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A review on method of synthesis and clinical pharmacokinetics of etodolac

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1. ABSTRACT:

Etodolac is nonsteroidal anti-inflammatory drug. It blocks cyclooxygenase 2 prostaglandins. It works by blocking your body production of natural substances that cause inflammation. It is used in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and in the alleviation of postoperative pain. It generally avoided during pregnancy and nursing. The R-enantiomer of etodolac is inactive against COX enzyme, but inhibits beta catenin level in hepatoma cell.

Key Word: Etodolac, steroid, cyclooxygenase 2, NSAIDS, etc.

1. INTRODUCTION:

Etodolac is a non-steroidal anti-inflammatory drug. It was patented in 1971 for medical use. It was approved in the US in 1991[11]. Etodolac do not inhibit cyclooxygenase 1 prostaglandins which occur in the stomach and kidney. But more selectivity block cyclooxygenase 2 prostaglandins, which cause arthritic inflammation[5]. It is clinically effective in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and in the alleviation of postoperative pain. It also provides relief of other type of pain, including that arising from gouty conditions and traumatic injury. The incidence of clinical adverse effect other than

dyspepsia and abdominal pain is similar to that observed with placebo and etodolac has been associated with a low rate of gastrointestinal ulceration and other serious events[3].

2. CHEMISTRY :

It is chemically designed as 1,8-Diethyl-4,9-dihydro-3*H*-pyrano[3,4-b]indol-1-yl acetic acid[1].

Etodolac is white crystalline powder. It is soluble in water.

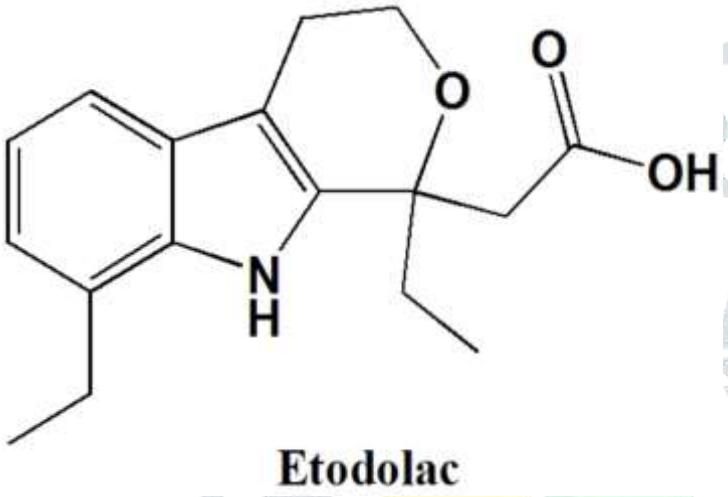


Fig : Structure of etodolac

Properties	Description
Chemical name	1,8-Diethyl-4,9-dihydro-3*H*-pyrano[3,4-b]indol-1-yl
Brand name	Etogesic, *Etova*, *Dualgan*
Formula	C17H12NO3
Molar mass	287.359 g·mol^{-1}
CAS Registry no.	41340-25-4
Melting point	145 to 148 °C
Refractive index	1.597
UV Spectrum	279.5 nm
Storage	Store in room temperature
Density	1.2±0.1 g/cm^3

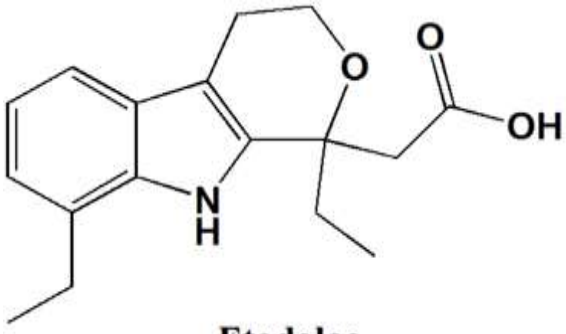
3. Mechanism of action :

1. Etodolac inhibits COX enzyme by binding with the upper portion of the COX enzyme active site and prevents arachidonic acid by binding with the active site[4].
2. Etodolac is 5-50 times more selective for COX-2 than COX-1.
3. It also produces central action on the hypothalamus and produces antipyresis effects, which results in peripheral dilation, increased cutaneous blood flow and subsequent heat loss

4. Structure Activity Relationship:

1. Substitution on the pyran ring with R_1 as an alkyl group and R_2 as an acetic acid function increases the anti-inflammatory activity.

2. On increasing the length of the acid chain, or ester or amide derivatives inactivates the drug[8].

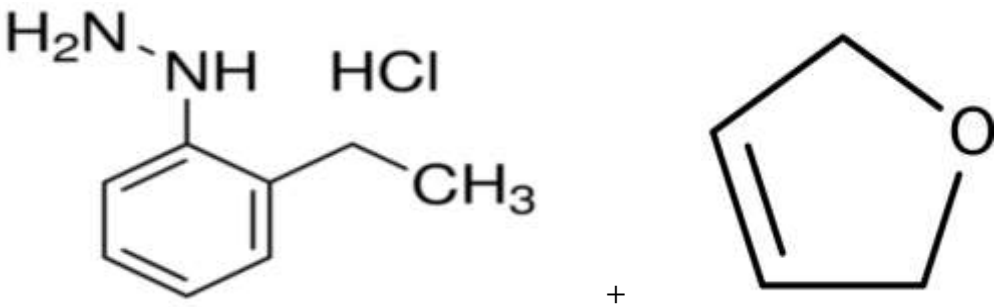


Etodolac

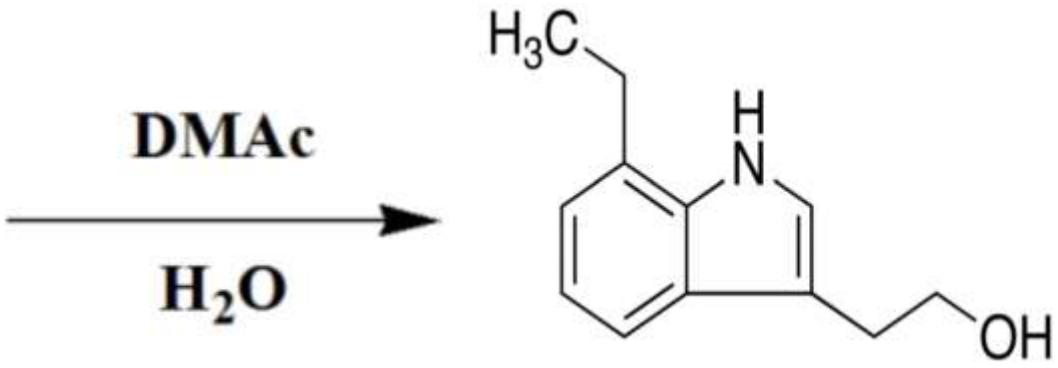
3. A-methyl acetic acid derivatives are also found to be inactive compounds.
4. Substitution of R1 as ethyl or n-propyl gives the compounds 20 times more active than methyl. Substitution on the 8th position of the aromatic ring is most beneficial.
5. Most active compounds of this class were found to be 8-ethyl, 8-n-propyl, and 7-fluoro-8-methyl derivatives.

6. METHOD OF SYNTHESIS :

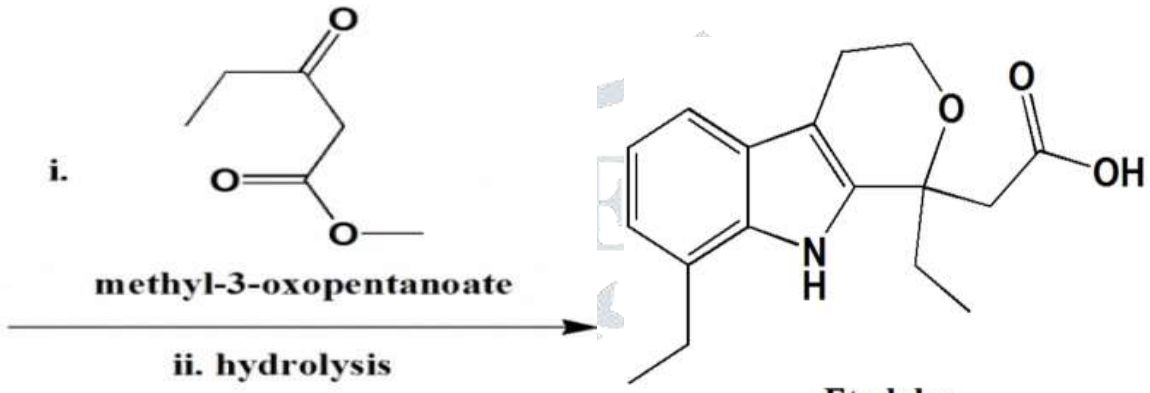
1. To the solution of 2-ethyl phenyl hydrazine hydrochloride in DMAc-H2O; 2,3-dihydrofuran is added dropwise and heated to get 7-ethyl tryptophol.
2. 7-ethyltryptophol is reach with methyl 3-oxopentanoate followed by hydrolysis to give etodolac[2].



2-ethyl phenyl hydrazine hydrochloride 2,3-dihydrofuran



7-ethyltryptophol



Etodolac

7.Pharmacokinetic Properties :

New information has recently become available regarding the penetration of etodolac into synovial fluid and its pharmacokinetics in special risk patients (including the elderly and those with impaired hepatic or renal function) Concentrations of etodolac and its metabolites in biological specimens have been quantified using high performance liquid chromatography (Ferdinandi et al. 1986; Kraml et al. 1984; Scatina et al. 1986)[6].

Table1. Mean pharmacokinetic parameters of etodolac in healthy young and elderly volunteers, and in subjects with renal or hepatic impairment

Reference	Subject (number)	Dose	Cmax (mg/L)	Tmax (h)	AUC	T1/2 (h)
Brater & Lasseter (1989)	Healthy volunteers (10)	200	11.5	1.8	55.1d	
	Renal insufficiency patients(10)a		12.9	1.2	43.8d	
Ferdinandi et al. (1986)	Healthy volunteers (4)	200	14.5	2.0	84g	6.1
Lasseter et al. (1988)	Healthy volunteers (10)	200	15.4	1.4	63.9e	5.7
	Hepatic cirrhosis patient (10)		17.4	1.1	67.4e	6.0
Scatina et al. (1986)	Healthy volunteers (20)b	200	15.9	1.2	65.8f	6.0
	Elderly subjects(24)c		15.3 16.7	1.2	60.4f	6.1

Reference	Subject (number)	Dose	Cmax (mg/L)	Tmax (h)	AUC	T1/2 (h)
	Elderly osteoarthritis patients(20)c			1.3	69.5f	6.5
Kraml et al.(1984)	Healthy volunteers (18)	400	21.0	1.6	115.1 g	6.5

a. Creatinine clearance 40-80 ml/min. B. Aged 19-34 years.
C. Aged ~ 70 years. D. 0-10 hours.
E. 0-co. f. 0-24 hours.
G. 0-48 hours.

Abbreviations: Cmax = maximum plasma concentration; tmax = time to Cmax; AUC = area under the plasma concentration-time curve; t'l2 = terminal plasma elimination half-life.

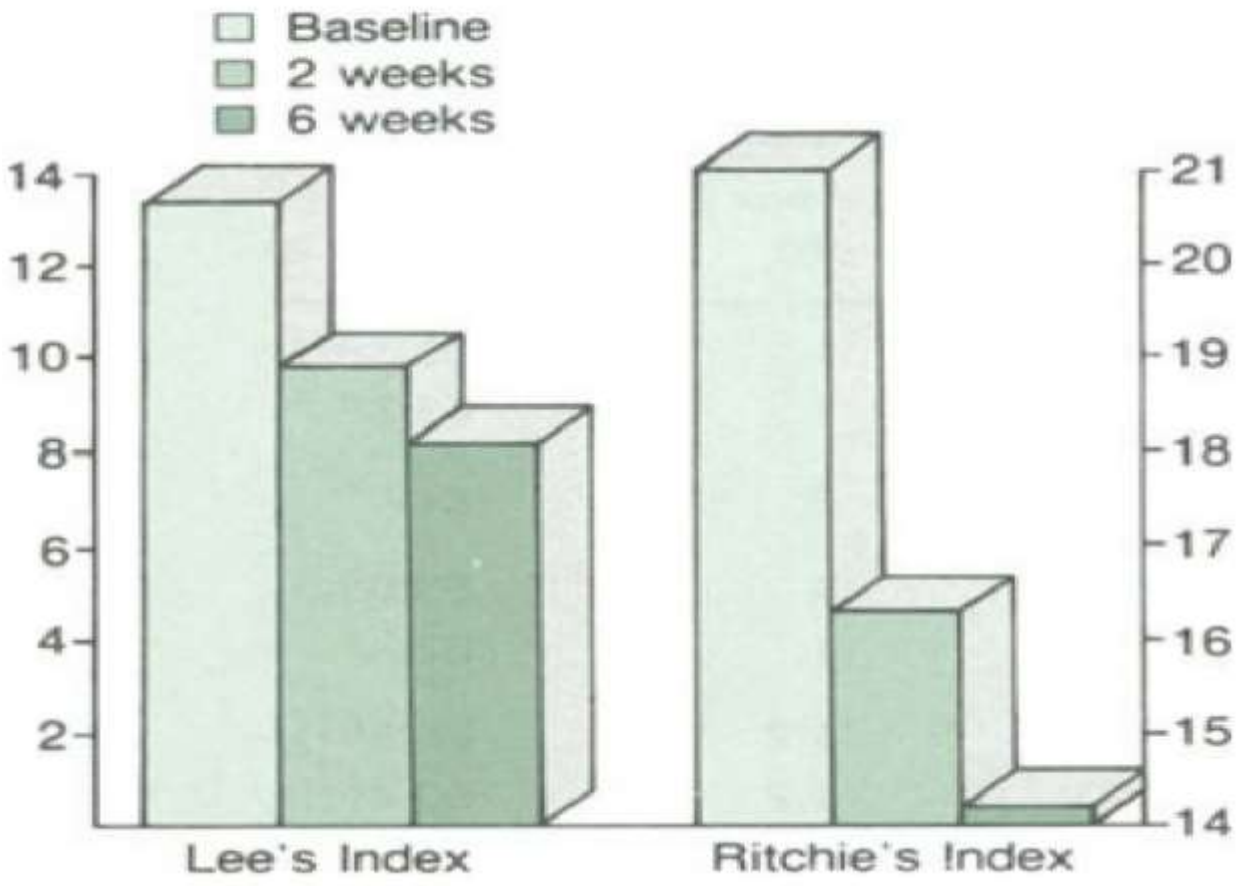
7.1 Absorption and Plasma Concentrations:

Peak plasma concentrations (Cmax) of etodolac are attained I to 2 hours after administration of the drug. In healthy subjects, For 200mg dose mean Cmax values were 11.5 to 15.9 mgfL a and 21.0 mgfL following 400mg. shows a typical plasma concentration-time curve for etodolac in healthy volunteers[6].

Etodolac absorption rate was enhanced by micronisation of the drug (Kraml et al. 1984) and decreased in the presence of food (Troy et al. 1990), neither of these factors affected its bioavailability (Kraml et al. 1984; Troy et al. 1990). Administration of antacid (unspecified) had no apparent effect on the rate or extent of absorption of etodolac (Troy et al. 1990)[30].

At 2 to 6 hours after administration of 14C-Iabelled etodolac, unchanged drug accounted for 70 to 80% of the plasma radioactivity (Ferdinandi et al. 1986). Mean area under the plasma concentration-time curve (AVC) values ranged from 55.1 to 84 mgfL . h following a single 200mg dose, and after a dose of 400mg, 115.1 mg/L· h value was recorded However, comparison is difficult because of the various time limits used for calculating AVCs in these different studies[13].

Fig : Mean values of Lee's and Ritchie's index at baseline, after 2 weeks' treatment and after 6 weeks' treatment with etodolac 400 to 600 mg/day in 1352 patients with rheumatoid arthritis (data from Benhamou et al.1989).



7.2 Distribution :

In common with most other NSAIDs, etodolac is extensively bound to plasma proteins and the amount bound is not dose-dependent at therapeutic concentrations (Brater & Lasseter 1989). Although Cayen et al. (1981) estimated plasma protein binding of etodolac at 95%, more recent studies reported values> 99% (e.g. Brater & Lasseter 1989; Chiang et al. 1990; Ferdinandi et

al. 1986; Scatina et al. 1986). An apparent volume of distribution of 0.41 L/kg was estimated in the healthy volunteers, following a single dose of etodolac 400mg (Cayen et al. 1981)[30].

Etodolac penetrated readily into synovial fluid following oral administration in 5 patients with active rheumatoid arthritis, who received 7 days' treatment at a dosage of 200mg twice daily (Kraml et al. 1988). Nevertheless, as might be expected, Cmax values for free and total etodolac were significantly lower, and tmax significantly prolonged, in synovial fluid vs serum (2.6 vs 15.6 mg/L and Drugs 42 (2) 1991 3.2 vs 1.2 hours for total etodolac), reflecting the time required for distribution of the drug from serum into synovial fluid. In the post distributive phase, synovial fluid: serum ratios of l.l8 and 3.25, respectively, between 8 and 32 hours post dose however, total and free etodolac concentrations in synovial fluid consistently exceeded those in serum. Albumin and total protein concentrations were lower in synovial fluid than in serum, resulting in a larger fraction of unbound etodolac in synovial fluid (2.47 vs 0.93% in serum). The relative availability (assessed as AVCO-24) of the drug in synovial fluid compared to serum was 67 and 172% for total and free etodolac, respectively.

Comparison of values for synovial fluid: serum ratios reported in the literature for tolmetin, piroxicam, ibuprofen, diclofenac, isoxicam and tenoxicam revealed that only diclofenac obtained better penetration into synovial fluid than etodolac (Kraml et al. 1988).

7.3 Elimination :

Following administration of single doses of 14C_ labelled etodolac 200mg to 4 healthy subjects, 73% ofthe dose was recovered in the urine (61% during the first 24 hours), and 14% in the faeces, within 7 days. Glucuronide conjugates of 3 hydroxylated metabolites and etodolac represented > 60% of urinary radioactivity (Ferdinandi et al. 1986). Significant enterohepatic recirculation of etodolac has been observed in dogs and rats (Kraml et al. 1984). The plasma clearance of etodolac was reported to be 40.8 ml/kg·h (Cayen et al. 1981) and the terminal elimination naif-life is around 6 hours (table IV). The half-life of etodolac in synovial fluid was similar to that in serum, at 6.2 hours[30].

7.4 Influence of Age and Renal or Hepatic Impairment :

Studies in elderly subjects with and without arthritis, and in those with impaired renal or hepatic function, including those with end-stage renal failure, have indicated that the pharmacokinetics of etodolac in such persons are generally not significantly different from those in healthy young subjects (Brater & Lasseter 1989; see table IV)[6]. Modification of etodolac dosage would not therefore seem to be important in these patients, although frequent clinical monitoring would be prudent precaution (Brater & Lasseter 1989).

A small but significant ($p < 0.05$) decrease in tmax compared with values in healthy subjects was observed in patients with hepatic cirrhosis, but was not thought to be of any clinical importance (Brater & Lasseter 1989). Although plasma protein binding appeared to be decreased, nonsignificantly in patients with moderate renal insufficiency, and substantially in those with end-stage renal failure, free drug concentrations were not increased. Etodolac is not removed by haemodialysis (Brater & Lasseter 1989).

8.Pharmacokinetic Profile in Special Populations

8.1 Effects of Aging : The pharmacokinetics of etodolac in elderly individuals were compared with those in young individuals by Scatina et al. (1986). In each group after repeated administration of etodo1ac (every 12 hours) for 7 days, the pharmacokinetic parameters did not differ significantly between young and elderly individuals. In the elderly there was a significant increase of 13% in the AUCO-12 between the first and the seventh days of administration; however, the investigators considered that this would be of little importance clinically[6]. It was concluded that dosage adjustments were probably not required in elderly patients. Aging also had no discernible effect on the plasma concentration of etodolac enantiomers in nonarthritic elderly volunteers with normal renal and hepatic function. Furthermore, there was no difference between young and elderly individuals in the cumulative renal excretion and renal clearance of the acylglucuronidated enantiomers. There are no data available describing the pharmacokinetics in children or infants[17].

8.2 Pharmacokinetics in Osteoarthritis : In their study involving the elderly, Scatina et al. (1986) also included a group of 20 elderly patients with osteoarthritis. The pharmacokinetics and serum protein binding of etodolac in this group of individuals were similar to those of the young individuals[24]. However, after multiple doses there was no detectable accumulation of drug in the osteoarthritic patients, unlike the healthy elderly individuals. The influence of

osteoarthritis on the pharmacokinetics of the pharmacologically active enantiomer of etodolac has not been reported[26].

8.3 Pharmacokinetics in Patients with Hepatic Cirrhosis : In a published abstract, the pharmacokinetics of etodolac in patients with hepatic cirrhosis were reported (Lasseter et al. 1988). There were no differences in AUC, Cmax, tmax, tI/z/3 or protein binding in serum between patients with hepatic cirrhosis and a control group of young healthy volunteers. It was concluded that dosage adjustments in such patients are not necessary. However, this conclusion must be viewed with some prudence because stereochemical concerns were not addressed. Specifically, a change in plasma concentrations of the Senantiomer might be obscured by the much higher concentrations of the R-enantiomer in plasma and serum[19].

8.4 Pharmacokinetics in Renal Disease : To date there is no published report describing the pharmacokinetics of etodolac in patients with renal failure. Nevertheless, it is of interest that the concentrations of acyl-glucuronidated etodolac enantiomer in the plasma of patients with rheumatoid arthritis. were somewhat higher than those in young and elderly individuals. Unfortunately, the renal function of these patients was not known. Due to the severity of their disease, which probably resulted from years of therapy with other NSAIDs, it is possible that some degree of diminished renal function was present that could explain the relatively high plasma concentrations of acylglucuronides in patients with rheumatoid arthritis. It is notable that after administration of ketoprofen, concentrations of acyl-glucuronidated ketoprofen were elevated in elderly patients with osteoarthritis or rheumatoid arthritis, but not healthy individual or young patients with osteoarthritis or rheumatoid arthritis (Foster et al. 1988a,b). Excretion of the glucuronidated metabolic products of NSAIDs appears to be highly dependent upon kidney function. Although these metabolites are inactive, they may result in elevation of the parent drug concentration because of they are unstable[6]. The validity of this suggestion and its clinical significance is yet to be tested.

8.5 Post-Surgical Patients : In 3 patients given etodolac after cholecystectomy, there appeared to be a delay in absorption (Brocks et al. 1992). The tmax for each patient was greater than 4 hours compared with a tmax of 2 hours or less in 11 of 12 healthy individuals (Brocks et al. 1992). Decreases in gastrointestinal transit time post-surgery, opiate analgesics and lack of ambulation might have caused the apparent delay in absorption [28].

9. Implications of Pharmacokinetics for therapeutic Use:

9.1 Therapeutic Dosage: The usual dosage range for etodolac is between 600 and 1200mg daily, given in 2 to 4 divided doses daily. For patients weighing less than 60kg, the maximum recommended total daily dose is 20 mg/kg (Wyeth-Ayerst 1992). There are no reports describing a relationship between serum concentrations of etodolac and anti-inflammatory, analgesic, or adverse effects[10].

9.2 Drug Interactions: There are no published studies describing pharmacokinetic interactions between etodolac and other drugs. The manufacturer has performed some unpublished studies, which are summarised in the prescribing information (Wyeth-Ayerst 1992) [20].

Antacids reduce the Cmax by up to 20%, but do not influence the bioavailability of etodolac. In the absence of conclusive data, discretion is advised when administering etodolac with warfarin, cyclosporin, digoxin, lithium and methotrexate. In common with other NSAIDs, etodolac could possibly cause an increase in the plasma concentrations of each of these drugs[29].

10.Conclusion:

Conclusions Similar to other NSAIDs, etodolac is well absorbed, highly protein bound and extensively metabolised. The acyl-glucuronides of etodolac accumulate to a considerable degree in the plasma of healthy young and elderly individuals. Therefore, it is important to determine the concentrations of etodolac and its conjugated metabolites in patients with some degree of compromised renal function. Acyl-glucuronidated etodolac also appears to be well distributed to the synovial fluid. From a pharmacokinetic viewpoint, etodolac is an interesting and unique drug due to the stereoselectivity present in its pharmacokinetics. Because the concentrations of the R-enantiomer are much higher than those of S-etodolac, studies that have used non stereospecific assays are mostly reflective of the inactive substance. Furthermore, the presence oflabile acyl-glucuronidated etodolac and its stability during sample handling are important considerations in pharmacokinetic studies of etodolac. If the primary objective of a pharmacokinetic study is to obtain information designed to correlate concentration with effect, then use of a nonspecific assay for a drug such as etodolac is not likely to achieve the desired outcome. This point is clearly illustrated by viewing the substantial stereoselectivity reported in the distribution of the enantiomers and the presence of acyl glucuronides in the synovial fluid, the proposed site of action in of NSAIDs in patients with arthritis. Hence, future

pharmacokinetic studies involving etodolac should ideally use stereospecific assay methodology for the determination of body fluid concentrations.

11.Acknowledgment :

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