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REVIEW ARTICLE

VARIOUS DRUG DELIVERY SYSTEM OF KETOROLAC TROMETHAMINE FORMULATIONS: AN OVERVIEW

Prateek Porwal [*1, 2], Dilip Kumar Chanchal [1, 3], Km. Pratiksha [2], Vikash Jha [4], Chandan Kumar Singh [5], and Neetu Singh [6, 7]

PhD. Research Scholar [1], Glocal School of Pharmacy, The Glocal University, Mirzapur Pole, Saharanpur - 247001, Uttar Pradesh, India.

Assistant Professor [2], SRAM College of Pharmacy, Tundla, Firozabad - 283204, Uttar Pradesh, India.

Assistant Professor [3], Smt. Vidyawati College of Pharmacy, Jhansi - 284128, Uttar Pradesh, India.

Assistant Professor [4], FS College of Pharmacy & Research Center, FS University, Shikohabad, Firozabad - 283135, Uttar Pradesh, India.

Research Scholar [5], Department of Bioengineering, Integral University, Lucknow - 226026, Uttar Pradesh, India.

PhD Research Scholar [6], BN College of Pharmacy, Bhupal Nobels University, Udaipur - 313001, Rajasthan, India.

Associate Professor [7], BSA College of Engineering & Technology Mathura - 281004, Uttar Pradesh, India.

Corresponding author

Prateek Porwal

PhD. Research Scholar, Glocal School of Pharmacy, The Glocal University, Mirzapur Pole, Saharanpur - 247001, Uttar Pradesh, India.

Email: prateekgupta2525@gmail.com

Abstract: Non-steroidal anti-inflammatory medicine ketorolac tromethamine (KT) is a heteroaryl acetic acid derivative and works by reducing inflammation. It is a racemate version of a nonselective cyclooxygenase (COX) inhibitor. In particular, the S-isomer retains its analgesic and COX-inhibiting properties. The tromethamine salt of ketorolac may be taken orally, injected intramuscularly or intravenously, or used topically in the form of an ocular solution. Several formulation techniques have been developed for the correct distribution of KT due to the short mean plasma half-life (t1/2, 5.5 h) and the high incidence of gastrointestinal problems such as gastrointestinal bleeding, perforation, and peptic ulcers. This article summarises the key ideas that have guided the development of diverse pharmacological dosage forms for the therapeutically efficient distribution of the drug candidate through different pathways. The development of prolonged-release formulations of the medicine is now receiving a lot of attention since it may help achieve the desired therapeutic effectiveness and improved tolerance with fewer gastrointestinal side effects.

Keywords: Ketorolac Tromethamine, Parenteral delivery, and Transdermal delivery.

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INTRODUCTION:

NSAIDs are the most often prescribed medications globally due to their anti-inflammatory, anti-thrombotic, antipyretic, and analgesic properties [1]. Over the last 30 years, NSAID prescriptions have surged, increasing clinical access to them. 30 million individuals use NSAIDs. Pharmaceutical corporations want to improve the delivery of an NSAID because they make $6 billion a year. NSAIDs are nonselective COX inhibitors (coxibs). KT, a non-selective COX-2 inhibitor, is structurally similar to indomethacin [2].

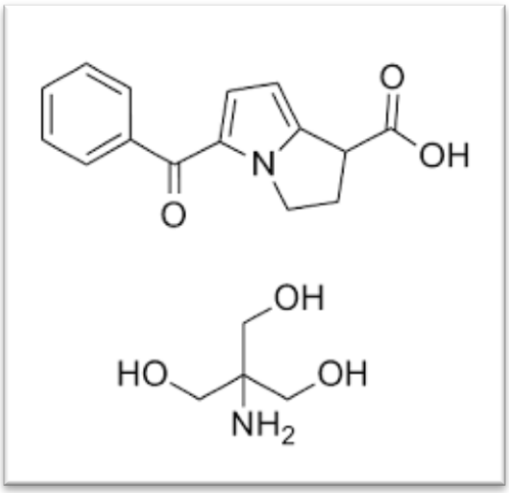

Fig. 1: Structure of Ketorolac tromethamine

Ketorolac, the racemic NSAID, is used commercially. On May 16, 1978, Muchowski & Kluge (Syntex) received US Patent No. 4,089,969 for ketorolac and its pharmaceutically acceptable, non-toxic esters and salts [3]. Levorotatory medicine is twice as anti-inflammatory as dextrorotatory medication. The S-isomer provides most of the drug's analgesic and COX-inhibiting effects. Ketorolac (tromethamine salt) may be taken orally, injected intramuscularly or intravenously, or used topically as an eye solution. The Orange Book currently mentions three KT dosage forms: a tablet (10 mg, Mylan, Ketorolac Tromethamine), an eye solution or drops (0.5 percent, Allergan, Acular; 0.4 percent, Acular LS), and an injection (15-30 mg/ml, Bedford) [4].

Roche Products Ltd.'s Toradol tablets and injectable, Allergan's Acular, and Beacon Pharmaceuticals' Acular PF (preservative-free) ophthalmic eye drops are all available in the UK. Ketorolac and other NSAIDs share substituted arylacetic acid. Three crystalline forms may occur. Each has a pKa of 3.5, an n-octanol/water partition coefficient of 0.26, and equal water solubility. KT is 376.41 Da. Interrupting arachidonic acid metabolism's cyclooxygenase pathway prevents prostaglandin synthesis. A non-centrally acting medication produces considerable analgesia (or morphine-like agent). KT inhibits arachidonic acid and collagen-induced platelet aggregation. Prothrombin, partial thromboplastin, and kaolin-cephalin clotting times were unaffected [5].

KT, a potent non-narcotic analgesic, may relieve postoperative abdominal, gynecologic, oral, orthopaedic, and urologic pain. Before, during, and after surgery, it has been utilised for analgesia. It works like steroidal and opioid drugs. Long-term opiate usage causes tolerance, dependency, withdrawal, and other problems. KT also treats acute renal colic pain following shock and visceral cancer pain [6].

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Its intramuscular analgesia is comparable to morphine, pentazocine, and meperidine. Even at modest doses, the drug outperformed sodium naproxen, morphine, and glafenine in multiple clinical studies. In the post-anesthesia care unit, 30 mg of ketorolac provided better postoperative analgesia and antiemesis than 4 mg of dexamethasone or 12 mg of bethamethasone (PACU). Ketorolac is an excellent opioid substitute after abdominal surgery, particularly in neonates and premature babies. It's safe and effective with opioid-based analgesia following partial nephrectomy. KT may be a better first-line treatment for severe cancer pain than opioids, according to clinical research [7].

KT is more analgesic than anti-inflammatory. KT reduced carrageenan-induced paw edoema in rats 36 times better than phenylbutazone, nearly twice better than indomethacin, and three times better than naproxen. KT 0.5 percent may treat Candida albicans and Pseudomonas aeruginosa-related conjunctivitis [8]. The medication reduces intraocular inflammation and cystoid macular edoema after cataract removal and lens implantation. KT is also antipyretic. Its great analgesic action, minimal risk of adverse effects, absence of sedation, and inexpensive cost make it a good opioid alternative (morphine and meperidine). Seems suitable for moderate to severe discomfort. That's why the previous decade has seen so many pharmaceutical delivery technology improvements [9].

Most persons with KT have stomach or intestine problems, including as bleeding (especially in the elderly), perforation, and peptic ulcers. It may also induce injection-site pain. Applying the drug straight to the eye may produce brief stinging and discomfort [10].

2. Various drug delivery systems of KT

Considering the rise in the number of reported adverse events associated with KT, researchers are placing a premium on finding an optimal delivery strategy that maximises therapeutic benefit while minimising risk [11]. There are a number of different formulation techniques for delivering KT effectively, some of which are still in the works. Current administration options include oral pills, ophthalmic solutions, and injectable forms. Researchers throughout the globe are exploring various routes of administration (nasal, otic, transdermal, etc.) to boost the drug candidate's therapeutic effectiveness [12]. It is currently taken orally, intramuscularly, intravenously, and topically (ophthalmic solution). The development of prolonged-release formulations of the medicine is a major research priority since it will help achieve the necessary therapeutic effectiveness and greater tolerance. Ketorolac tromethamine may be administered in a number of different ways, and this section will cover all of those options [13].

2.2 Parenteral delivery

For the treatment of severe pain, KT was the first non-steroidal analgesic medication to be administered through injection. For systemic effect, KT may be injected intramuscularly (i.m., 30–60 mg) or intravenously (i.v., 15–30 mg). Several nations, including the UK, have authorised the use of an intravenous version of KT [14]. Patient noncompliance and invasive delivery for a somewhat longer duration (5-6 days in severe pain circumstances associated with major surgery) are two drawbacks of administering KT through parenteral routes (i.m. and i.v.). While the oral administration of KT avoids the problems associated with invasive administration, the drug's short biological half-life ($t_{1/2}$ = 5.2 h) necessitates frequent dosing to keep blood levels consistent and allow for the successful management of severe pain. A

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extended release formulation of KT would be ideal to reduce the need for dosage and the associated patient discomfort [15]. After intravenous (i.v.) or intramuscular (i.m.) injection, the analgesic effect starts in 30 minutes and peaks in 1 to 2 hours. The pain-relieving effects of an opioid typically last between four and six hours. Since then, several innovations in technology have been achieved in the field of parenteral drug administration, leading to the creation of novel systems that enable drug targeting and the sustained or controlled release of parenteral medications. Controlled-release medication delivery technologies for parenteral administration have expanded dramatically in recent years. Due to issues with poor absorption and limited bioavailability, the parenteral route has emerged as the best option for sustained drug administration [16].

Parenteral depot formulations may keep the blood drug level in the therapeutically effective range for extended periods of time, avoiding issues like the requirement for direct medical care and hospitalisation. Compared to traditional injectable drug delivery, the inherent drawbacks of sustained release parenteral formulations are greatly reduced, making them functionally equivalent to intravenous infusion [17]. This kind of medication preparation also results in a lower overall drug dosage, fewer adverse effects, and increased drug efficacy. Long-acting parenteral formulations can be developed in a number of ways, including emulsions, suspensions, liposomes, and so on; however, these approaches all have their limitations, such as the fact that it is difficult to achieve a prolonged effect and to adjust the drug's release profile to meet individual patient needs. Many laborious efforts have been undertaken over the last decade to create effective microsphere-based drug delivery devices for the medication. The main benefit of systems based on biodegradable microspheres is that they solve the issues of the previously described methods and allow for controlled drug release over a prolonged period of time (days, weeks, or months) [18].

2.1 Oral delivery

In 1992, the medicine was first introduced orally in the United Kingdom; now, it is sold in over 25 countries across the globe. Only as a follow-up to KT (intravenously or intramuscularly), is KT used orally for the treatment of moderate-to-severe acute pain in a dosage range of 5 to 30 mg; this is the opioid dose range at which it is most effective. When administered orally, KT is absorbed entirely, and its pharmacokinetics mimic those when injected into the muscle. Oral administration of the medicine is favoured since it causes pain relief to kick in more quickly for many people [19]. Numerous case control, cohort, and post-marketing monitoring studies, as well as spontaneously reported adverse medication responses, have shown that instant release NSAIDs are linked to widespread side effects, the most common of which are disruptions of the upper gastrointestinal system. Modified release dosage forms, such as enteric-coated (EC) or SR formulations, have recently been developed for NSAIDs in an effort to increase therapeutic effectiveness and decrease the severity of upper gastrointestinal tract adverse effects. To counteract the stomach upset that often occur when taking NSAIDs orally, researchers have created KT controlled release matrix tablets. However, KT's plasma half-life is just 2.5 to 5.6 hours, and its recommended dosage is only 10 to 20 mg twice day. Researchers have looked at the results of utilising a wide range of methods to delay KT release [20].

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In order to determine how cellulose ethers (CEs) such HPMC, HEC, and CMC affected the in vitro release of KT from tablets manufactured using the direct compression approach, Genc and Jalvand tested various amounts of CEs (10-20%). Tablets made with HPMC: HEC:CMC (1:1:1) were determined to be the most appropriate formulations due to their full drug release in 7.5 h, as shown by the in vitro drug release profiles produced [21]. After absorbing water, the matrices expanded, and the medication was released mostly by diffusion and erosion due to the breakdown of the gel layer created by the CEs. Furthermore, the authors have created a film-coated enteric tablet version of KT. Materials for spray-coating KT tablets were narrowed down to Eudragit S-100 and L-100 in this investigation. It was a plasticizer called PEG 4000 polyethylene glycol. Both coated and uncoated tablets were disintegrated into a liquid in dissolution tests. The data showed that after 4 hours, about 97% of the medication was released in the coated systems' simulated intestinal fluid [22].

This osmotic drug delivery device for KT was developed by Arora et al. for regulated release. As a first step, they mixed 1:5 KT:HPMC swellable matrices. A cellulose acetate film was then applied to the surface of these matrices, acting as both a reservoir and a matrix for the medication. By adding PEG 400 and triacetin into the coating solutions, we were able to alter the film's permeability. Tablets with PEG 400 in the coat offered a greater rate and extent of drug release compared to tablets with triacetin, as shown by the in vitro drug release profiles. Research into the role of osmotic contribution in drug release led to the discovery that the osmolality of the dissolving media had an impact on the semipermeable barrier. Permselective membrane-coated osmotic matrix tablets were shown to be unsuccessful due to the pH and hydrodynamic conditions of the gastrointestinal system [23].

In 2002, Vatsaraj investigated the impact of varying the drug dose (between 30 and 40 mg), the ratio of hydroxypropyl methylcellulose (HPMC) to sodium carboxymethylcellulose (NaCMC) (between 240 and 40 mg), and the amount of ethylcellulose (between 140 and 180 mg) in controlled release matrix tablets. A series of in vitro dissolving studies were conducted at a range of pH values using USP equipment 3 (Bio-Dis II) to simulate the conditions found in the digestive system. Analyzing the dissolving data using ANOVA revealed that the ratio of HPMC to NaCMC and drug quantity affected the time needed to release 50% of the medication. Super-case II transport was determined to be the release mechanism [24].

2.4 Nasal delivery

The goals of developing a nasal formulation for the treatment of postoperative pain and migraine are to reduce the risk of adverse effects on the digestive system, increase patient compliance, provide a controlled blood level profile, and improve therapeutic efficacy compared to more traditional dosage forms. As a consequence of the enormous surface area and minimal enzymatic breakdown of the nasal mucosa, medicines are rapidly absorbed into the systemic circulation, resulting in high plasma levels comparable to those supplied by injections. Studies are being conducted extensively to perfect a nasal administration mechanism for KT [25].

Microspheres of KT for intranasal systemic distribution were described by Sankar and Mishra utilising Gelatin A, a biodegradable and biocompatible polymer, and an emulsification-crosslinking process. Using glutaraldehyde as the crosslinking agent and chitosan as the

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copolymer, the medication was disseminated in gelatin and then formed into a w/o emulsion with liquid paraffin. There was clear spherical form and excellent bioadhesive characteristics in the produced microspheres. The effects of several formulation factors on the pace and extent of drug release were investigated. These variables included polymer concentration, crosslinking agent percentage, and drug loading. According to the findings, the microspheres' particle size increased in tandem with an increase in the drug or polymer concentration, leading to improved drug incorporation efficiency [26]. As a consequence of interacting with the negatively charged mucin, the addition of chitosan to the solution caused the microspheres to grow in size and significantly increased their bioadhesive strength. The in vitro data showed a biphasic release profile. There was a correlation between the amount of gelatin in a batch and the rate of drug release; when the percentage of gelatin was greater, the diffusional route length in the polymeric matrix was longer, slowing drug release. It took longer for the active ingredient to be released from the chitosan-gelatin microspheres. Microspheres provided diffusion-controlled drug release according to the Higuchi model, as determined by a comparison of the coefficient of correlation derived from several release kinetic models [27].

2.3 Ocular delivery

Just 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 following surface ablation and other ocular disorders like seasonal allergic conjunctivitis [28]. Under licence from Roche Bioscience, Allergan sells an ocular version of ketorolac to treat allergic conjunctivitis in the United States and postoperative inflammation in Europe. Allergan's ACULAR LS formulation has just been approved by the US Food and Drug Administration (FDA) for use in the management of ocular discomfort after corneal refractive surgery. Licensee Santen has also investigated the drug's potential use in ocular conditions. The potential of KT in treating eye problems is being heavily explored. Ketorolac has been shown to successfully cure allergic conjunctivitis in a number of investigations. When taken alone or in combination with steroids, ketorolac 0.4% is very effective. In contrast to nepafenac, which causes a healing delay and increased corneal haze following LASIK, KT has been shown to be superior in a randomised, double-masked, multi-center research of the contralateral eye. Concerns about the subjects' safety led to the study's termination [29].

The effectiveness of 0.4% KT ophthalmic solution compared to that of 0.5% KT ophthalmic solution has been shown in a number of research. To successfully alleviate pain before to, during, and after ophthalmic surgery, topical NSAIDs are useful. Current practise requires the ophthalmologist to weigh the pros and cons of using topical corticosteroids, which may have negative effects on ocular pressure, wound healing, and the cornea, with those of using topical NSAIDs, which may have positive benefits on these same factors. According to results from many randomised, controlled trials conducted at several sites, KT is preferable to standard steroids for preventing intraoperative miosis and postoperative inflammation during cataract surgery, and it does so at a lower cost. Ketorolac is generally well tolerated when used topically in ophthalmology. Patients with a history of aspirin intolerance or NSAID

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allergy, especially those with asthma and nasal polyps, should not be given NSAID eye drops unless the patient can take aspirin without adverse effects [30].

Glaucoma, cystoid macular edoema, uveitis, diabetic retinopathy, and conjunctivitis, as well as any damage induced by eye surgery or injury, are all disorders that ophthalmic formulations of KT may be used to treat. Fu and Lidgate created KT (0.001 - 10.0 percent w/v) ophthalmic formulations with a quaternary ammonium preservative, such benzalkonium chloride (0.001 - 1. 0 percent w/v), and a non-ionic surfactant, like polyethoxylated octylphenol compounds (0.001 - 1. 0 percent w/v). Some of the excipients included in these formulations include chelating agents, tonicifiers, buffering systems, viscosity enhancers, and stabilisers. The formulation was sterilised after all the components were combined and dissolved in sterile water, the pH was adjusted to 7.4 0.4, and the final volume was made up with sterile water. Using non-ionic surfactants and an appropriate preservative, the suggested procedure yielded physically stable, transparent, and antimicrobially effective formulations [31].

Dispersing an aqueous solution of the medication in a simple eye ointment base according to step 2, as outlined in the Indian Pharmacopoeia, yielded an ophthalmic ointment containing 0.5 percent (w/w) KT (in dissolved state) (IP). It increased transcorneal permeability in vitro with little corneal toxicity. According to the study's findings, the drug's ocular penetration of KT is affected by its chemical form and physical condition [32].

2.5 Transdermal delivery

Clinical acceptance of transdermal delivery methods for systemic administration of different medications has been widespread. Maintaining a constant medication concentration, transdermal administration avoids hepatic first-pass metabolism and gastrointestinal disturbances/side effects. The therapeutic impact of transdermal KT devices is longer lasting and associated with fewer adverse outcomes. The medication has been reported to be used in adhesive matrix, reservoir, and monolithic matrix transdermal patches. Roche Bioscience is conducting clinical studies on suppository and topical gel forms of this medication in addition to the injectable version [33].

Cho and Gwak first conducted an extensive in vitro study to determine the potential for developing a successful transdermal system by examining the effects of different pure solvents, co-solvents, and penetration enhancers on the in vitro permeation of KT from solution formulation across hairless mouse skin. In vitro permeation investigations with hairless mouse skin were conducted utilising the flow-through diffusion cell technology. Propylene glycol monolaurate (PGML, Lauroglycol1 90), an ester-type vehicle, originally shown the greatest boosting impact on drug penetration as a result of its high diffusivity, partitioning, and solubility [34]. However, due to its relatively poor solubility, isopropyl myristate did not have a significant boosting impact. Diethylene glycol monoethyl ether (DGME) was shown to enhance the penetration fluxes by about two times at 20-60% of DGME compared to PGML alone, but PGMC alone showed a relatively low permeation rate. The permeability of KT increased as the propylene glycol (PG) content of the PG-oleyl alcohol co-solvent solution became larger. It was shown that raising the drug concentration above its solubility had a synergistic effect on the penetration rate. Also assessed was the PG-and-fatty-acid binary system. According to the postulated mechanism of action, drug

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penetration is increased by disrupting the intercellular multilaminate hydrophilic-lipophilic layers in the stratum corneum. The most potent boosting effect was achieved with 10% caprylic acid in PG, and its flux of 113.6 17.5 mg/ (cm2 h) [35].

2.6 Semisolids for skin

Nasseri and colleagues have created MBGs (microemulsion-based organogels) for the topical administration of KT at a concentration of 6.5% w/w. Lecithin/isopropyl myristate (IPM)/water or KT solutions were analysed in terms of their phase behaviour by drawing ternary phase diagrams at different lecithin/IPM weight ratios (Km). The medication was dissolved in a lecithin-in-IPM solution, and then gelation was induced by adding water. The medication was completely dissolved by heating the mixture for a brief period of time. The complete thickness of hairless guinea pig abdomen skin was used in *in-vitro* investigations, whereas silicone elastomer membranes and cellulose acetate membranes were used in ex vivo studies [36]. Drug release was shown to be greater via the cellulose acetate membrane than through the silicone elastomer, according to *in vitro* studies; this discrepancy is related to the different molecular mass cutoffs between the two membranes. Due to an increase in the drug's thermodynamic activity, a linear relationship between drug concentration and release rate was seen in in vitro and *ex vivo* investigations. Due to considerable entrapment of the medication at increasing concentrations of lecithin, the formulation's viscosity increased as lecithin content increased from 40% to 60%, and the permeation flux values decreased significantly. The best release profile was achieved by using water at a weight-percentage of 0.6% in the formulation. It was determined that the MBG with the highest lecithin content and the ideal quantity of water was the most effective vehicle for the transdermal administration of KT [37].

CONCLUSION:

One of the primary goals of any successful drug treatment plan is to maintain the medication concentration in the blood or tissues at a steady state level that is both therapeutically effective and non-toxic. There have been major breakthroughs in controlled medication delivery over the last quarter century, with a number of medicines finding commercial success after being reformulated as sustained release delivery systems and receiving longer patent protection as a result. KT is an effective nonsteroidal anti-inflammatory drug that dissolves in water. There are now tablet forms, as well as intramuscular and intravenous injections, allowing systemic administration of KT. But the oral delivery of KT is limited by the need for repeated administration, while parenteral administration of KT (i.m. and i.v.) has the disadvantages 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). Due to its short mean plasma half-life ($t_{1/2}$ 5.2 h) and frequent incidence of gastrointestinal adverse effects, a continuous drug delivery strategy is preferable for higher effectiveness of KT. A parenteral system is the most suitable method of delivering KT since it provides therapeutic protection for weeks to months after surgery with a single injection. In order to prevent photodegradation of KT, the medicine may be encapsulated in biodegradable microspheres. Many pharmaceutical researchers throughout the globe have created and tested effective parenteral depot systems that show great promise in this regard. Many researchers have worked on controlled and delayed release oral formulations for the drug's best delivery.

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Ocular delivery is more effective, therefore depot systems like occuserts may be created. Worldwide, several traditional methods have been explored for transdermal administration of KT. There has been a lot of success in the lab developing transdermal and nasal delivery methods, but more work is needed to prove their effectiveness in living organisms. An acceptable connection between in vitro data and in vivo outcomes is needed, as a consequence, to prove the industrial feasibility of the optimised sustained release techniques described for KT.

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CONFLICT OF INTEREST: Nil

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