Pharmacokinetics:

- Bioavailability (F): 55%
- Excretion: urine (65%) & feces (35%)
- Protein binding: > 99% (albmin)
  - → Reduced protein binding in inflammation (weakly acidic microenvironment)
  - → Increases [diclofenac] & free fraction at required site
- Diclofenac accumulates in synovial fluid at levels that exceed plasma concentration & persist after plasma levels have substantially decreased
  - → Therapeutic efficacy in OA/RA

Diclofenac acid: IR capsule = Zorvolex

- Diclofenac acid 200-800 nm particles = facilitates dissolution w/in the SI
- Single peak absorption profile (no precipitation) → reduces ADRs

ADRs: dose-related

- GI ADRs: due to systemically absorbed diclofenac
  - → Topical injury in mucosa in contact with the API plays a minor role
- CV ADRs: increases risk of thrombotic events >150 mg/d

Injectables

Voltarol:

- IM administration
- IV administration: unstable follow dilution (immediate administration); infuse over 30-120 min (NOT bolus)
- Significant ADRs due to organic solvents (vascular irritant, local necrosis)

Dyloject: HPβCD (cyclodextrin) removes need for organic solvents (reduces ADRs)

- → CD exterior: highly-water soluble
- → CD interior: hydrophobic (non-covalent interaction w/ diclofenac)
- Ready to use formulations
- More effective than Voltarol

Diclofenac sodium salt

Enteric coated: Voltaren

- Diclofenac sodium tablet coated with hypromellose polymer (HPMC)
  - → HPMC gradually dissolves at higher pH within the small intestine, exposing the diclofenac core that rapidly dissolves
- Diclofenac absorption is delayed 0.5 – 2h
  - → In SI, t_{max} in 0.5 – 1.5 h

Sustained release: Voltaren SR

- Multi-layer matrix tech: diclofenac sodium in polymer sandwiched b/w 2 non-erosive polymer layers
  - → Outer layers act as barrier that regulates the SA of diclofenac layer that is exposed = controls drug release rate
- Diclofenac released over 8-10 h period
  - → Reduces dosing frequency
- Bioavailability similar to Voltaren, but has lower C_{max} and delayed t_{max}

Do EC/SR tabs reduce ADRs?
NOT REALLY…

- → Transferring site of dissolution reduces risk of gastric ulcers while increasing risk for duodenal ulcers
- → Voltaren SR associated with elevated risk of serious GI/CV ADRs

Solution: ARTHROTEC = EC diclofenac sodium core and outer misoprostol shell

- → Reduces GI ulcer risks

Diclofenac potassium

Immediate release: Voltaren rapide

- Displays erratic absorption profile: > 1 peak within first hours of plasma concentration-time profile
  - → Due to pH-dependent dissolution of Voltaren Rapide & fractioned gastric-emptying:
    - Initial peak = rapid absorption of part of administered dose
    - Later peaks = gastric-emptying of remaining dose that precipitated in stomach
      - Size of precipitates formed is polydispersed = dissolve at different rates once within the SI

IR sachet: Cambia – used in migraines (onset in 15 min compared to 60 min in tablet)

- → Bicarbonate buffering agent: prevents potassium salts from precipitating out of stomach

Topical Diclofenac: Voltaren (carbomer -based hydrogel) or Pennsaid (with DMSO = penetration-enhancer)

- Used to treat local pain and/or inflammation while limiting systemic exposure; minimizes ADRs associated with systemic administration
- Stratum corneum: primary barrier to topical drug absorption (hydrophilic corneocyte in a hydrophobic lipid)
  - Diclofenac contains a carboxylic acid linked to hydrophobic ring structure → able to penetrate through stratum corneum in *transcellular fashion*
- Drug penetration depth of diclofenac is 3-4 mm; capillaries carry NSAID deeper
  - < 10% of applied dose is typically absorbed
  - < 5% systemic absorption compared to oral diclofenac formulations
    - Reduces GI ADRs
    - Higher [diclofenac] reached within the tissue below site of topical administration

Voltaren Suppositories:

- Used mainly by pediatric patients
- Suppositories bypass first-pass hepatic metabolism
  - Improved bioavailability compared to tablets in children
  - 0.5 mg/kg for suppositories compared to 1mg/kg for oral treatments
- Fairly rapid absorption & onset of analgesia (t_{max} <1h)

Voltaren Optha

- 0.1% w/v ophthalmic solution of diclofenac sodium solubilized with Cremopher EL
- 1 drops 3-5 times/day to treat inflammation after cataract surgery or non-penetrating eye injury
- ADRs:
  - Ocular: lacrimation, keratitis, IOP increase, transient burning/stinging
  - Systemic: minimal due to negligible drug absorption