Expert Opinion

Ketorolac tromethamine formulations: an overview

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Ketorolac tromethamine (KT) is a non-steroidal anti-inflammatory drug that belongs to the class of heteroaryl acetic acid derivatives. It is a non-selective cyclooxygenase (COX) inhibitor, being marketed in the racemate form. Most of its analgesic and COX inhibitory activity is retained in the S-isomer. Ketorolac is administered as its tromethamine salt orally, intramuscularly, intravenously and as a topical ophthalmic solution. The frequent occurrence of gastrointestinal disturbances including gastrointestinal bleeding, perforation and peptic ulceration along with the short mean plasma half-life ($t_{1/2}$ ~ 5.5 h) has prompted for the development of various formulation strategies for the appropriate delivery of KT. The article gives an overview of the main concepts used thus far to design various pharmaceutical dosage forms for the therapeutically effective delivery of the drug candidate through various routes. At present, a great deal of emphasis is being placed on the development of sustained release forms for the drug as this would aid in achieving the required therapeutic efficacy and better tolerance with fewer gastrointestinal side effects.

Keywords: gels, intraoral, ketorolac tromethamine, nasal, ocular, ointments, oral, parenteral, transdermal

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications globally owing to their efficacy as anti-inflammatory, antithrombotic, antipyretic and analgesic agents. During the past 30 years there has been a substantial increase in the number of clinically available NSAIDs, owing to the enormous increase in the prescribing frequency of this category of drugs. Every day nearly 30 million individuals are being exposed to NSAIDs. The annual sales of NSAIDs are very high, ~ $6 billion; as a result there is a lot of focus on the development of suitable dosage forms for the optimum delivery of a drug candidate belonging to this category. NSAIDs may be classified as non-selective cyclooxygenase (COX) inhibitors and selective COX-2 inhibitors (coxibs). Ketorolac tromethamine (KT) is structurally related to indomethacin and is a member of the heteroaryl acetic acid non-selective group of COX inhibitors [1]. Ketorolac is a chiral NSAID marketed as the racemic mixture, in tromethamine salt form. Ketorolac and its pharmaceutically acceptable non-toxic esters and salts thereof are disclosed in US Patent No. 4,089,969, assigned to Muchowski & Kluge (Syntex) on 16 May 1978. The anti-inflammatory activity of the levorotatory isomer of the drug is twice that of dextrorotatory isomer [2]. Most of its analgesic and COX inhibitory activity is retained within the S-isomer [3,4]. Ketorolac is administered as tromethamine salt orally, intramuscularly, intravenously and as a topical ophthalmic solution. At present, the dosage forms of KT listed in the *Orange Book* are tablet (10 mg, Mylan, Ketorolac Tromethamine), ophthalmic solution or drops (0.5%, Allergan, Acular; 0.4%, Allergan Acular LS) and injection (15 – 30 mg/ml, Bedford, Ketorolac

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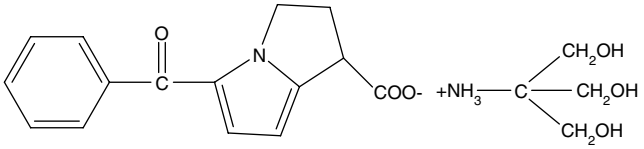

Chemical structure of ketorolac tromethamine.

Tromethamine) [5]. In the UK, it is marketed as tablets and injection (Roche Products Ltd, Toradol), ophthalmic eye drops (0.5%, Allergan, Acular and Acular PF (preservative-free)) and ketorolac solution for injection (30 mg/ml, Beacon Pharmaceuticals) [6].

Ketorolac contains substituted arylacetic acid, the common functional group of the NSAIDs. It may exist in three crystalline forms. All forms are equally soluble in water and have a pK_a of 3.5 and an *n*-octanol/water partition coefficient of 0.26.

The molecular mass of KT is 376.41 Da [7]. It acts at the cyclooxygenase pathway of arachidonic acid metabolism to inhibit prostaglandin biosynthesis. It has a highly potent analgesic activity and is not a centrally acting agent (or morphine-like agent) [8]. KT also appears to inhibit platelet aggregation induced by arachidonic acid and collagen. It does not affect prothrombin time, partial thromboplastin time or kaolin-cephalin clotting time [9,10].

KT is a potent non-narcotic analgesic agent used for the symptomatic relief of moderate to severe postoperative pain, including that associated with abdominal, gynecologic, oral, orthopedic, or urologic surgery [11,12]. It has been exploited extensively for its preoperative, intraoperative and immediate postoperative analgesic effects [13]. Its potency and efficacy are comparable to those of opioids and steroidal drugs. There are various drawbacks associated with the chronic administration of opioids, such as development of tolerance, physical and mental dependency, withdrawal symptoms and other side effects. KT has also been used for the relief of acute renal colic pain associated with trauma, and visceral pain associated with cancer [14,15]. On intramuscular administration, it produces analgesia comparable to that of intramuscular (i.m.) doses of meperidine, pentazocine, or morphine [16]. In some clinical studies, small doses of the drug have shown equal or better analgesia than well-established drugs such as naproxen sodium, morphine and glafenine [17,18]. In a study conducted in the post-anesthesia care unit (PACU), it was concluded that ketorolac 30 mg produces superior and prolonged postoperative analgesia and antiemesis than dexamethasone 4 mg or bethamethasone 12 mg [19]. Ketorolac has also been proved to be an efficacious analgesic alternative to opioids after abdominal surgical procedures, particularly in neonates and premature babies [20-22]. It is also a safe and effective supplement to opioid-based analgesia after partial nephrectomy [23]. Clinical studies indicate that KT can be successfully used as an alternative to opiates in the first-step treatment of severe cancer pain [24]. The anti-inflammatory activity of KT is inferior to its analgesic activity. KT was found to be 36 times more potent than phenylbutazone, approximately twice as potent as indomethacin, and 3 times more potent than naproxen in suppressing carrageenan-induced paw edema in rats [8]. The drug has been found to be effective at reducing intraocular irritation and cystoid macular edema after cataract extraction and lens implantation; 0.5% KT solution was found to be effective against various ocular infections caused by *Candida albicans* and *Pseudomonas aeruginosa* in the treatment of conjunctivitis [25]. KT has also been found to show antipyretic activity [26]. Owing to its superior analgesic activity [27,28], safety, non-sedative property and overall cost effectiveness when compared with narcotics in some clinical situations, it is recommended as an appropriate alternative for opioid analgesics (morphine and meperidine) [29]. It appears to be an excellent choice for treating moderate to acute pain. As a result, in the past decade enormous efforts have been made to develop suitable delivery systems for an effective site-specific delivery of the drug.

The most frequent adverse effects of KT are gastrointestinal disturbances including gastrointestinal bleeding (especially in the elderly), perforation and peptic ulceration. In some cases, it is also associated with pain at the site of injection. Ocular administration of the drug is also associated with transient stinging and ocular irritation [1,7].

1.1 Pharmacokinetic properties

KT is rapidly absorbed and maximum plasma concentration (C_{max}) of the drug is attained 30 – 40 min after oral administration and 45 – 50 min after i.m. administration. The mean plasma half-life of KT is consistent between peroral and i.m. administration, ranging from 5.21 to 5.56 h, and is independent of dose [30]. KT does not appear to undergo a significant pre-systemic metabolism. The bioavailability (F) of KT was estimated to be 87% [31,32]. The pharmacokinetics of KT is linear within therapeutically effective oral and i.m. dose ranges. Hepatic impairment has no effect on the half-life, whereas it increases significantly in renally impaired patients. The major metabolic pathway of its metabolism in humans is via glucoronic acid conjugation and hydroxylation in the liver. The metabolic products, along with some unchanged drug, are excreted in the urine. The pharmacokinetics of this drug is also greatly influenced during pregnancy and lactation [7].

1.2 Methods of analysis

KT is official in United States Pharmacopoeia (USP). Various methods of analysis like TLC, UV-spectrophotometric and HPLC methods are listed in its monograph [33]. The spectrophotometric determination of KT was validated by Kamath *et al.* in 1994 [34]. Several liquid chromatographic methods of analysis are available for the drug in both pharmaceutical formulations and biological samples. A very simple and cost-effective method

for analysis of KT by HPTLC was developed and validated by Devarajan *et al.* [35]. Recently, Eid and co-workers have developed a simple and sensitive flourometric method for determination of the drug in bulk, pharmaceutical dosage forms and biological fluids. The method depends on oxidation of the drug with cerium (IV) and subsequent monitoring of the fluorescence of the induced cerium (III) at an emission wavelength of 365 nm after excitation at 255 nm [36]. KT can also be analyzed by square-wave voltammetry using a glassy carbon electrode modified with a coating of polypyrrole [37]. Of all the salt forms of ketorolac, the tromethamine salt form is found to be the most susceptible to degradation at elevated temperatures and humidity. KT is a photosensitive molecule and should be stored in well-closed, light-resistant containers [33].

2. Drug delivery systems of KT

In light of the concern for the increase in the incidence of reported adverse events with KT, a great deal of emphasis is being placed on the requirement of a suitable delivery system, which would achieve maximum therapeutic efficacy along with minimum side effects. Various formulation strategies have been developed and are still in the developmental stages for the appropriate delivery of KT. It is available at present as tablets, ophthalmic solutions and injections. It is administered orally, intramuscularly, intravenously and topically (ophthalmic solution); but researchers worldwide are exploiting the other routes, such as nasal, otic, transdermal, and so on, to increase the therapeutic efficacy of the drug candidate. A great deal of the focus is on the development of sustained release forms for the drug as this would aid in achieving the required therapeutic efficacy and better tolerance. In the following section, all the available formulation strategies adopted for the delivery of ketorolac tromethamine through various routes are discussed.

2.1 Oral delivery

An oral formulation of the drug was launched in 1992 in the UK and is now marketed in ~ 25 countries worldwide. Orally, KT is indicated only as a continuation therapy to KT (i.v./i.m.) for management of moderately severe acute pain that requires analgesia at the opioid level in a dose ranging from 5 to 30 mg [1].

KT is absorbed completely on oral administration and the pharmacokinetics on oral administration is similar to that on intramuscular administration. Many individuals show faster absorption on oral administration of the drug, which is always preferred for the quicker onset of pain relief. Numerous spontaneously reported adverse drug reactions, case control, cohort and post-marketing surveillance studies have revealed that the immediate release NSAIDs are associated with extensive side effects, the most prevalent being upper gastrointestinal tract disturbances [38]. A recent trend in NSAID development has been to improve therapeutic efficacy and reduce the severity of upper gastrointestinal tract side effects through the development of suitable modified release dosage forms such as enteric-coated (EC) or SR formulations [39]. Controlled release matrix tablets of KT have been developed by various scientists to overcome the gastrointestinal side effects associated with the oral administration of NSAIDs. KT has a short plasma half-life ranging from 2.5 to 5.6 h and its dose is around 10 – 20 mg twice a day. Several investigators have studied the effect of using a variety of techniques to prolong KT release. Genc and Jalvand [40] investigated the effects of cellulose ethers (CEs) such as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC) and carboxymethyl cellulose (CMC) in different concentrations (10 – 20%) on the *in vitro* release of KT from tablets prepared by the direct compression technique. The *in vitro* drug release profiles obtained indicated that tablets prepared with HPMC:HEC:CMC (1:1:1) were found to be the more suitable formulations as they resulted in complete drug release in ~ 7.5 h. It was observed that the matrices swelled and release of the drug was achieved mainly by diffusion and erosion because of dissolution of the gel layer formed because of absorption of water by the CEs. The authors have also prepared a film-coated enteric tablet formulation of KT. In this study, Eudragit S-100 and L-100 were selected as materials for coating KT tablets by the spray technique. Polyethylene glycol (PEG) 4000 was used as a plasticizer. Dissolution studies were carried out on both coated and uncoated tablets. The results obtained indicated that nearly 97% of the drug was released in simulated intestinal fluid from the coated systems within 4 h [40,41].

Arora *et al.* [42] developed a controlled release osmotic drug delivery system for KT. Initially, they prepared swellable matrices of KT with HPMC in a ratio of 1:5. These matrices were further coated with a cellulose acetate film combining both matrix and reservoir properties for drug release. To modify the permeability of the film, PEG 400 and triacetin were used as canalizing agents in the coating solutions. The *in vitro* drug release profiles indicated that the tablets containing PEG 400 in the coat provided a higher rate and extent of drug release than the tablets containing triacetin. Further studies were carried out on the effect of osmotic contribution on drug release, wherein it was concluded that the semipermeable membrane was affected by the osmolality of the dissolution medium. The pH and the hydrodynamic conditions of the gastrointestinal tract were found to be ineffective in the case of permselective membrane-coated osmotic matrix tablets [42].

The effect of the amount of drug (30 and 40 mg), ratio of hydroxypropyl methylcellulose (HPMC)/sodium carboxymethylcellulose (NaCMC) (240/40 and 140/140 mg) and amount of ethylcellulose (140 and 180 mg) in controlled release matrix tablets was studied by Vatsaraj in 2002. *In vitro* dissolution tests were performed using USP apparatus 3 (Bio-Dis II) at various pHs to mimic the conditions that exist in the gastrointestinal tract. Application of analysis of

variance (ANOVA) to the dissolution data indicated that the time required to release 50% of the drug was influenced by the HPMC/NaCMC ratio and the amount of drug. The release mechanism was found to be super-case II transport [43].

Matrix-type formulations with dicalcium phosphate dihydrate (DCPD) using a polymeric binder (Eudragit RSPM) to obtain controlled release of KT have also been investigated. The *in vitro* drug release profiles were different, both in the presence and in the absence of a plasticizer. The amount of Eudragit also affected the drug release significantly [44].

Rahman *et al.* [45] have performed a small study to evaluate the effect of various fillers on the release of KT for the tablet formulation. In this study, it was observed that a combination of pregelatinized starch (Starch 1500) and microcrystalline cellulose (PH 102) showed higher release rates in comparison with other batches containing spray-dried lactose alone or in combination with microcrystalline cellulose or starch 1500.

In another study, Eudragit S-coated microcapsules (MCs) of KT were prepared by Genc *et al.* [46] by a coacervation phase separation technique induced by the addition of a non-solvent. Two sets of batches having a core-to-wall ratio of 1:1 and 1:2 were formulated. Coacervation was achieved by the addition of cyclohexane at a rate of 2 ml/min at 25°C and using a 1:4 so1vent (acetone):non-solvent (cyclohexane) ratio. The MCs thus obtained had an average particle size of 177 – 500 µm. Good yields in the range of 85 – 90% were obtained at both the coat levels. *In vitro* dissolution studies were carried out in simulated gastrointestinal fluid without enzymes and simulated intestinal medium. Dissolution study results indicated that release rate of the drug decreases as the drug-to-polymer ratio is increased. The prepared MCs showed best fit to modified Hixson–Crowell release kinetic model having the highest determination coefficient value ($r^2 = 0.9937$).

Recently, Etman *et al.* [47] prepared sustained-release pellets of KT to be given twice a day to maintain the effective therapeutic concentration for ~ 12 h. KT pellets were prepared using nonpareil seeds as an inert carrier and Eudragit RL: Eudragit RS as coating polymers. The drug release of KT from the pellets coated with Eudragit RL and Eudragit RS individually as well as in a ratio of 1:3 and 1:2, was studied. In this study, it was observed that increasing the proportion of the less-permeable polymer (Eudragit RS) in the coating blend from 1:0 to 1:3 (Eudragit RL: Eudragit RS, respectively) resulted in a further reduction in drug release. Batch coated at a ratio of 1:3 was concluded to be optimum as it provided sustained KT release over 12 h (~ 92%) and showed good physical and chemical stability. The Higuchi square-root of time kinetic equation was found to be the best fit mathematical model, indicating diffusion-controlled release of drug from the pellets. After 3 months of storage at 40°C, the color of the pellets changed from white to yellowish-white. The discoloration was attributed to the Millard reaction of the free amino groups of tromethamine with trace reducing sugars arising from the sugar-based nonpareil seeds. On exposure to accelerated stability conditions (40°C and 75% relative humidity [RH]), an appreciable increase in drug release was observed, which was attributed to the elevated moisture content of the pellets (from 2.2 9 to 2. 99 after 2 months), along with a modification in the integrity of the Eudragit coat. Therefore, storage at 25°C and 60% RH was recommended to maintain the required controlled release profile over a period of 12 h.

Lee *et al.* [48] developed an enteric coated system for KT. The formulation consisted of an inert core coated with a drug layer along with a binder and disintegrant, followed by a protective layer of an opaque agent such as titanium oxide (TiO_2) to prevent the drug from exposure to light and moisture. Furthermore, an enteric layer was applied to protect the patients from its ulcerogenic effects.

The development of effervescent granules for analgesics has gained a lot of impetus in the past few years. A fast melt tablet composition of KT having a controlled rate of effervescence was developed by compressing ketorolac effervescent granules (KET-EFG). KET-EFG were prepared by mixing the drug, sodium bicarbonate, anhydrous citric acid, binders (poloxamer and xylitol) and microcrystalline cellulose and extruding in a hot melt extruder at ~ 70 – 100°C. The granules were mixed further with mannitol, microcrystalline cellulose, magnesium stearate and fused silicon dioxide and compressed into single-unit dosage forms. The tablets thus obtained disintegrated in ~ 15 – 40 s in water at 37°C [49].

Oral administration of KT shows 100% bioavailability of ketorolac due to complete absorption and no first-pass metabolism, which correspondingly results in faster relief of pain. The key factor governing the efficacy of the drug is its absorption. A couple of studies have been performed to study the correlation between the *in vitro* release profile and the pharmacokinetic profile of the drug on oral administration. Earlier, Gordon *et al.* [50] performed a comparative study of the bioavailability of KT from tablet, capsule and oral solution. The study results supported the fact that the solution was absorbed more rapidly (t_{max} = 23 min) as compared with the tablet and capsule (t_{max} = 35 and 42 min, respectively). However, the mean plasma level at 20 min was highest for the solution (0.935 µg/ml), followed by the tablet (0.663 µg/ml) and then the capsule (0.288 µg/ml). The half-life values observed were 5.2 and 4.8 h for the tablet and capsule, respectively. All other pharmacokinetic parameters (C_{max}, AUC and $t_{1/2}$) were comparable for the solution and the capsule with the tablet. The results clearly indicated that the tablet and the capsule were similar with respect to the rate and extent of ketorolac absorption and the solution had a faster rate of absorption than the tablet. These results support the fact that solution and the capsule formulation designed for KT can be used as effective alternatives to the commercially available tablet formulations.

Gordon and Chowhan [51] proposed that the *in vitro* dissolution testing for ketorolac tablets can be a useful indicator of the time to attain maximum plasma concentrations

in vivo. They developed four different tablet formulations for ketorolac that demonstrated different dissolution rates, that is, (fast-dissolving tablets > medium-dissolving tablets (2 batches) > slow-dissolving tablets) and compared the *in vitro* release profile with their respective *in vivo* data. The single-dose mean pharmacokinetic characteristics and relative bioavailability of the 4 different 10 mg KT tablets were evaluated. The pharmacokinetic study was conducted in 12 healthy volunteers, the profiles of the average plasma concentrations for ketorolac were similar and the mean time for peak plasma concentration for the fast, the two medium-dissolving tablet batches and slow-dissolving tablets was 20 – 40 min, 40 min – 1 h and 40 min – 2 h, respectively. However, the peak plasma concentrations attained with these batches were not significantly different. Good correlations were obtained between the pharmacokinetic parameters (total AUC and mean plasma half-lifes, mean t_{max}) and the percentage dissolved at 20, 30 and 45 min. The rate of absorption of the slow-dissolving tablets was slowest among the other batches, whereas the medium-dissolving tablets were found to be bioequivalent to the fast-dissolving tablets. Similarly, Flores-Murrieta *et al.* [52] evaluated the bioavailability of ketorolac after administration of Exodol and Dolac containing 10 mg of KT each. They compared the *in vivo* release profiles from the two formulations. Exodol gave a mean concentration maxima of 934 ng/ml after 0.57 h of administration, whereas for Dolac the values were 1026 ng/ml and 0.48 h, respectively. The study indicated that KT was rapidly absorbed on oral administration as the peak concentration was observed for both the formulations within a period of 30 min. The study demonstrated that both the analyzed formulations were bioequivalent as per the limits set by US FDA.

2.2 Parenteral delivery

KT is the first injectable non-steroidal analgesic drug approved for the management of acute pain [1]. KT is available in the form of i.m. (30 – 60 mg) or i.v. (15 – 30 mg) injections for systemic action. An intravenous formulation of KT is approved in several countries, including the UK. The parenteral administration of KT (i.m. and i.v.) has limitations of patient non-compliance and invasive delivery for a reasonably longer period of time (5 – 6 days in severe pain conditions associated with major surgery). On the other hand, although the oral delivery of KT overcomes the disadvantages associated with invasive delivery, there is need for repeated administration because of its short biological half-life ($t_{1/2}$ = 5.2 h), making it difficult to maintain constant blood levels for effective treatment of severe pain conditions. To avoid frequent dosing and inconvenience caused to the patient, it is desired to develop prolonged release preparation of KT. The analgesic effect begins in 30 min with maximum effect in 1 – 2 h after i.v. or i.m. administration. Duration of analgesic effect is usually 4 – 6 h [7]. Several technological advances have since been made in the area of parenteral drug delivery, leading to the development of new systems that allow drug targeting and the sustained or controlled release of parenteral medicines. Parenteral controlled release drug delivery systems have shown tremendous growth in recent years. As all non-invasive routes are eclipsed with problems of poor absorption and low bioavailability, the parenteral route has become the most viable route for long-term delivery of drugs.

Parenteral depot formulations can overcome problems such as need of direct medical supervision and hospitalization and maintain the blood drug level in a therapeutically effective range for longer durations. Sustained release parenteral formulations duplicate the benefits of intravenous infusion and reduce the inherent disadvantages of conventional injectable drug administration. Such formulations also lead to decreased drug dose, reduced side effects and better drug utilization. However, there are various means of development of long-acting parenteral formulations such as emulsions, suspensions, liposomes, and so on, but each suffers from the drawback of difficulty in achieving long duration of action and tailoring of the release profile of drug according to patient requirement. Thus, various elaborative attempts have been made to design suitable microsphere-based drug delivery systems for the drug in the past decade. The principal advantage associated with the biodegradable microsphere-based systems is that they alleviate the problems associated with the above-mentioned systems and control the drug release over a predetermined time span usually on the order of days to weeks or months.

Prolonged release biodegradable polylactic acid/poly (lactic-*co*-glycolic acid) (PLA/PLGA) microspheres of KT for parenteral delivery were developed for the alleviation of postoperative pain in patients. Six different batches having drug-to-polymer ratios of 1:1 to 1:3 were prepared using both the polymers. *In vitro* dissolution studies were performed in a dialysis bag using pH 7.4 phosphate buffer for 36 h. An initial burst release of 20 – 30% was observed in the first 5 h followed by release in a controlled manner, releasing up to 80% of the drug within 36 h. The release of the drug decreased on increasing the polymer ratio owing to lower permeability of polymer. Release kinetics study demonstrated that diffusion is the main mechanism of release through PLA/PLGA microspheres. Scanning electron micrographs of drug-loaded PLA and PLG microspheres revealed a spherical shape with a smooth surface and microporous structures with open channels. The average diameter of the microspheres varied from 14 to 18 mm for all preparations. The microspheres were found to be stable at all temperature conditions. The formulation was found to be sterile and syringeable [53].

The normal treatment protocol with KT for treatment of moderate to severe postoperative or postsurgery pain, acute musculoskeletal pain, chronic pain states, postpartum or labor pains, and post-traumatic pain involves two to three injections a day. Thus, by developing a parenteral depot of biodegradable

microspheres using different polymers, therapeutic levels of the drug can be maintained for longer periods in the body, which can prevent painful injections given several times per day. In another study, Sinha and Trehan [54,55] prepared drug-loaded microspheres by an o/w (oil in water) solvent evaporation technique. Polycaprolactone (PCL), different grades of poly lactic glycolic acid (PLGA (65:35), PLGA(85:15)) and their blends with PCL in varying ratios were used in the preparation of microspheres. Solubility of KT is affected by the pH of the medium, thus in order to increase the encapsulation efficiency (EE) of the proposed systems, an acidic environment was created in the aqueous phase to prevent partitioning of the drug in this phase. EE was found to be higher in the case of the pure polymers PLGA (65:35) and PLGA (85:15) as compared with the respective blends with PCL. *In vitro* release profiles indicated an initial burst effect in the case of all the batches. Faster release in PLGA65/35 batches as compared with PLGA85/15 batches was observed owing to the lower lactic acid fraction in the former (lactic acid is hydrophobic in nature and decreases the water uptake by the system). Microspheres prepared with blends containing PCL showed a faster release rate as the semicrystalline nature of the polymer aids in faster water penetration and hence drug release. Studies revealed that with pure PLGA 65/35 and pure PLGA85/15 the release of drug was sustained for up to 30 and 60 days, respectively. When these polymers were blended with PCL in different ratios, drug release could be tailored from 5 days to 60 days. The results of the *in vivo* pharmacodynamic studies performed using the tail flick method revealed a significant difference in analgesic response between control and microspheres at almost all time points. Although the drug release was obtained for up to 30 days in the *in vitro* studies, the *in vivo* percent analgesic response was observed for 7 days only. This may be attributed to the balance between percent drug released and simultaneous degradation of drug in plasma. Subsequent to this study, the potential of polycaprolactone, poly-D,L-lactide (Resomer) and PLA was explored. To tailor the release profile of drug for several days, blends of Resomer and PLA were prepared with polycaprolactone in different ratios. Microspheres made with pure Resomer revealed higher encapsulation efficiency. Studies revealed that with pure PLA and pure Resomer, drug release was sustained for up to 60 days. When these polymers were blended with PCL in different ratios, drug release could be tailored from days up to months. Drug release from the proposed systems was basically governed by diffusion through the polymer and, also, by matrix erosion mechanism of a major part of the drug, which is bound to the polymeric matrix.

Mathew ST 2007 prepared albumin microspheres by a modified emulsion crosslinking method for once-a-day intramuscular administration of KT. In this study, liquid paraffin, glutaraldehyde-saturated toluene and 1% w/v Span 80 were used as the oil phase, chemical crosslinking agent and the surfactant, respectively. Spherical, non-porous and uniform microspheres were formed with a smooth surface. As the drug is photosensitive, the whole of the experiment was carried out under subdued light conditions. *In vitro* release studies of the pure drug as well as the microspheres were performed in a dialysis bag using phosphate buffer pH 7.4 as the dissolution or receptor medium. The drug polymer ratio was varied during the study and it was observed that a higher ratio of polymer supported a prolonged release profile for the drug along with higher encapsulation efficiency (20 – 60%) owing to the availability of a higher amount of polymer to coat the drug. A biphasic pattern of drug release was observed for most of the batches. Initially, the loosely bound or surface-embedded drug (~ 30%) is released in the first 30 min, followed by a slower release pattern due to the diffusion-controlled release kinetics. A comparison of the coefficient of correlation values indicated that the release data fitted best into Higuchi and Peppas kinetic models. The maximum particle size observed for the prepared batches was found to be < 40 µm, which makes them suitable for i.m. administration [56].

Puri and Bansal [57] developed a sustained release parenteral preparation of KT by incorporating polyvinylpyrrolidone, glyceryl monooleate and castor oil as the major release-retarding excipients. *In vitro* release studies were performed on the Franz diffusion cell assembly using an artificial filter membrane of hydrophilized polytetrafluorethylene (PTFE) with 0.45 µm pore size. The results obtained showed that the formulation containing castor oil and benzyl alcohol (vehicle) produced the maximum sustained effect followed by glyceryl monooleate (95% v/v) and polyvinylpyrrolidone (0.9% w/v), respectively. An acetic acid-induced writhing test was performed in male Swiss albino mice to determine the *in vivo* analgesic response of the drug formulation on i.m. administration of the formulations a saline solution of the drug was taken for comparison. All the standard and test formulations were injected into mice at a dose of 7.5 mg/kg and response was measured at 2 definite intervals of 15 min and 4 h. The test formulations produced a higher analgesic effect after 4 h as compared with the immediate release solution for the drug. A human dose of 85 mg/kg body weight was also calculated for the drug using the principle of superposition. The pharmacokinetic profiles of standard and test formulations were found to be significantly different, $p < 0.05$. The batch containing glyceryl monooleate produced a C_{max} of ~ 65 mg/ml, which was higher than the desired $C_{ss\ max}$. In this study, the drug blood levels were maintained within the desired therapeutic window (between 30.0 and 51. 39 mg/ml) for ~ 11 h. However, the batch containing castor oil produced the highest C_{max} of 100 mg/ml with a shorter duration of action. From this study it was concluded that glyceryl monooleate can form a successful depot system to control the release of the drug based on diffusional exchange of water from the surrounding medium into the matrix.

Considering the benefits achieved using the new drug delivery systems such as niosomes, liposomes and nanoparticles, Alsarra *et al.* [58] designed a proniosomal gel for the delivery

of KT. The gel was formulated by mixing 100 mg of the drug with surfactant, lecithin and cholesterol with absolute alcohol and phosphate buffer pH 7.4 sequentially. The proniosomal gel was mixed further with one of the following 2% polymeric gels (HPMC, CMC, or Carbopol) to give a final concentration of 0.5% KT. The drug was successfully encapsulated (~ 99%) in all the prepared batches. *In vitro* studies were performed in a glass tube containing a glass disk on which the gel was mounted and the dissolution medium was circulated over the membrane surface in a closed circle at a rate of 5 ml/min using a Watson–Marlow peristaltic pump. The study results indicated that incorporation of the proniosomes into the HPMC gel did not affect the drug release rate, whereas incorporation of the proniosomal system into the CMC and Carbopol gels produced retardation in drug release. It was also observed that proniosomes prepared with Span 60 provided a higher ketorolac flux across the skin than did those prepared with Tween 20 (sevenfold and fourfold the control, respectively), which is concluded to be because of the emulsification effect of the surfactant after the hydration of the proniosomes by the dissolution medium and formation of elution channels within the gel structure due to loss of lipid bilayers. *In vitro* permeation was investigated across excised rabbit skin from the various proniosome gel formulations using Franz diffusion cells. The results obtained indicated that a decrease in the amount of lecithin in the proniosomal system resulted in a corresponding decrease in the permeation flux, which is attributed to the premature leakage of the drug from the vesicles before its fusion with the stratum corneum. Hence, proniosomes were considered to be successful for effective delivery of the drug.

Recently Lichtenberger and Dial [59] developed a parenteral preparation of KT associated with phospholipids (PL) such as phosphatidylcholine (PC) to treat pain and inflammation, with a reduced occurrence of gastrointestinal (GI) toxicity due to its binding with PL during its passage from the GI lumen after being secreted into bile from the blood. The key benefits of these preparations are that they are effective for inducing the closure of the ductus arteriosus and prevent retinopathy in neonates, with a lower incidence of gastrointestinal side effects. Two basic preparation methods have been proposed in the study: i) mixing of the drug with the phospholipid fraction in a polar solvent, which is removed, and the resulting complex suspended in an aqueous medium and sterilized by filtration; and ii) mixing of an injectable anti-inflammatory pharmaceutical such as Toradol® (Roche Laboratories, Nutley, NJ), ketorolac tromethamine, with a phospholipid in the absence of an organic solvent, accompanied by agitating the composition and finally sterilizing it by filtration.

An alcohol-free injectable formulation was developed by Lee *et al.* [60] to obtain a more stable composition, as KT parenteral solution sold on the market is susceptible to light owing to the presence of alcohol. It is also contraindicated for intrathecal and epidural injections because of the 10% (w/v) alcohol content. The composition consisted of ~ 0.1 – 15% w/w of drug, 0.01 – 10% by weight of a phosphate solution, and 0.1 – 10% by weight of an isotonic agent. A pH-adjusting agent is also added to maintain the pH in the range 6.9 – 7.9.

2.3 Ocular delivery

So far, only two topical NSAIDs, Acular LS (ketorolac tromethamine ophthalmic solution 0.4%; Allergan, Inc., Irvine, CA) and Voltaren (diclofenac sodium ophthalmic solution 0.1%; Novartis Ophthalmics, East Hanover, NJ), have been approved by the US FDA for the treatment of ocular pain after surface ablation and other ocular disorders such as seasonal allergic conjunctivitis. Allergan markets an ophthalmic formulation of ketorolac for allergic conjunctivitis in the US and for postoperative inflammation in Europe under license from Roche Bioscience. Recently, Allergan has also received US FDA approval for use of its ACULAR LS formulation for the treatment of ocular pain following corneal refractive surgery. Use of the drug for ophthalmic indications has also been studied by licensee Santen. KT is being exploited extensively for its potential in the treatment of various ocular disorders. Several studies have confirmed that ketorolac effectively treats allergic conjunctivitis. Ketorolac 0.4% is effective when used as either monotherapy or as adjunct therapy to steroids [61]. A multi-center, masked, contralateral eye study indicated that KT is superior to nepafenac after LASIK because the latter produces delay in healing associated with increased corneal haze. The study was brought to an end because of safety concerns [62]. Several studies support the fact that 0.4% KT ophthalmic solution is more efficacious than 0.5% KT ophthalmic solution [63]. Ophthalmic topical NSAIDs aid in reducing both preoperative, intraoperative and postoperative-associated discomfort effectively [64,65]. At present, the ophthalmologist has to make a decision between the use of topical corticosteroids, with their potential adverse effects, or of topical NSAIDs, with their possibly increased benefit, effect on ocular pressure, wound healing and corneal tissue [66,67]. Data from various multi-center clinical studies support the fact that KT provides a cost-effective treatment in order to prevent intraoperative miosis and postoperative inflammation in cataract surgery over established steroids [68,69]. Topical application of ketorolac is safe in the vast majority of ophthalmology patients. However, NSAID eye drops should not be prescribed for patients with aspirin or NSAID allergy or a combination of asthma and nasal polyps unless the patient is known to tolerate aspirin without trouble [70]. Ophthalmic formulations of KT are useful for treating diseases that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. Ophthalmic formulations of KT (0.001 – 10.0% w/v) containing a quaternary ammonium preservative such as benzalkonium chloride (0.001 – 1. 0% w/v) and a non-ionic

surfactant (0.001 – 1. 0% w/v) such as polyethoxylated octylphenol compounds were developed by Fu and Lidgate. These formulations also contain other excipients, such as a chelating agent, a tonicifier, a buffering system, a viscosity-enhancing agent and other stabilizing agents. All the ingredients were mixed and dissolved in purified water and the pH was adjusted to 7.4 ± 0.4 and the final volume of the formulation was made up with purified water followed by sterilization. With the proposed method, physically stable, clear and antimicrobially effective formulations were obtained using non-ionic surfactants and a suitable preservative [71]. An ophthalmic ointment containing 0.5% (w/w) KT (in dissolved state) was prepared by dispersing aqueous solution of drug in simple eye ointment base using process 2, specified in the Indian Pharmacopoeia (IP). It showed higher *in vitro* transcorneal permeation with minimum corneal damage. The study results indicated that the chemical form and physical state of the drug affect its ocular permeation of KT [72].

Later on, Malhotra and Majumdar [73] studied the ocular availability of ketorolac following ocular instillation of aqueous, non-aqueous and ointment formulations of the drug on normal corneas of rabbits. The results of the *in vivo* studies depicted that the rate (T_{max}) and extent of absorption (AUC) of the ocular administration of the formulations based on sesame oil were equivalent to soyabean oil-containing preparations and higher than the ocular ointment. Similarly, the aqueous drops with BAC and EDTA improved the rate but not the extent of ocular absorption of KT. T_{max} observed with ointment was shorter and $t_{1/2}$ was longer, indicating faster absorption and sustained effect. This improved rate of ocular absorption is a result of higher clearance by increased lacrymation owing to the ocular irritant potential of the added ingredients. In another study performed in PGE2-induced ocular inflammation in rabbits, they concluded that KT ocular formulations are safe during chronic administration. They also evaluated the effect of these ocular systems against prostaglandin (PGE2)-induced ocular inflammation in rabbits. The measure of blinking rate and the migration of polymorphonuclear leukocytes in the tear fluid were evaluated for all the formulations. The study results supported the fact that chronic administration of KT through the ocular route is very safe and reduced the occurrence of gastrointestinal side effects even on chronic therapy [74].

Recently, a study has been conducted to examine the efficacy of 0.5% ketorolac ophthalmic solution (Acular) diluted to 0.25% with Refresh artificial tears in reducing ocular discomfort. The patients were exposed to a controlled adverse environment (CAE), which allowed the precise evaluation of agents that can act to treat dry eye and/or ocular irritation. Eighteen subjects participated in the study, and were exposed to 1 – 2 drops of 0.5% ketorolac, 0.25% ketorolac, or placebo (Refresh Tears – artificial tears). Ocular discomfort of each eye was assessed on a standardized 0 – 4 ocular discomfort scale. The study results indicated that 0.25% ketorolac produced a lower reduction in ocular discomfort as compared with 0.5% ketorolac, but it was as comfortable as the placebo immediately following instillation in the eye. A further dose range testing is proposed to identify a higher concentration than 0.25% but lesser than 0.5% to achieve a desired therapeutic efficacy accompanied with ease of administration [75].

Inserts containing 0.5% KT and poly(butyl methacrylate) (pBMA), poly(2-hydroxyethyl methacrylate) (pHEMA) and poly(2-hydroxypropyl methacrylate) (pHPMA) hydrogels were prepared by Karatas and Baykara [76] using the film casting method. Polyethylene Glycol 300 was added to inserts as a plasticizer. Swelling studies were performed by placing the insert into 5 ml of the buffer solution having pH 7.4 at 35 ± 0.5°C. The results indicated that pHPMA hydrogel swells rapidly in comparison with the pBMA and pHPMA hydrogels. Addition of PEG to the inserts also leads to a corresponding increase in the drug release as well as the swelling index, which is attributed to the hydrophilic nature of the excipient. The inserts were irradiated with an absorbed dose of 1.2 Mrad by means of a Co-60 source for sterilization. Sterility tests were also performed by incubating the insert into soya bean casein digest medium (pH 7.3) at 35 ± 0.5°C for 14 days. None of the prepared batches showed microbial growth. The drug release mechanism was found to be diffusion controlled for the hydrogel matrices as the n value was in the range 0.489 – 0.690.

Muller *et al.* [77] developed an aqueous sterile composition containing 0.35 – 0.45% KT for controlling ocular postoperative inflammation or ocular postoperative pain as a result of photorefractive keratectomy (PRK) surgery. The designed formulation contained 0.4% of KT and significantly lower concentrations of preservative, surfactant and chelating agent. A multi-center, randomized, double-masked, vehicle-controlled, parallel-group study was carried out to check the efficacy of the designed formulation. It was observed that the pain intensity was significantly less for the subjects who received KT 0.4% ($p < 0.001$), along with a quicker onset of action during the first 12 h post-PRK compared with those who received the vehicle only.

2.4 Nasal delivery

Nasal formulations are designed with the aim of avoiding gastrointestinal complications, improving patient compliance, as an alternative therapy to conventional dosage forms, to achieve controlled blood level profiles, and to obtain improved therapeutic efficacy in the treatment of postoperative pain and migraine. The nasal mucosa offers a large surface area and relatively low enzymatic degradation resulting in a rapid absorption of drugs into the systemic circulation producing high plasma levels similar to those provided by injections. Tremendous research is being done to develop a successful nasal delivery system for KT.

Sankar and Mishra [78] reported microspheres of KT for intranasal systemic delivery by an emulsification-crosslinking technique using Gelatin A, a biodegradable and biocompatible

polymer. The drug was dispersed in gelatin and formulated into a w/o emulsion with liquid paraffin, using glutaraldehyde as a crosslinking agent and chitosan as the copolymer. The prepared microspheres demonstrated good bioadhesive properties with discrete spherical shape. Formulation variables such as polymer concentration, percentage of the crosslinking agent and also the drug loading were varied to study the effect on the rate and extent of drug release. The study results indicated that an increase in concentration of the drug or polymer resulted in a corresponding increase in the particle size of the microspheres, which in turn resulted in higher drug incorporation efficiency. Addition of chitosan to the system resulted in larger microspheres and a significant increase in their bioadhesive strength owing to the interaction of the microspheres with the negatively charged mucin. *In vitro* study results indicated a biphasic release profile. Batches containing a higher percentage of gelatin showed a decrease in rate of drug release that was attributed to an increase in the diffusional path length in the polymeric matrix. Chitosan-gelatin microspheres produced a slower release rate. A comparison of the coefficient of correlation obtained from various release kinetic models indicated that the microspheres produced diffusion-controlled drug release following the Higuchi model.

Nasal spray of KT admixed with an aqueous bioadhesive cellulosic polymer or phospholipid was developed by Zia *et al.* [79] to provide a therapeutic blood level comparable to that of its injection and alleviate inconvenience associated with intravenous administration, especially in the case of migraine headaches. The formulation contained a colloidal microcrystalline cellulose suspension containing 5% by weight of KT and 0.25% v/v of 2-phenyl ethyl alcohol as a preservative and anti-caking agent. The pH of the final formulation was adjusted with HCl or NaOH to 5.8 – 6.1. Ketorolac formulations were administered either by the intravenous or the intranasal route to male New Zealand white rabbits for *in vivo* studies. As expected, an increase in bioavailability of nearly 46% was observed in the case of the polymeric nasal formulation as compared with the aqueous nasal suspension of the drug. The serum concentration after 3 h was higher in the case of the nasal polymeric formulation than in i.v. injection, which depicts a longer period of drug action. Recently, Whiting and Thriucote have observed that incorporation of a local anesthetic such as lidocaine hydrochloride along with KT in a nasal preparation provides an extra benefit of reduced stinging and improved efficacy, as compared with known nasally administered compositions [80].

A successful non-thermosetting intranasally administrable dosage form that achieves blood levels in a host, effective for analgesic or anti-inflammatory use, was developed by Santus *et al.* [81]. The formulation was designed to be free of polymers, providing a low viscosity at room temperature but an increased viscosity composition at body temperature. This formulation is indicated for the treatment of inflammatory processes and pain of traumatic or pathologic origin.

Quadir *et al.* [82] studied the pharmacokinetics of a series of spray and lyophilized powder formulations of KT using solid phase extraction followed by HPLC analysis. The spray and powder formulations were compared through their pharmacokinetic parameters and absolute bioavailability. The proposed study demonstrated that nasal spray formulations were significantly better absorbed than the powder formulations. The absolute bioavailability of ~ 91% was obtained with a spray formulation as compared with 38% with the powder formulation, irrespective of the polymers used. The lower bioavailability is predicted to be because of incomplete drug release from the polymer matrix before being removed from the nasal epithelium by mucocilliary clearance.

2.5 Intraoral delivery

Ketorolac tromethamine, (-) S enantiomer, in a concentration of 0.01% to ~ 0.15% by weight of ketorolac, is used for the prevention and treatment of primary and/or recurring squamous cell carcinomas of the oral cavity or oropharynx. Cavanaugh and Paul [83] developed various topical formulations such as mouthwash, mouthspray, dental solution and toothpaste for administration of KT to the oral cavity or oropharynx, alone or as an adjunct to surgery and/or radiation therapy. These formulations were administered either topically to the oral cavity or held therein for a period of time (preferably from ~ 20 s to ~ 10 min) and then expectorated rather than being swallowed, in order to achieve minimal systemic delivery of the drug. All the formulations were prepared using the conventional excipients. Similarly Kelm *et al.* have used oral rinses and dentifrices containing KT in the treatment of periodontitis [84]. Recently, bioadhesive films containing various polymers such as sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), HPMC and Carbopol 934 were prepared by Alanazi *et al.* by casting aqueous and organic solutions of the respective polymers [85]. *In vitro* bioadhesion of the prepared films was examined using chicken pouch as a model mucosal membrane. Films composed of 0.5% carbopol and 0.5% HPMC produced the desired *in vitro* bioadhesion and resulted in approximately sufficient drug release (90%) in 6 h. *In vivo* release study of KT from selected formulation was performed in six healthy volunteers. Drug levels were analyzed in the saliva samples using a validated HPLC method. The results of the study revealed that the film formulation in a dose equivalent to 10 mg KT was able to maintain therapeutic concentration of the drug > 3 µg/ml for up to 6 h in the oral cavity, which is effective for treating painful oral stimulations or stopping postoperative dental or gingival pain.

2.6 Transdermal delivery

Transdermal delivery systems have been widely accepted clinically for administration of various drugs systemically. The transdermal delivery bypasses hepatic first-pass and prevents gastrointestinal disturbances/side effects, maintaining a steady

drug concentration. Transdermal systems of KT have a prolonged therapeutic effect with reduced occurrence of toxic events. Transdermal patches of the adhesive matrix type, reservoir type and monolithic matrix type have been reported for the drug. In addition to the injectable formulation, Roche Bioscience is also developing suppository and topical gel formulations of this product in clinical trials.

Initially, an exhaustive study was conducted by Cho and Gwak [86] to investigate the effects of various pure solvents, co-solvents and penetration enhancers on the *in vitro* permeation of KT from solution formulation across hairless mouse skin to examine the feasibility of developing a successful transdermal system. The flow-through diffusion cell system was used for the *in vitro* permeation studies using hairless mouse skin. Ester-type vehicles such as propylene glycol monolaurate (PGML, Lauroglycol1 90) showed the highest enhancing effect initially, on drug permeation, owing to high diffusivity, partitioning and solubility. Isopropyl myristate on the other hand did not exert a very high enhancing effect, because of its extremely low solubility. It was observed that propylene glycol monocaprylate (PGMC) alone did not show high permeation rate, but the addition of diethylene glycol monoethyl ether (DGME) as a co-solvent increased the permeation fluxes almost two times at 20 – 60% of DGME as compared with PGML alone. An increase in the propylene glycol (PG) fraction in the PG-oleyl alcohol co-solvent system led to a corresponding increase in the permeation rate of KT. Using a drug concentration higher than its solubility was observed to be quite synergistic in increasing the permeation rate. The binary system composed of PG and various fatty acids was also evaluated. The proposed mechanism of action involves disorganization of the multilaminate hydrophilic-lipophilic layers located intercellularly in the stratum corneum, resulting in a corresponding increase in the drug permeation. The highest enhancing effect was attained with 10% caprylic acid in PG with a flux of 113.6 ± 17.5 mg/(cm^2 h).

A pressure-sensitive matrix system has been prepared in an organic solvent-based acrylic pressure-sensitive adhesive (TSR) at concentrations equivalent to 1% (w/w) of the tromethamine salt. The salt form of the drug did not dissolve completely in the organic solvent system and appeared as crystals in the final formulation. An adhesive matrix system was also prepared using KT at 1% (w/w) and a comparable water-based acrylic adhesive dispersion (NACOR 72-9965). The tromethamine salt dissolved completely in the water/emulsion system, and the dried matrix was free of drug crystals. *In vitro* skin flux experiments showed that the matrix systems manufactured using the salt and the water adhesive dispersion have significantly improved skin flux relative to systems produced using the organic solvent system or the conventional technique of combining the hydrophobic free acid form with a comparable organic solvent-based pressure sensitive adhesive [87].

Choi *et al.* [88] also evaluated the effects of pressure-sensitive adhesives and vehicles on the *in vitro* permeation of KT. They prepared various pressure-sensitive adhesive systems by incorporating the drug solution into the polymer solution followed by casting solutions on polyester release liner coated with silicone. The film thus obtained was oven-dried at 90°C for 20 min to remove the residual organic solvents. Skin permeation studies were performed using hairless mouse skin. Duro-Tak 87-2196, an acrylate-vinylacetate copolymer, produced the highest penetration rate (3.25 ± 1.69 μg(cm^2 h)), which was attributed to the presence of carboxyl functional group in the polymer. An increase in drug loading also resulted in an increase in the permeation flux. Propylene glycol monolaurate-DGME (60:40, v/v) and propylene glycol monocaprylate-DGME (60:40, v/v) were added as co-solvents in the dosage form. Both of them proved to be effective and resulted in higher flux of the drug, that is, 8.2 ± 2.7 and 6.3 ± 1.0 μg/(cm^2 h), respectively. *In vivo* pharmacokinetic studies were performed in male Sprague–Dawley rats using a dose of 661 – 746 μg. An overall decrease in the C_{max} and a corresponding increase in the t_{max} and $t_{1/2}$ values were observed in comparison with the oral delivery, indicating the efficacy of the designed transdermal delivery system for effective delivery of KT.

Uhrich and Schmalenberg [89] proposed the design of a therapeutic device for tissue regeneration, comprising biodegradable polymer that biodegrades to provide sustained release of anti-inflammatory compound to tissue. These agents are stably adsorbed onto or covalently attached to the device in selected patterns. The rationale behind the development of such a system was to facilitate formation of appropriate tissue connections by providing polymeric anti-inflammatory agents in a variety of forms that facilitated the growth of various tissues and cellular processes. They have proposed the development of such a system for many NSAIDs, including KT.

Kim *et al.* [90] prepared a film-forming agent for skin application of KT, using a combination of thermoplastic polymer polyurethane and a polymer having a functional group of carboxylic acid derivative at the main chain or side chain (e.g., Eudragit E) as the film-forming polymer. The film obtained with the proposed method had excellent elasticity and flexibility. It also showed superior adhesion power when formed on the skin, and resulted in a non-sticky film. A polymeric matrix containing 5 – 15% of KT dispersed in a biocompatible polymer such as ethylvinylacetate (EVA) and containing a radio-opacifying agent, for example, bismuth subcarbonate, was developed by Miller *et al.* [91]. As the drug is prone to degradation by heat and/or mechanical shear, the other two components are premixed at a temperature of 170 – 180°C in a twin extruder. Finally, the drug is combined with the premixed composition and subjected to further thermoplastic processing at permissible conditions of temperature and mechanical shear. This medical device thus obtained is adapted for implantation or insertion at a site associated with

pain or discomfort. Lee *et al.* [92] developed a transdermal patch of KT containing glycerin and sorbitan monolaurate and an acrylic adhesive polymer. The developed patch provided increased skin permeation of drug and improved drug stability within the adhesive layer. A monolithic matrix transdermal delivery system for administration of KT was developed by Wong and Nguyen [93]. The patch includes a copolymer of 2-ethylhexyl acrylate, 2-hydroxyethylmethacrylate and methacrylic acid in the matrix layer. The patch is prepared by suspending, or dissolving or dispersing the drug in a suitable vehicle followed by mixing with a selected polymer system to form a homogeneous suspension, solution, or dispersion. The resulting material, containing the active ingredient and the polymer system, is homogeneously dissolved or suspended in the vehicle and spread into a film and dried. *In vitro* skin flux studies were performed using human cadaver epidermis using a modified Franz vertical diffusion cell assembly. A significantly high rate of skin permeation flux was obtained through matrices formulated with acrylic polymers rather than those formulated using lipophilic polymers, which is attributable to the lack of solubility of the hydrophilic salt form of the drug. Of all the matrices examined, only the acrylic AE 2390 matrix gave a very high release rate (211 $\mu g/(h^{1/2}\ cm^2)$).

In view of the benefits such as higher affinity for biological membranes, better skin rehydration and toxicological safety offered by liposomes in the optimum transdermal delivery of a drug candidate, Ruozi *et al.* [94] developed these systems for KT by a thin-layer evaporation method. Cationic liposomes containing cationic lipids (dimethyldioctadecylammonium bromide and *N*-[1-(2,3-dioleoyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride) and phosphatidylcholine improved the entrapment of KT and resulted in an optimum release of the drug. Similarly, niosomes containing KT were prepared by an ether injection method by incorporating a mixture of polyglyceryl-3-di-isostearate, myristyl alcohol and polysorbate-80 and fatty alcohols as membrane stabilizers instead of cholesterol. Interestingly, niosomes containing fatty alcohols showed a similar release pattern to those containing cholesterol. In addition, the fatty acid chain length of polyoxyethylene sorbitan ester also affected the release rate and encapsulation efficiency [95].

2.7 Semisolids for skin

Nasseri and co-workers have developed microemulsion-based organogels (MBGs) for the topical application of 6.5% w/w KT. Earlier they constructed ternary phase diagrams to study the phase behavior of systems composed of lecithin/isopropyl myristate (IPM)/water or KT solutions at various lecithin/IPM weight ratios (K_m). MBGs were then prepared by dissolving the drug into a solution of lecithin in IPM followed by addition of water to induce gelation. The mixture was heated for a short duration to achieve complete solubilization of the drug. *In vitro* and *ex vivo* studies were performed using cellulose acetate or silicone elastomer membranes and full thickness hairless guinea-pig abdominal skin, respectively. *In vitro* study results indicated a higher drug release from the cellulose acetate membrane as compared with that offered by the silicone elastomer, which is attributed to the difference in the molecular mass cutoffs for both the membranes. A direct correlation between the drug concentration and release rate was observed in both the *in vitro* and *ex vivo* studies owing to an increase in the thermodynamic activity of the drug. An increase in the quantity of lecithin (40 – 60%) in the formulation led to an increase in the viscosity of the formulations along with a significant decrease in the permeation flux values because of extensive entrapment of the drug at higher concentrations of lecithin. The addition of 0.6% w/w of water in the formulation was found to be optimum for the desired release profile. The MBG containing a higher proportion of lecithin and optimum amount of water was concluded to be a desirable vehicle for transdermal delivery of KT [96,97].

Ong *et al.* [98] prepared a ketorolac topical gel formulation containing KT in concentrations varying from 1 to 5% w/w. The gel was prepared by adding an aqueous solution containing the drug, EDTA and tromethamine to an alcoholic solution of diisopropyl adipate and butylated hydroxytoluene. Carbopol 940 was added in the organic phase of the formulation to prevent initial gelling. The resulting formulation was then slowly stirred at temperatures < 20°C to obtain gelling, after which it was filled into Glaminate® dispensing tubes, to maintain chemical stability of the formulation and physical integrity of the container.

Phonophoresis is an effective physical mode for increasing transdermal drug delivery with minimal damage to skin or sensitization of the skin tissue. Recently, Tiwari *et al.* [99] evaluated a bimodality approach of using ultrasound, both in the presence and in the absence of a chemical enhancer (5% D-limonene in ethanol) pretreatment, for the *in vitro* permeation of KT. Ultrasound was applied in a continuous mode at 3 W/cm^2 for 30 min and diffusion studies were continued for 6 h using skin from the abdominal portion of male Wistar rats. The results depicted that application of chemical enhancer pretreatment alone significantly enhanced the passive flux of the drug irrespective of the distance of the donor compartment from the epithelium.

Yang and his team worked extensively on the development of a suitable gel delivery system for KT using ultrasound for the therapy of musculoskeletal lesions. They administered KT gel solution using pulsed ultrasound and examined its anti-hyperalgesic and anti-inflammatory effects in a rat carrageenan inflammation model. The changes in the mechanical and thermal hyperalgesia, nociceptive flexor reflex (NFR), as well as the swelling changes were determined. The study results supported the fact that phonophoretic transdermal delivery of KT showed significantly more noticeable anti-hyperalgesic and anti-inflammatory effects than those treated with the simple application of a KT gel. Yang and co-workers also identified the synergisitic effects of KT with a few products obtained from natural sources, such as genepin and biacalein for the treatment of gingivitis in

the periodontal pocket and rheumatoid arthritis, respectively. KT gel containing genipin (KTG gel) was prepared and evaluated. The skin permeation rate of ketorolac from the KT gel and KTG gel was 5.75 ± 0.53 and 5.82 ± 0.74 μg/(cm^2 h), respectively. The skin permeation rate of genipin from the KTG gel was 10.13 ± 1. 47 μg/(cm^2 h). The tensile strength of the KTG gel was greater than the KT gel. Skin permeation rate studies and *in vivo* studies performed on hairless mouse skin supported the fact that KTG gel is more effective against gingivitis in the periodontal pocket through its increased anti-inflammatory activity and the crosslinking of genipin with the biological tissue than KT alone [100-102].

A newer strategy of drug administration, which enables preferential delivery of a single enantiomer of a chiral drug such as KT, has been worked on by Gupta *et al.* [103]. This was achieved by electrotransport (by electromigration, electroporation, electroosmosis), which is stereospecific in nature. It offers numerous advantages, including higher transport of a stereospecific drug in a shorter time period through a smaller, more acceptable coverage area as compared with other passive delivery systems. It also alleviates the need for expensive stereospecific synthesis or complicated purification procedures for the selective delivery of one isomer of a chiral drug. *In vivo* studies demonstrated that the mean amount of R-ketorolac absorbed was found to be lower than that of S-ketorolac absorbed following electrotransport.

3. Expert opinion

The basic goal of an efficient drug therapy is to attain a steady-state blood or tissue level of the drug within the therapeutically effective and non-toxic range for an extended period of time. During the past 25 years, significant advances in controlled drug delivery have been recorded and several products have enjoyed commercial success and an extended patent protection on being reformulated as sustained release delivery systems. KT is a freely water soluble, potent NSAID. At present, KT is available in the form of oral tablets and i.m. or i.v. injections for systemic action. However, the parenteral administration of KT (i.m. and i.v.) has limitations of patient non-compliance and invasive delivery for a reasonably longer period of time (5 – 6 days in severe pain conditions associated with major surgery), whereas the oral delivery is associated with the limitation of repetitive administration. Thus, a sustained drug delivery system is more desirable for better efficacy of KT owing to its short mean plasma half-life ($t_{1/2}$ ~ 5.2 h) and frequent occurrence of gastrointestinal side effects. Keeping in mind the requirement of a delivery system for KT that provides the therapeutic protection for weeks to months with the single injection in severe postoperative pain conditions, formulating a parenteral system is most appropriate. As KT is susceptible to light, so encapsulation of the drug into biodegradable microspheres will simultaneously protect the drug from photodegradation. Several parenteral depot systems have been successfully developed by many pharmaceutical scientists worldwide and have shown promising potential to achieve this goal. Up to now, many investigators have also developed oral controlled and delayed release formulations for optimum delivery of the drug. Owing to the higher efficacy of the ocular delivery of the drug, depot systems such as occuserts can also be developed. Similarly, transdermal delivery of KT has also been attempted using various conventional approaches worldwide. Although many successful transdermal and nasal delivery systems have been developed on the laboratory scale, more research needs to be directed towards the establishment of their respective *in vivo* efficacy. It is concluded that for establishing the industrial viability of the optimized sustained release approaches proposed for KT, an appropriate correlation of the *in vitro* data with the *in vivo* results is desirable.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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