

Bioavailability File: KETOPROFEN

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Summary

Ketoprofen is a 2-(3-benzoylphenyl)propionic acid with anti-inflammatory, analgesic and antipyretic properties. It is used in the treatment of variety of acute and chronic inflammatory diseases and including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis as well as menstrual abdominal cramps. Ketoprofen's oral, dermal, rectal or intravenous formulations are available. The average ketoprofen elimination half-life is 2-4 hours. It has a simple metabolism, and a broad therapeutic window, and does not show accumulation in the body following multiple administration. It is metabolized in the liver and excreted in to urine and to a lesser extent in the faeces. In this review, physicochemical, pharmacological and pharmacokinetic properties in addition to bioavailability of ketoprofen are discussed.

Key Words: Ketoprofen, bioavailability, pharmacokinetics, stability, physicochemical properties.

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Özet

Ketoprofen, antiinflamatuar, analjezik ve antipiretik etkisi olan 2-(3-benzoylphenyl)propiyonik asit türevidir. Akut ve kronik inflamatuvar hastalıkların ve romatoid artrit, osteoartrit, ankilozan spondilit ve menstrüel karın kramplarının tedavisinde yaygın olarak kullanılır. Ketoprofenin, oral, dermal, rektal ve intravenöz formülasyonları bulunmaktadır. Ketoprofenin ortalama eliminasyon yarı ömrü 2-4 saattir. Ketoprofen basit bir metabolizmaya ve geniş bir terapötik pencereye sahiptir ve çoklu dozlarla birikme yapmaz. Karaciğerde metabolize ve atılımı, idrarla ve daha az olarak feçesle olur. Bu derlemede, ketoprofenin fizikokimyasal, farmakolojik ve farmakokinetik özellikleri ile birlikte biyoyarlanımını tartışılmıştır.

Anahtar Kelimeler: Ketoprofen, biyoyarlanım, farmakokinetik, stabilite, fizikokimyasal özellikler.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAID) present an important therapeutic class used to relieve pain and inflammation. NSAIDs can be further classified based on their chemical structure: salicylates, propionic, acetic, enolic (Oxicam) and fenamic acid derivatives; selective cyclooxygenase-2 (COX-2) inhibitors, sulphonanilides and others (1). Ketoprofen (KP) is a member of the propionic acid derivatives class of NSAIDs (2).

KP was originally synthesized by Rhone-Poulenc Research Laboratories, Paris, in 1967 and was initially approved for clinical use in France and the United Kingdom in 1973. Later, it has been approved by FDA for the treatment of osteoarthritis and rheumatoid arthritis (3,4).

KP is named as 2-(3-benzoyl phenyl) propionic acid. It is known effects are antiinflammatory, analgesic and

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antipyretic. It is used in a wide variety of acute and chronic inflammatory diseases and in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and abdominal cramps associated with menstruation (4–8). Recently, additional interest in KP lies in their possible therapeutic benefits in the prevention of various cancers including colorectal and lung cancers as well as in the treatment of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease (9,10). The drug is currently available in: capsul, tablet, solution, injectable solution, suppository, and topical gel formulations (11).

Common adverse effects of KP are nausea, diarrhea, dyspepsia, vomiting, abdominal pain, dizziness and headache (3,12,13).

It is a photolabile drug. Therefore must be protected from light as well as moisture (1,14). The plasma elimination half-life is 2 to 4 hours. Having simple metabolism and it does not accumulate with multiple doses. These features contribute to a rapid onset of action, flexible dosing and a reliable tolerance profile (3,6,13-17).

Physicochemical Properties

KP is named as 2-(3-benzolphenyl)propionic acid. KP's ($C_{16}H_{14}O_3$) chemical formula can be seen in Figure 1. Molecular weight is 254.3 (13,18). pKa of KP is 5.94 in methanol: water (3:1) and an n-octanol: water partition coefficient is 0.97 (buffer pH 7.4) (19).

It has one asymmetric carbon, a chiral centre, which gives rise to two enantiomers R (-) and S (+). Stereochemistry of KP can be seen in Figure 2. Both enantiomers possesses different biological activities. KP exhibits enantiomeric selectivity, only the S (+)-enantiomer is responsible for the pharmacological

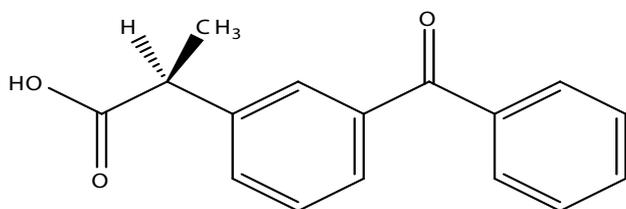
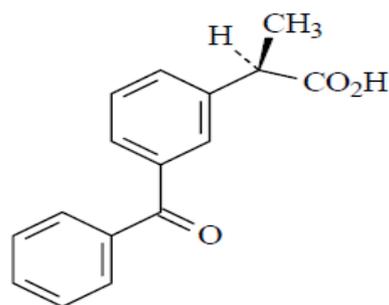


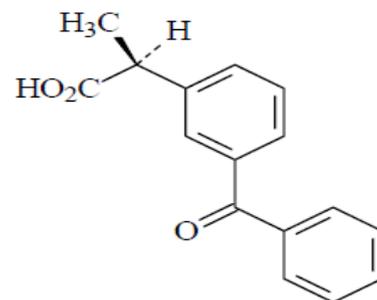
Figure 1. The chemical structure of KP (33)

and pharmacodynamic effects. R (-)-enantiomer is therapeutically less active or inactive (20). Interestingly, the inactive R (-)-enantiomer (the distomer) can undergo a configurational inversion into the active enantiomer in the presence of some enzymes and microorganisms. This metabolic conversion has been found to also yield some profen residues in fatty tissues by reaction of the R (-)-enantiomer–enzyme complex with endogenous triacylglycerols. The R (-)-enantiomers are unable to inhibit COX-activity. They can influence the adverse gastrointestinal effects caused by racemic forms. R (-)-enantiomers can induce modifications in neutrophil functions and intestinal permeability (4,21,22).

KP is odorless, white or almost white crystalline powder form, melting between 93-96°C. It is practically soluble in acetone, ethanol, methylene chlorid and strong alkali pH (4,8,12,13,19). It is poorly soluble in water and acidic conditions due to its pH-dependent solubility profile. It is known that poor solubility is generally leads to decrease in bioavailability, presenting a major challenge in drug formulation (23,24). KP belongs to class II of



R (-)-enantiomer



S (+)-enantiomer

Figure 2. Stereochemistry of KP (22)

Biopharmaceutical Classification Systems (BCS), which means that its low water solubility is the limiting step for absorption and bioavailability. This class also exhibit high permeability and low solubility and low dissolution rate related to the administered dose (24-28).

KP is also a photolabile drug. Therefore, KP must be protected from light as well as moisture. Exposure of aqueous KP solutions (eg: sodium salt) to visible light and ultraviolet radiation at 254 nm or daylight, for an hour at room temperature, it yields (3-benzoylphenyl) ethane which was subsequently converted to (3-benzoylphenyl) ethanol and (3-benzoylphenyl) ethanone analysis by thin layer chromatography and high-performance liquid chromatography. Samples stored at dark show negligible decomposition over 24 months (4,14).

In one study, stability of KP was tested for room temperature, +4°C and -80°C for 1 week and for three freeze-thaw cycles at two different concentrations (200 and 5000 ng/ml). The results were compared to aliquot of the same solution processed immediately after thawing and no significant change has been observed (29).

In another study, physical mixtures of KP were prepared using different excipients, including, lactose, mannitol, sorbitol, beta-cyclodextrin, polyvinylpyrrolidone K30, polyethyleneglycol 20.000 and urea in a ratio of 2:1 (drug/excipient). Samples and KP alone were stored at 40°C, 50°C and 60°C in sealed glass vials for 12 weeks. KP alone or when mixed with either lactose, mannitol, sorbitol or beta-cyclodextrin for 12 weeks at 60°C was found to be physically stable. However, KP in polyvinylpyrrolidone K30, polyethyleneglycol 20.000 or urea on stored at 40°C, 50°C and 60°C were unstable (30).

Analytical Methods

KP can be determined via spectrophotometric methods, Thin Layer Chromatographic Method (TLC), Gas Chromatography–Mass Spectrometry (GC–MS) and High-Pressure Liquid Chromatography (HPLC),

Capillary Electrophoresis, Capillary Isotachopheresis, combined use of headspace solid-phase micro-extraction and isotopic dilution, Flow-Injection (FI) technique and Capillary Electrochromatography (31-38). HPLC–MS or Micellar Chromatography are also used in KP determination. Ultraviolet (UV) and Infrared (IR) spectrophotometry and HPLC are preferred for KP analysis in biological fluids.

Other analytical procedures published for KP determination in topical preparations include a FT-near Infrared (FTIR) spectroscopy and solid-phase extraction (SPE)-UV spectrophotometric procedure, spectrophotometric and HPLC procedure (31,34,39-45).

FI-UV spectrophotometry has been extensively applied in routine analysis of KP gels and ampules. Quantitative determination was also performed using a new HPLC from a reference method, HPLC results were compared to those obtained from FI-UV spectrophotometry (39,46).

KP's organic and inorganic metabolites are excreted into urine. The HPLC determination of KP (formulated and spiked urine) samples carried out at 270 nm with mobile phase composed of acetonitrile:double distilled water:acetic acid. The practical utility of proposed method was examined on commercially available formulation and spiked human urine samples and it was concluded that the present method works well in identification of KP in pharmaceutical formulations as well as in urine (47).

In one study, KP alone and in binary mixtures with Eudragit S100 was compacted by an ultrasound-assisted (US) tableting machine applying an energy ranging from 50 to 400 J. The final material was analysed by TLC and HPLC. No decomposition product of KP was detected. IR spectra and Hot Stage Microscopy (HSM) revealed the absence of any interaction between the two components. Differential Scanning Calorimetry (DSC) showed that KP inside the mixtures was transformed into an amorphous state, confirmed by the decreased ΔH_{fus} as the Eudragit/KP ratio increases with elevated US energy. While pure KP recovers quickly after the US

treatment in crystalline state, the presence of Eudragit slows down or possibly prevents the regeneration of the crystallinity (48).

In another study, the inclusion complex of the KP with α -cyclodextrin (α -CD), β -CD, hydroxyl β -CD (HP- β -CD), sulfated β -CD, and γ -CD was prepared by mixing and shaking in solution, and then was freeze-dried for its solid products. The inclusion complex and physical mixture of the KP with CDs in the solid state were characterized by FT-Raman and FT-IR spectroscopy (49).

PHARMACOLOGY

Mechanism of action

KP is a NSAID with analgesic and antipyretic properties. As with all NSAIDs, the physiological basis of the pharmacodynamic activities of KP is resulted from inhibition of cyclooxygenase pathway of the arachidonic acid metabolism (Figure 3) (3). Arachidonic acid is the most abundant and probably the most important of the precursors of the eicosanoids. Free release of arachidonic acid from membrane phospholipids is catalysed by the enzymatic activation of phospholipid A₂. It is then converted to various forms of prostaglandins. KP is one of the most powerful inhibitors of cyclooxygenase at concentrations well within the range of therapeutic plasma concentrations (EC₅₀ 2 µg/L) (4). KP is 6 and 12 times more potent than naproxen and indomethacin, respectively, in inhibiting prostaglandin synthesis in isolated guinea pig lung preparations perfused

with arachidonic acid. Ibuprofen, phenylbutazone, and aspirin are reportedly 800-1500 times less potent than KP (3).

The antipyretic effect is due to a resetting of hypothalamic thermoregulatory center, whereas the anti-inflammatory and analgesic effects are due to inhibition of prostoglandin synthesis (6,7,50).

Uses and Administrations

KP is used to treat musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and in peri-articular disorders such as bursitis and tendinitis. It is also used to relieve postoperative pain, painful and inflammatory conditions such as acute gout or soft tissue disorders and to reduce fever (3,4,12,43). It is also indicated for the management of acute painful shoulder syndrome and juvenile rheumatoid arthritis (4). It is therapeutically equivalent to aspirin, indomethacin and ibuprofen in rheumatoid arthritis and to aspirin in osteoarthritis. KP can also be used in the following conditions (13).

- Prophylaxis and treatment of migraine headaches.
- Surgical and traumatic situations where analgesic action is required for sports injuries, orthopaedic manipulations, dental extraction.
- Infectious diseases which require analgesic, anti-inflammatory and anti-pyretic effects.
- Gynaecological conditions which involve the management of dysmenorrhoea following

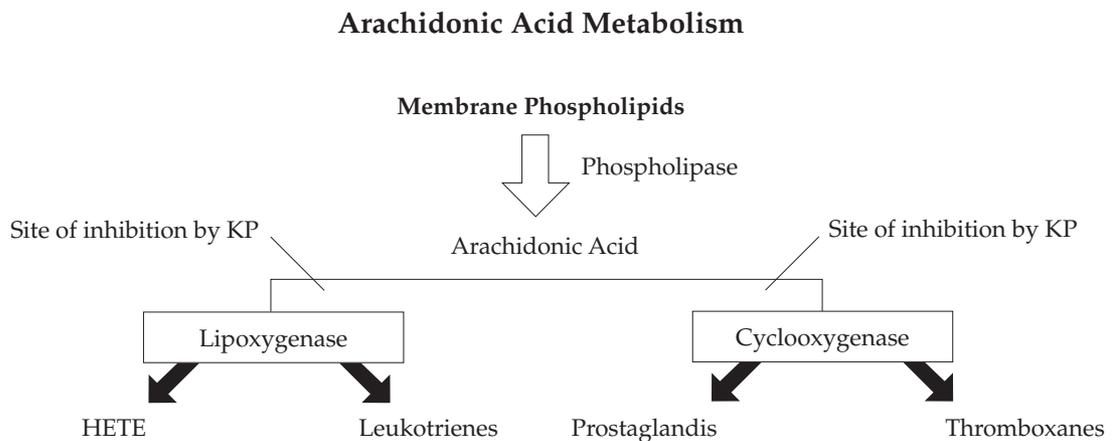


Figure 3. Schematic diagram of arachidonic acid metabolism (3).

intra-uterine device (IUD) insertion and for uterine relaxation and analgesia in post-partum, non-nursing women.

A quantitative systematic review of published controlled efficacy studies showed that at least one out of three felt 50% reduction in acute pain (soft tissue trauma, strains and sprains) after topical treatment with KP (51).

Recently, additional interest in KP lies in their possible therapeutic benefits in the prevention of various cancers including colorectal and lung cancers, and even in the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (9,10).

A study compared the efficacy and safety of single doses of 100 mg or 50 mg KP, the combination of 650 mg acetaminophen plus 10 mg oxycodone hydrochloride, 650 mg acetaminophen, or placebo in 240 patients with severe postoperative pain after cesarean section. Multiple doses of 100 mg or 50 mg KP and the combination at half the dose (325 mg acetaminophen plus 5 mg oxycodone) were also assessed for up to 7 days. A dose dependent effect was observed between the two doses of KP 100 mg provided significantly greater analgesia over the lower dose. KP, 100 mg, was as effective as the combination and analgesia lasted longer, with the exception of hour 1 when the combination was superior. Significantly more patients who took repeated doses of the combination (84%) than those who took either dose of KP (70%) had adverse effects. KP at both dose levels was shown to be effective, long-lasting, and well tolerated. It should be considered to be a drug of choice for the management of moderate to severe postoperative pain (52).

KP is currently marketed throughout the world in a variety of forms (capsul, tablet, solution, injectable solution, suppository and topical gel). The usual oral dose is 150 mg twice daily with meal, whereas 200 mg commercially controlled release preparations may be administered once daily (11).

Several topical preparations of KP have been shown to be effective. At the same time, it eliminates the adverse effects of oral KP. KP cream has been administered to the gingiva for treatment of periodontal disease. KP cream and intra-oral gel have been applied on the anterior skin of the neck to treat osteopenia, tension-type headache and migraine and reduced postoperative sore throat. Gel has been administered into oral surgical sites produced greater analgesic effect. A transdermal KP delivery system on reducing delayed onset muscle soreness have also been studied (53-60). Also, the effect of different ointment bases on the efficacy of KP topical preparations, dissolution rate of the KP nanoparticle gels forms, transdermal delivery of KP microemulsions and transdermal delivery of the drug from a new soya-lecithin aggregate, have been studied as well (61-64).

Precautions and Adverse Effects

KP is contraindicated in the following medical conditions:

i. Bronchospasm

Patients with rhinitis, nasal polyps and asthma associated with aspirin use may show cross-sensitivity with other NSAIDs including KP. KP can affect the lungs through inhibition of prostaglandins and increased concentrations of leukotrienes, leading to asthma exacerbation in susceptible patients (65).

ii. Peptic ulceration

KP should not be administered to patients with active peptic ulceration or with a history of recurrent peptic ulceration or chronic dyspepsia. KP irritates the gastrointestinal tract (GIT) through both local and systemic effects. Although it has been theoretically possible to prevent upper GIT damage at the local level, systemic effects are responsible for injury via inhibition of protective prostaglandins (65).

iii. Severe renal insufficiency

Prostaglandins synthesised in kidneys are potent vasodilators that balance the effects of vasoconstrictive stimuli (norepinephrine, angiotensin II and renin) on renal blood flow. Therefore, prevents of their production can affect renal function in some

situations. As expected, the presence of pathologic conditions such as congestive heart failure, high renal state, cirrhosis and renal disease predisposition and renal ischaemia can be seen on the patients during KP treatment (3,65). Any patient with these risks is highly dependent on prostaglandins for renal flow. Renal functional changes induced by KP, whether asymptomatic or accompanied by oedema, are reversible upon withdrawal of the drug (3) Unwanted side effects of KP are due to inhibition of COX-1, while their therapeutic effects are due to inhibition of Cyclooxygenase-2 (66). Most of the adverse reactions are mild upper gastrointestinal complaints such as nausea, dyspepsia or epigastric discomfort. Less frequent are subjective nervous system symptoms (headache, drowsiness and dizziness) and complaints referable to the lower gastrointestinal tract (diarrhoea, gastritis, ulcerations, abdominal burning, constipation and flatulence) (3,26,67). The central nervous system related side effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm and rashes (8,12,67). Haematological adverse effects of KP include anaemias, thrombocytopenia, neutropenia, eosinophilia and agranulocytosis. KP has been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome. KP may also provoke renal failure especially in patients with pre-existing renal impairment. Fluid retention may occur, rarely precipitating heart failure in elderly patients (68,69). Other adverse effects include photosensitivity, eczema, alveolitis and pancreatitis (70-72).

PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

The absorption of KP has been studied in a variety of dosage forms including solid dispersions, oral tablets or capsules, extended-release tablets or capsules, topical gels, microspheres, microemulsions, nanocapsules and rectal suppositories.

Pharmacokinetic studies in human subjects showed that orally administered KP is rapidly absorbed, metabolized and excreted. It is almost completely

absorbed from the GIT (6,7,67,73). Total bioavailability is dose proportional in the range of 75-200 mg (23). The plasma half-life is approximately 2-4 hours in healthy young volunteers (23,36,76). Absorption is more than 90% complete; peak plasma levels (t_{max}) are reached within 1-2 hours (6,36,74-76). At a single dose of 150 mg, KP plasma concentration reaches values upto 15-25 $\mu\text{g/ml}$, which are much higher than the therapeutic levels (77). KP concentrations in the synovial fluid peak approximately 2 hours after the peak plasma levels and decrease more slowly, so that synovial fluid levels exceed plasma levels from 4 hours after PO administration. When taken with meal, KP's bioavailability is not altered, but food intake reduces C_{max} by approximately one half, and increases the mean time to peak concentration. The fluctuation of plasma peaks may also be influenced by circadian changes in the absorption process (5,75).

KP is rapidly eliminated from the blood after dosing. Thus, it must be administered frequently to maintain therapeutic plasma levels, without marked fluctuations between the maximum and minimum levels. Frequent dose administration is considered to be one of the possible causes of patient non-compliance. Thus, the use of a sustained-release, dosage form, once daily has both pharmacokinetic and clinical advantages in NSAID therapy. It was suggested that the sustained-release pellet formulation is a suitable formulation for once-daily use (78).

Distribution

Plasma protein binding of KP is approximately 99%. Therefore, it is primarily confined to the plasma compartment, as reflected by its relatively small apparent volume of distribution (20).

KP penetrates the skin in sufficient amounts to be effective for topical treatment of localized musculoskeletal diseases. A study compares the bioavailability of KP in a photostabilised gel formulation without photoprotection using a new dermatopharmacokinetic tape-stripping model and an established *ex vivo* penetration method performed on human skin. Analyses of the stratum corneum showed that about $12\mu\text{g/cm}^2$ KP is absorbed into the

skin from the formulations during the first 45 min. The rate of penetration of KP through isolated skin is approximately $0.2 \mu\text{g}/\text{cm}^2\text{h}$ for both formulations (14).

In a different study, the cerebrospinal fluid (CSF) distribution of KP was evaluated in children, between 4 and 144 months. Simultaneous venous blood and CSF samples were collected once from each child 7-67 minutes after KP administration. In the children, the CSF to total plasma concentration ratios of KP remained less than 0.01 in all cases. The KP concentration in the CSF ranged from 1.4 to 24 ng/ml (median 6.6 ng/ml) after the dose of 1 mg/kg (79).

In another study was used a synthesized triglyceride prodrug of KP (1,3-diacetyl-2-ketoprofen glyceride, DAKG) as a model prodrug for Central Nervous System (CNS) delivery. The permeability of KP in the brain-from-plasma direction is very low, due to complete ionization of KP's carboxyl group at physiological pH and moderate lipophilicity. Owing to these physicochemical and physiological characteristics, the distribution of KP into the brain is highly restricted. Coupling of diacetylglyceride to the KP's carboxylic group results in a increased lipophilicity, but this structural modification completely prevents the ionization of the KP carboxylic acid group. Indeed, results showed that DAKG improved the delivery of KP into the brain via increased permeability through the Blood Brain Barrier (BBB), followed by rapid hydrolysis to KP within the brain (80).

Another study, racemic KP in plasma and CSF after an administration of a nanocapsule suspension was compared to a reference formulation. In this study of the pharmacokinetic constants of KP in elderly subjects and young healthy volunteers were compared. Following oral administration of a 150 mg dose of KP, no difference in time to peak concentration (t_{max}) was observed between each groups. However, comparable to the younger subjects, elderly patients showed a significant increase in half-life ($t_{1/2}$) and area under plasma concentration-time curve (AUC), a non-significant reduction of volume of distribution

($V_{d/F}$) per kg bodyweight and a decrease in total clearance. These results suggest that the glucuronic conjugation of KP is slowed down with aging (81).

Metabolization

KP is metabolized in the liver to inactive metabolites that are eliminated by renal excretion. Similar to other NSAIDs, KP is extensively metabolised to acyl-glucuronide conjugates by hepatic microsomal enzymes. Indeed, little measurable quantity of unchanged KP has been found in urine and bile of subjects regardless of their age and kidney function. Most studies in which urinary cumulative excretion determined, show that up to 80% of the dose was recovered in the form of glucuroconjugated metabolite. However, other studies show up to 50% of the given dose is excreted in urine unchanged. As already discussed above, these findings are artefactual as glucuronide acyl-conjugates are readily susceptible to *in vitro* hydrolysis to the parent compound. Figure 4 shows the metabolic products of ketoprofen (3,4,13).

Elimination

KP is eliminated after virtually complete metabolism. The elimination is so fast that little or no accumulation is detected in plasma even after repeated administration. It is excreted in the urine as the unchanged drug (82).

The plasma clearance of KP is approximately 0.08 L/kg/h with a volume of distribution (V_d) of 0.1 L/kg after i.v. administration. The elimination half-life of KP has been reported to be 2.05 ± 0.58 h for i.v. and 2 to 4 hours for capsule formulations. In case of slow drug absorption, the elimination rate is dependent on the absorption rate and, thus, half-life ($t_{1/2}$) relative to an i.v. dose appeared to be prolonged. In a 24 hour-period, approximately 80% of given KP is excreted in the urine, primarily as glucuronide metabolite. Although enterohepatic recirculation of the drug has been postulated, biliary levels have never been measured to confirm this (83).

Recently, the systemic clearance of KP was shown to be significantly decreased in elderly patients.

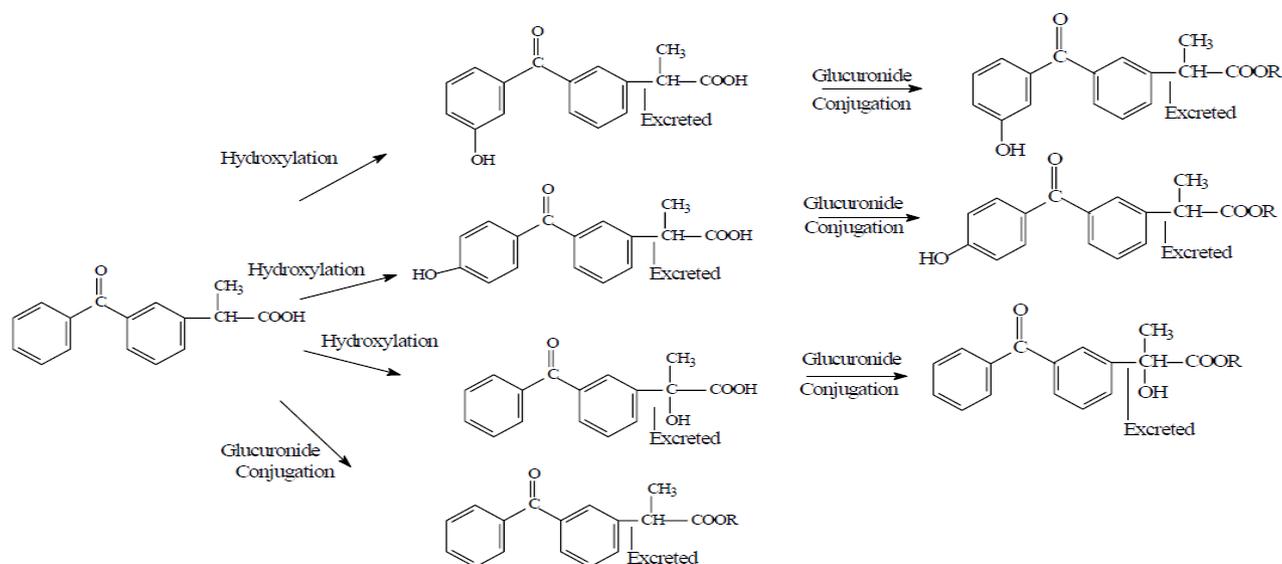


Figure 4. Metabolism of KP (3,13)

Conjugation with glucuronic acid is the major route for KP elimination. Approximately 65% of an oral dose is recovered in urine as KP glucuronide. Urinary excretion of unchanged drug accounts for only a very small fraction of the overall elimination. Therefore, it can be concluded that the observed reduction in KP elimination is due to decreased glucuronidation levels (81,84).

Drug Interactions

Despite 99% protein binding affinity, KP does not appear to alter the pharmacokinetics of other highly protein-binding drugs such as oral antidiabetic agents or anticoagulants. Single-dose bioavailability was unchanged when KP was given with food or with antacid. KP is influenced with following drugs.

Paracetamol

KP and paracetamol combination results in a significant decrease in morphine requirement comparable to analgesic treatment alone (85,86).

The pharmacokinetic studies revealed that this synergistic (supra-additive) effect doesn't due to pharmacokinetic interaction, but might be associated with protein binding. This synergistic analgesic effect may be of great clinical interest, providing an alternative for pain management as lower doses of each components may cause fewer adverse effects (87).

Aspirin

Williams et al. (73) studied the possibility of an interaction between these 2 drugs in 14 healthy volunteers, given 13 doses of KP 50 mg every 6 hours with or without aspirin 975 mg every 6 hours. A complex drug interaction is seen with this combination. Salicylate pharmacokinetics are unaffected by KP, presumably due to the relatively high molar doses of aspirin compared with KP. Concomitant use of multiple NSAIDs should be avoided because of increased risk of adverse effects. Simultaneous use of KP and aspirin may result in reduced serum KP levels.

Diuretics

Concomitant hydrochlorothiazide administration with KP, reduces urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients under diuretic treatment are at a greater risk of developing renal failure secondary to decreased renal blood flow due to inhibition of prostaglandin synthesis (83).

Warfarin

KP doesn't significantly interfere the effects of warfarin on prothrombin time. Multiple bleeding sites may be a complication of warfarin treatment and GI bleeding a complication of KP treatment. Because prostaglandins play an important role in

hemostasis and KP has an effect on platelet function, concurrent therapy with KP and warfarin requires close monitoring of patients on both drug (3).

Lithium

NSAIDs elevates plasma lithium levels and decreases renal lithium clearance (3).

Methotrexate

KP may change the elimination of methotrexate leading to elevated serum KP levels and increased its toxicity. KP competitively inhibits methotrexate accumulation in rabbit kidney slices. This may indicate that KP could enhance the toxicity of methotrexate. KP is administered cautiously when used concomitantly with methotrexate (3).

Furosemide and angiotensin converting enzyme (ACE) inhibitors

Similar to other NSAIDs, KP slightly inhibits the sodium diuresis induced by furosemide and other diuretics. It may increase the risk of hyperkalaemia occurred with potassium-sparing diuretics and ACE inhibitors (83).

β -blockers

KP may reduce the antihypertensive effect of β -blockers (3). In a double-blind, placebo-controlled study, 40 elderly hypertensive patients treated with acebutolol or atenolol, together with furosemide, are randomized to receive either KP, 200 mg/day (50 mg q.i.d.), or matching placebo for 7 days. No clinically significant side effects or blood pressure or heart rate alterations are observed during the trial. It was concluded that KP does not interfere with blood pressure control in elderly hypertensive patients being treated with a combination of beta-blockers and diuretics (88).

Antiacids

Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with the rate or extent of the absorption of KP given in capsule formulation (83).

Probenecid

Probenecid increases both free and bound KP by reducing the plasma clearance of KP to about

one-third, as well as decreasing its protein binding. Therefore, KP and probenecid combination is not recommended (89, 90).

Alternative Formulation Types of KP

In one study, poly(ethylene glycol-diacrylate) (PEG-DA) hydrogels with two different concentrations, 30% and 50% w/w, were prepared by free radical polymerization method. The model drug KP has been incorporated into the hydrogel during photopolymerization and its release kinetics was tested spectrophotometrically at 256 nm in different buffer solutions of pH 7.5, 4.5, and 1.2. The results showed that the release of KP strongly depends on the dissolution of drug, initial polymer concentration, and the pH of the release medium. The release mechanism was found to fit Higuchi and first order kinetics when the release data of the formulations were applied to the models in the different pH mediums (16).

Ali et al. (28) prepared KP solid dispersions. This study probes the molecular interactions between KP and poloxamers that facilitate dissolution rate improvements using solid dispersions. KP solid dispersions were prepared at different mole ratios using poloxamers 407 and 188. By altering the ratio of drug to carrier concentration, different forms of solid dispersions were generated with the 2:1 mole ratio compositions producing solid solutions for all drug:poloxamer combinations employed. At higher drug contents, other forms of solid dispersions coexist with the solid solutions, including eutectic systems and microcrystalline drug in the carriers, depending on the ratio of drug to carrier. All our dispersions improved the dissolution rate of KP compared to drug alone or in a physical mix with the poloxamer, but the solid solution systems provided the fastest release whereas the eutectic composition offered a dissolution rate improvement, however to a lesser extent than the solid solution system.

Puglia et al. (91) prepared KP-loaded lipid nanoparticles (NLCs) incorporated into gels and compared to reference gels containing KP solution. Percutaneous absorption, their *in vivo* active localization in the stratum corneum and the anti-inflammatory effects were also investigated. NLCs

were able to reduce the drug penetration through excised human skin as dedected via tape-stripping test. Results showed that the drug permeation and drug accumulation in the horny layer were increased. Furthermore, a prolonged anti-inflammatory effect could also be seen with drug-loaded NLC compared to drug solution.

For another study, encapsulated of KP particles with polyions and gelatin to control the release of the drug in aqueous solutions were also tested. The release of KP from the coated microparticles was measured in aqueous solutions of pH 1.4, 4.1, and 7.4. The release rate has changed at these different pH values. At pH 7.4 the release rate of KP from the encapsulated particles was 107 times lower than that from uncoated KP. The results provide a method extending the drug release through self-assembly of polymeric shells on drug crystals (92).

In encapsulated KP in the electrospun fibers as a new approach for drug delivery system using electrospinning technique has been developed. These fibers were biodegradable polymers such as partially and fully hydrolyzed poly(vinyl alcohol) (PVA). The release was monitored in phosphate buffer of pH 7.4 at the body temperature (37°C) and at room temperature (20°C). The treatment of electrospun PVA with alcohol, results showed that the burst release was eliminated (93).

Targeting Studies

Enzyme-dependent pectin–KP (PT-KP) prodrug formulations were prepared for colon targeted delivery systems. A sensitive quantitative HPLC method was established for the determination of concentration of KP in rats. Preliminary experiments showed that KP distributes mainly in stomach, proximal and distal small intestine. However, KP released from PT-KP mainly distributes in cecum and colon. Confirming that PT-KP prodrug formulation has good colon targeting properties (94).

CONCLUSIONS

KP is a member of the propionic acid derivatives class of NSAIDs. The average half-life of elimination from human plasma is 2 to 4 hours. It reaches the highest

plasma concentration in 1-2 hours. Oral absorption of the drug is almost complete, with bioavailability of 90%. Plasma protein binding is approximately 99%.

KP is one of the most interesting chemicals and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and abdominal cramps associated with menstruation. Recently, additional interest in KP lies in their possible therapeutic benefits in the prevention of various cancers including colorectal and lung cancers and even in the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.

KP has a large spectrum of activity and can be given in different dosage forms. Moreover, this compound is an effective drug which is relatively safe and produces only minimal side effects.

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