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IMPACTS OF KETOROLAC TROMETHAMINE IN TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems which employ a structure as a reservoir for the drugs. A number of drugs have reached the market in transdermal delivery form that has become an increasingly acceptable mode for administration of prescription and nonprescription drugs. Transdermal drug delivery system possesses many advantages over conventional modes of drug administration. Ketorolac when combined with tromethamine forms a salt ('ketorolac tromethamine'), which has a greater aqueous solubility than ketorolac. Ketorolac tromethamine is a Nonsteroidal anti-inflammatory drug useful for short-term management of moderate to severe pain. Ketorolac tromethamine has high analgesic and anti-inflammatory potency; administered orally. The focus of this review article is to bring out different aspect related with the administration and its future impacts on human body after administration of ketorolac in transdermal drug delivery system.

INTRODUCTION:

Transdermal Drug Delivery System: Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications [1]. Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin [2]. The skin consisting of lipid structure provides a significant barrier to the penetration of highly lipophilic drug into blood. The entrapments of drug through skin are shown in **figure 1** [3].

Intensive research has shown that transdermal route is a potential mode of developing lipophilic drugs in systemic circulation [4]. Transdermal drug delivery system to be effective, the drug must obviously be able to penetrate the skin barrier and reach to target site [5]. The different drugs administered in the conventional patches are shown in **table 1** [6].

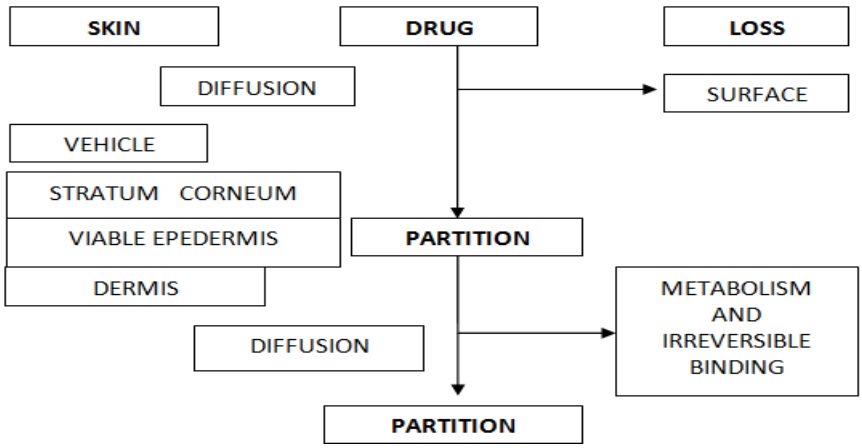

FIG. 1: SEQUENTIAL PHYSIOCHEMICAL STEP INVOLVED IN PERCUTANEOUS ABSORPTION

TABLE 1: TRANDERMAL PATCHES AVAILABLE IN MARKET

BRAND NAME	DRUG	MANUFACTURER	INDICATION
Alora	Estradiol	Thera tech/Protocol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	Thera tech/GlaxoSmith Kline	Hypogonadism in males
Catapress	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical holding/Wyeth-Ayerest	Postmenstrual syndrome
Climra	Estradiol	3M Pharmaceutical Labs	Postmenstrual syndrome
Deponit	Nitroglycerine	Schwarz-pharma	Angina Pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Moderate/severe Pain
Estraderm	Estradiol	Alza/Novertis	Postmenstrual Syndrome
Fematrix	Estrogen	Ethical Holding	Postmenstrual Syndrome
FemPatch	Estradiol	Parke Davis	Postmenstrual Syndrome
Habitraol	Nicotine	Novartis	Smoking Cessation
Minitran	Nitroglycerine	3M Pharmaceutical	Angina Pectoris
Nicoderm	Nicotine	Alza/Glaxo Smithkline	Smoking cessation
Nitrodisc	Nitroglycerine	Roberts Pharmaceutical	Angina Pectoris
Nitro-dur	Nitroglycerine	Key Pharmaceutical	Angina Pectoris
Nuvelle TS	Estrogen/Progesterone	Ethical Holding/Schering	Angina Pectoris Hormone
Prostep	Nicotine	Elan Corp	Smoking cessation
Testoderm	Testosterone	Alza	Hypogonadism in males

Ketorolac tromethamine: Ketorolac is an isostere of ketoprofen. More precisely, it is a dihydropyrrolizine carboxylic acid derivative structurally related to indomethacin [7]. Ketorolac have a chiral center and is used as a racemate marketed under the name Toradol, the (-)-S isomer has many times greater analgesic potency than the (+)-R isomer [8]. Ketorolac tromethamine is an off-white crystalline powder and has a pK a value of 3.49. Ketorolac is quite lipophilic with a log PC (partition coefficient) value of 2.72 [9]. Ketorolac tromethamine is extremely stable in aqueous solutions at pH 4-8, with a very long shelf-life at 25°C.

However, it is light sensitive with decarboxylation, especially in the presence of oxygen [10, 11]. Ketorolac tromethamine are administered either in the form of oral tablet, or in injected dosage form. Ketorolac is not available on the Pharmaceutical Benefits scheme [12, 13].

Entrapment of Ketorolac tromethamine drugs in the form of TDDS: Ketorolac is a nonsteroidal anti-inflammatory drug with potent analgesic and moderate anti-inflammatory activities by inhibiting prostaglandin synthesis [14, 15]. The transdermal delivery of ketorolac tromethamine plays a vital role in the therapeutics action of the drugs. To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen with oral administration, a transdermal drug delivery system has been studied as an alternative dosage form.

In addition to the noninvasive therapy and maintaining the drug blood levels for an extended period of time, the transdermal delivery system has several advantages: it avoids first-pass metabolism, it is easy to discontinue the administration, and it reduces side effects. Despite these advantages, only a limited number of drugs can be administered percutaneously, due to low skin permeability of most drugs through the skin. The stratum corneum was recognized as an excellent barrier against skin penetration. To overcome this problem, vehicles, penetration enhancers, and electron transport facilitated transdermal systems have been attempted in the development [16, 17, 18].

Advantage of Ketorolac Tromethamine in TDDS: As if oral bioavailability of ketorolac was reported to be 90% with a very low first-pass metabolism, its short biological half-life (4–6hr) insisted many adverse effects, such as upper abdominal pain and gastrointestinal ulceration, restricted for oral administration [19]. By then, the concept regarding delivery of ketorolac in the form of transdermal delivery has been suggested. Yu et al describes percutaneous absorption of ketorolac and ketorolac tromethamine in Rhesus monkeys using a number of solution formulations. Two vehicle combinations (propylene glycol and linoleic acid, and propylene glycol and oleic acid) were shown to be effective in enhancing percutaneous absorption of both ketorolac and ketorolac tromethamine. High C max values were achieved within 8 hours [20].

Concept regarding the Formulation of Ketorolac Tromethamine TDDS: The physiological properties of the drug and the material used in the TDDS such as molecular mass, lipid/water partition coefficient and solubility constraint in the subcutaneous influence transdermal permeation [21]. More widely it is found that most of the NSAIDS drugs get influenced by lipid/water partition coefficient to predict the bioavailability at constant solubility [22]. The lipid protein partitioning (LPP) theory has been formulated to describe the potential modes of action of penetration enhancer. More commonly used penetration enhancer are listed in **table 2** [23].

TABLE 2: CATEGORY BASED PENETRATION ENHANCER

CATEGORY	EXAMPLE	REFERENCE
Solvent	Menthol	24
	Ethanol	25
	Dimethyl Sulfoxide	26
	Propylene Glycol	27
	2-Pyrrolidone	28
	Isopropyl myristate	29
	Laurocapram (Azone)	39
Anionic surfactant	Sodium lauryl sulfate	31
Nonionic surfactant	Sorbitan monolaurate	32
	Pluronic	33
Essential oils	Cardamon oil	34
	Caraway oil, Lemon oil	35
	Menthol	36
	d-limmone	37
	Linoleic acid	38

Side Effects: Side effects of Ketorolac tromethamine cannot be anticipated. Only a medical practitioner can determine if it is safe for you to continue using Ketorolac or not. Generally the side effects that are seen to the initial phase are diarrhea, dizziness, drowsiness, headache, indigestion, nausea, stomach and intestinal pain, swelling due to fluid retention [39]. In patients taking ketorolac or other NSAIDs in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are listed in **table 3**.

TABLE 3: MORE WIDELY SEEN GASTRO INTESTINAL SIDE EFFECTS

Gastro Intestinal Disorders Include		
Abdominal Pain	Constipation/Diarrhoea	Dyspepsia
Flatulence	Gastro Fullness	Gastro ulcer
Gross Bleeding/Perforation	Heartburn	Nausea
Stomatitis	Vomiting	
Other Gastro Intestinal Disorder		
Abnormal renal function	Anemia	Dizziness
Drowsiness	Edema	Elevated Liver Enzyme
Headache	Hypertension	Increased bleeding time
Injection Site Pain	Pruritus	Purpura
Rashes	Tinnitus	Sweating

Additional adverse experiences reported occasionally (< 1% in patients taking Ketorolac in clinical trials) include:

1. Body as a Whole: fever, infections, sepsis
2. Cardiovascular: congestive heart failure, palpitation, pallor, tachycardia, syncope
3. Dermatologic: alopecia, photosensitivity, urticaria
4. Gastrointestinal: anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, rectal bleeding
5. Hemic and Lymphatic: ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia
6. Metabolic and Nutritional: weight change
7. Nervous System: abnormal dreams, abnormal thinking, anxiety, asthenia, confusion, depression, euphoria, extrapyramidal symptoms, hallucinations, hyperkinesis, inability to concentrate, insomnia, nervousness, paresthesia, somnolence, stupor, tremors, vertigo, malaise
8. Reproductive, female: infertility
9. Respiratory: asthma, cough, dyspnea, pulmonary edema, rhinitis
10. Special Senses: abnormal taste, abnormal vision, blurred vision, hearing loss
11. Urogenital: cystitis, dysuria, hematuria, increased urinary frequency, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure, urinary retention [40].

Necessary precaution taken for a patient: Ketorolac may infrequently cause serious (rarely fatal) bleeding from the stomach/intestines. Also, drugs related to ketorolac have caused blood clots to form, resulting in serious possibly fatal heart attacks and strokes. Ketorolac must not be administered in labor, breast-feeding, or have

stomach/intestinal problems (e.g., ulcers, bleeding), severe kidney problems, severe loss of body water (dehydration), or bleeding/clotting problems. It must be avoid before/after heart bypass surgery or before any surgery. Do not use ketorolac with high doses of aspirin or with other Nonsteroidal anti-inflammatory drugs (NSAIDs).

CONCLUSION: The use of the transdermal route has been well established since the 1800s as safe and effective drug delivery devices. Due to recent advances in technology and the ability to apply the drug to the site of action without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. Transdermal drug delivery technologies are becoming one of the fastest growing sectors within the pharmaceutical industry. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment, thus concept of administration of drug through transdermal route approaches successful enhancement of a drug as like ketorolac tromethamine. As if it posses a low incidence of side effect and its easy availability makes a good administration of analgesic by transdermal drug delivery system.

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