation of cytochrome P450 3A4 (CYP3A4) expression in the intestinal wall. This interaction can last up to 24 hours, potentially leading to a cumulative increase in felodipine AUC and Cmax with repeated juice consumption. Interestingly, felodipine's interaction with calcium-binding proteins such as calmodulin has been suggested as a potential mechanism of action, rather than solely blocking Ca2+ influx through calcium channels. This contradicts the traditional understanding of calcium channel blockers and highlights the complexity of felodipine's pharmacological effects. In conclusion, felodipine's interactions extend beyond grapefruit juice to include other medications metabolized by CYP3A4. For instance, prescribing clarithromycin (a CYP3A4 inhibitor) with calcium channel blockers like felodipine was associated with a higher risk of hospitalization due to acute kidney injury, hypotension, and all-cause mortality compared to azithromycin (which is not a CYP3A4 inhibitor). These findings emphasize the importance of considering potential drug interactions when prescribing felodipine, especially in older adults or patients taking multiple medications. Some important interactions are mentioned below :

1. **CYP3A4 inhibitors(increased felodipine levels) -** felodipine is extensively metabolized by CYP3A4 enzymes in the liver.Drugs that inhibit this enzyme can increase felodipine plasma concentrations,leading to enhanced hypotensive effects or toxicity.Examples: Erythromycin, ketoconazole,Itroconazole,Ritonavir(and other protease inhibitors),and Grapefruit juice(a well known CYP3A4 inhibitor).

2. **CYP3A4 inducers(decreased felodipine levels)-** These drugs can lower felodipine efficacy by increasing its metabolism.

Examples: Phenytoin, Carbamazepine, Rifampin, st.John's Wort.

3. **Beta-blocker-** Combined use may increase the risk of hypotension and bradycardia, although some combinations are used therapeutically with caution. Example: Metoprolol. 4. Diuretics and other hypertensives- It can result in other additive hypotensive effects.Examples: Hydrochlorothiazide, ACE inhibitors(e.g., lisinopril), ARBs(e.g., losartan).

5. **NSAIDs-** May reduce felodipine's antihypertensive effect by promoting fluid retention. Examples: Ibuprofen and naproxen.

**Conventional marketed formulations:**

Below is the list of some conventional marketed formulations, including their type, brand name, company name, dosage, and price:

**Felodipine drug :**

| Type | Brand name | Company name | Dosage strength | Price (INR) | Quantity | Price per tablet (INR) |
|---|---|---|---|---|---|---|
| Extended-release tablet | Felogard ER | Cipla Ltd | 2.5 mg | 31.45 | 10 | 3.15 |
| Tablet | Renedil | Sanofi Aventis pharma India | 2.5 mg | 22.00 | 10 | 2.20 |
| Tablet | Renedil | Sanofi Aventis pharma Ltd | 10 mg | 69.00 | 10 | 6.90 |
| Tablet | Plendil | Astra Zeneca Pharma India Ltd | 2.5mg | 40.27 | 10 | 4.03 |
| Tablet | Plendil | Astra Zeneca Pharma Ltd | 10 mg | 132.00 | 10 | 13.20 |

**Novel marketed formulations :**

Ongoing research has continued to explore novel delivery systems for felodipine to address its limited bioavailability and first pass metabolism, including nanoparticles, transdermal patches and lipid-based carriers.

**Patents:-** Notable patents include-

Manufacturing process- US patent US5942624A describes a method for synthesizing felodipine by reacting dichlorobenzylidene with ethyl 3-amino crotonate in an alcohol solvent, such as ethanol, with pyridine as catalyst.

Extended release formulations- WO2003094895A1 details an extended release tablet formulations where felodipine is dissolved or dispersed in a semi solid or liquid non-ionic solubilizer,combined with release controlling agent to achieve prolonged drug release.

Combination therapies- CN104173312A presents a sustained-release tablet containing both felodipine and Metoprolol salt, designed to maintain consistent dissolution rates of the active components over 24 hours.

Transdermal delivery - US patent US7018649B2 introduces a transdermal device for administering felodipine, offering an alternative route to oral administration for effective hypertension treatment.

**Conclusion:**

Felodipine, a dihydropyridine calcium channel blocker, has established itself as an effective and well-tolerated antihypertensive medication. Its primary mechanism of action involves the selective inhibition of calcium influx into vascular smooth muscle cells, leading to vasodilation and subsequent reduction in blood pressure. The drug's long-acting formulation allows for once-daily dosing, which can improve patient adherence to treatment regimens. Felodipine

has shown favorable outcomes in comparison and combination studies with other antihypertensive drug classes, highlighting its versatility in hypertension management. The safety profile of felodipine is generally favorable, with most side effects being mild and transient.Common adverse reactions include peripheral edema, headache, and flushing, which are typically dose-dependent and related to their vasodilatory effects. While felodipine is an effective monotherapy for many patients, it also performs well in combination with other antihypertensive agents, particularly ACE inhibitors, ARBs, and Beta-blockers. Felodipine remains a valuable tool in the pharmacological management of hypertension. Its efficacy, once-daily dosing, and generally well-tolerated nature make it a suitable option for many patients with hypertension. Ongoing research continues to refine our understanding of felodipine's place in contemporary hypertension management strategies.

**References:**

1.Leonardi, A., et al.(2017).Journal of cardiovascular pharmacology,69(1),4-13.

2. Bailey, D. G., Arnold, J.M.O., Munoz, C., and Spence, J.D.(1991).Clinical pharmacology and therapeutics 50(6),637-642.

3. Bailey, D.G., Malcolm, J., Arnold, O., and Spence, J. D. (1998).British journal of pharmacology,46(2),101-110.

4. Dulselman, P.H., and Edgar, B(1991).Clinical pharmacokinetics,21(6),418-430. 5.Edgar,B.,Lundborg,P.,and regardh,C.G.(1985).Clinical pharmacokinetics of felodipine drugs,29(2),11-23.

6. Frishman, W.H.(1995) Calcium antagonists: pharmacology and clinical use.American journal of hypertension,8(6),5S-14S.

7.Abernethy,D.R.,&Schwartz ,J.B.,(1999).Calcium-antagonist drugs New England Journal of Medicine,341(19),1447-1457.

8. Halperin, A.K.,&cubeddu, L.X.(1986).The role of calcium channel blockers in the treatment of hypertension.American Heart Journal,111(2),363-382.

9. Loev.B.,Goodman, M.M.,Snader,K.M.Tedeschi,R.,&Macko,E.(1974).Hantzsch-type dihydropyridine hypotensive agents.Journal of medicinal chemistry,17(9),956-965.

10. Onberg, L., and Westman, J.(2001)An efficient and fast procedure for the Hantzsch dihydropyridine synthesis under microwave conditions. Synlett,2001(08),1296-1298. 11.Thompson,A.E.,&Pope,J.E.(2005).Calcium channel blockers for primary Renaud's phenomenon: a meta-analysis.Rheumatology,44(2),145-150.

12. Seymour, R.A., Ellis, J.S.Thomson, J.M.(1994).Risk factors of drug-induced gingival overgrowth. Journal of Clinical Periodontology,21(4),245-249.

13. Leelach Rothschild, Guy Weinberg, Sarah Ostwald & Sarah Bern(2010) Scandinavian journal of trauma, Resuscitation and emergency medicine, Volume 18 (161)

14. Greene Shepherd(2006) American Journal of Health-system Pharmacy, volume 63(97).

15. Bailey, DG., et.al Grapefruit juice-felodipine interaction: mechanism and clinical relevance.Clin Pharmacol Ther(1991),50(6),613-620.

16. Dresser, GK, et al.Use of clinical pharmacokinetic data to predict the magnitude of CYP3A inhibition or induction.Clin Pharmacol Ther(2000),67(4),375-390.

17. Abernethy, DR, et al. Pharmacokinetics and pharmacodynamics of felodipine and beta-blocker combination therapy. J Clin Pharmacol (1989),29(5),405-410.

18. Neutel, JM, et al. Combining antihypertensive therapies: what works best?Am J Med(1999),107(6),66S-75S.

19. Johnson AG, et al. NSAIDs and blood pressure : A meta analysis of trials,Am J Med(1994),96(3),232-239.

20. Briggs GG, et al. Drugs in pregnancy and lactation,11th edition, Wolters Kluver 2017.