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RESEARCH PAPER

In Vitro–In Vivo Characterization of Release Modifying Agents for Parenteral Sustained-Release Ketorolac Formulation

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ABSTRACT

One of the prerequisites for a parenteral preparation is that the excipients incorporated are biocompatible and biodegradable. In the present study hydrophilic and hydrophobic excipients were investigated for developing an intramuscular sustained-release formulation of ketorolac. Kollidon® 17 PF, Peceol (glyceryl monooleate), and castor oil were chosen as the potential release-retarding agents, each with a distinct mechanism of action. They were evaluated by in vitro drug-release profiles and in vivo pharmacodynamic and pharmacokinetic study in mice. Cumulative drug release was determined for standard and test formulations in modified Franz diffusion cell. Pharmacodynamic parameter, T = 70% response of peak analgesic response, was used to compare the performance of test formulations. Based on pharmacodynamic/pharmacokinetic correlation in the animal studies, Css_{max} and Css_{min} of 51.39 and 30.0 μg/mL, respectively, were determined and considered as performance markers for pharmacokinetic evaluation of test formulations. The study suggested that the sustained-release capability of glyceryl monooleate was maximum followed by that of castor oil and Kollidon 17 PF, when compared to conventional ketorolac tromethamine formulation. It was inferred that water soluble excipient, though, showed release retarding property in vitro but could not maintain it in the in vivo environment. Glyceryl monooloeate-based formulation produced the most favorable drug blood concentration vs. time profile.

Key Words: Biodegradable; Biocompatible; Ketorolac.

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INTRODUCTION

Pain is an unpleasant sensational and emotional experience elicited by the activation of specific nociceptors. Pain derived from tissue injury is exhibited in the form of local edema, inflammation, and hyperalgesia.[1] Tissue trauma is further accompanied by mechanical and thermal damage to nerve endings, which induces release of sensory neuropeptides (substance P, neurokinin A, and calcium gene–related peptides) and catecholamines from sympathetic nerve fibers resulting in sensitization of nociceptors.[2] Traditionally, parenteral opioid analgesics or local anesthetics have been used for relief of postoperative pain after abdominal and orthopedic surgery. However, the elucidation of the role of arachidonic acid cascade metabolites in inducing and mediating pain and inflammation, has suggested nonsteroidal anti-inflammatory drugs (NSAIDs) as potential adjuvants to other reversible inhibitors of prostaglandin synthesis.[1]

Ketorolac is an NSAID that displays potent analgesic and modest anti-inflammatory activity. It has been evaluated for analgesic action and found to be comparable to opioids and is, primarily, being marketed for use in postoperative conditions. Ketorolac is further finding application in acute pain states of renal colic, migraine headache, and cancer pain.[3,4] Ketorolac relieves pain through peripheral mechanism.[3] Experimental studies in animal models of pain indicate ketorolac may exert a modulatory effect on opioid receptors or alter opioid pharmacokinetics. Alternatively it may cause the release of endorphins or enkephalins.[5]

Ketorolac is marketed as a racemate, the S (−) enantiomer is biologically more active than the R (+) enantiomer. Ketorolac tromethamine (KTM) 1H-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, compounded with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)[6] is a freely water soluble salt. At physiological pH the salt form dissociates to form a free anionic molecule, which is less hydrophilic. Ketorolac follows linear kinetics and has characteristics of a two-compartment model. Mean terminal elimination half life ($t_{1/2}$) of ketorolac is within 5–6 hrs. Oral bioavailability of the drug is 80%–100%. The bioavailability of drug after intravenous (IV) and intramuscular (IM) administration is the same.[3,4,7] The economic implications of using ketorolac vs. an opioid drug as the primary analgesic in the postoperative settings has been investigated in retrospective cohort studies of hospitalized patients and recipients of ketorolac demonstrated an overall more rapid recovery, shorter hospital stay, and reduction in hospitalization cost.[3]

Ketorolac has an IM dose of 30 mg, four times a day, making it desirable to develop a sustained-release injection. The present study was aimed at developing an intramuscular sustained-release formulation of ketorolac using hydrophilic and hydrophobic parenteral excipients with release-rate-retarding properties, while simultaneously maintaining other physical properties like viscosity and syringeability. Polyvinylpyrrolidone (Kollidon® 17 PF), glyceryl monooleate (Peceol®), and castor oil were selected, each of which has a distinct mechanism of release retardation. Polymers have been reported to interact with drug molecules via electrostatic bonds (ion to ion, ion to dipole, dipole to dipole bonds) or Van der Waals forces and hydrogen bridges to form a complex and, thus, influence the availability of drug as well as the rate of drug transfer from aqueous drug formulation.[8] Kollidon 17 PF, is a pyrogen-free grade, recommended for parenteral administration.[9] The molecular weight of these products is low, permitting rapid renal elimination.

Parenteral sustained-release systems can be achieved by oil systems where apparent partition coefficient (k) of the drug governs the dynamic equilibrium between oil and aqueous phase. Castor oil was selected for formulation development as ketorolac is reported to have adequate solubility in it,[10] and it has been used in injectable preparations.[11] Glyceryl monooleate undergoes phase transitions in response to changes in composition (% water content) and temperature conditions.[12] The drug-release modifying ability may be attributed to spontaneous formation of a transparent and stiff gel-like structure called cubic phase, when placed in aqueous medium.[13] Glyceryl monooleate is metabolized by the lipase enzyme in the body to glycerol and oleic acid. Hence the excipient is biodegradable primarily by lipolysis.[14] Various works have been published on the incorporation of drugs such as lidocaine, clotrimazole, and vitamin E in glyceryl monoleate.[15]

MATERIALS AND METHODS

Materials

Ketorolac tromethamine was obtained as a gift sample from Ranbaxy Laboratories Ltd., India. Peceol (glyceryl monooleate) was provided by Gattefosse, France. Kollidon 17 PF was provided by BASF, Germany. Castor oil (Agarwal Pharmaceuticals, Delhi, India) was of U.S.P grade. Acetic acid was supplied by

Table 1. Composition of formulation batches.

S. no.	Batch code	Release-retarding agent	Other excipients
1	KTM-IR	None	Sodium chloride 0.9% w/v Water for injection
2	KTM-SR-01	Kollidon 17PF (0.9% w/v)	Sodium chloride 0.9% w/v Water for injection
3	KTM-SR-02	Glyceryl monooleate (95 % v/v)	Sodium chloride 0.9% w/v Water for injection
4	KTM-SR-03	Castor oil q.s.	Benzyl alcohol 4% w/v

E. Merck, Mumbai, India. The water used was double distilled in glass apparatus.

All protocols for animal studies, were approved by the institutional animal ethical committee. Male Swiss Albino mice weighing 16–25 g were procured from the institute's Central Animal Facility and housed at a temperature of 22±2°C. Animals were fasted overnight before the experiment and water was allowed ad libitum throughout the study.

Methods

Formulation Development

Polyvinylpyrrolidone, glyceryl monooleate, and castor oil were selected as potential release-retarding excipients. An individual excipient-drug blend was prepared. Composition of formulations is listed in Table 1. Ketorolac tromethamine is a freely water soluble salt. Test formulations KTM-IR, KTM-SR-01, and KTM-SR-02 contained ketorolac tromethamine 30 mg/mL and were adjusted for isotonicity, with sodium chloride, before administration. Formulation KTM-SR-03 contained ketorolac 20.43 mg/mL in castor oil with 4% w/v benzyl alcohol. Ketorolac-free acid was prepared from ketorolac tromethamine by a method reported earlier,[10] and was characterized using spectral techniques. Solubility characteristic of ketorolac were studied in various vegetable oils and benzyl alcohol; castor oil showed the highest solubility, about 2.5 mg/mL. The solubility of ketorolac ranges from 300–400 mg/mL in benzyl alcohol.

In Vitro Drug Release Evaluation

Modified Franz diffusion cell was designed to perform in vitro release studies. A receptor compartment, volume 16.5±1.0 mL with a side arm for sampling, was maintained at 37±0.5°C. The drug concentration per unit volume of buffer was calculated using actual volume of buffer in the receptor compartment. Sink conditions were maintained in the receptor compartment, with respect to drug solubility. An artificial filter membrane of hydrophilized polytetrafluorethylene (PTFE), polyvinylidene chloride (PVDC), and nylon were evaluated for least resistance to diffusion and binding capacity for ketorolac tromethamine, from which hydrophilized PTFE membrane, 0.45 μm pore size was selected as the support membrane. The interfacial area between sample and release buffer was 0.385 cm sq. Receptor medium was isotonic phosphate saline buffer (pH 7.4) and was agitated at 540±20 rpm. Samples were withdrawn at predetermined time points and replaced with buffer maintained at 37°C. Samples were analyzed by ultraviolet (UV) spectrophotometer at a λ_{max} of 323 nm. Analytical method for drug quantification by UV spectroscopy was determined and validated. Calibration curves were developed for ketorolac tromethamine and ketorolac. Methods were validated for linearity and precision. Student's t-test was applied, for comparison of cumulative amount of drug released per cm sq in 12 hrs (M_{12}) for standard and test formulations.

In Vivo Evaluation

Pharmacodynamic Evaluation

The writhing test in mice was performed to determine the analgesic response of drug formulation administered intramuscularly.[5,16] Saline or the drug formulation was injected intramuscularly at predetermined time points prior to intraperitoneal (IP) administration of 3% v/v acetic acid (0.01 mL/g). Control and standard response were determined by injecting intramuscular (IM) saline and aqueous drug solution at a dose of ketorolac tromethamine 7.5 mg/kg bw,[5] respectively. Similarly the test formulations were administered and percentage response was determined at time points 5, 15, and 30 min and then at 1, 2, 4, 6, 8, 10, 15, and 20 hrs. For each time point response was evaluated in one group (n=6).

Data and statistical analysis:

Male Swiss Albino mice of weight 16–25 g were used in groups of six. Number of writhings displayed by each mouse was counted for 20 minutes after the administration of acetic acid. Percentage response for the formulations was calculated considering the peak response by aqueous conventional drug solution as the maximal possible effect. Percentage inhibition was calculated as shown below.[16]

$$\% \text{ inhibition} = \frac{\text{Average writhes in the control group} - \text{Average writhes in treated group}}{\text{Average writhes in the control group}} \times 100$$

All data was presented as mean±S.E.M. Student's t-test was applied, for comparison of mean response for standard and test formulation at a single time point, $P<0.05$. Two-way analysis of variance (ANOVA) was employed for comparison of analgesic response for standard and test treatment over a period of time, $P<0.05$.

Pharmacokinetic Evaluation

For in vivo evaluation of each formulation male Swiss Albino mice in groups of four were taken. Zero hour blood samples were collected by intraocular route and then the test formulation was injected intramuscularly. Blood samples were withdrawn at three time points from one group. At sampling time point 0.25 mL blood was withdrawn and 0.25 mL saline was administered i.p. The time points for sample collection were 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 15 and 20 hrs. Pharmacokinetic proflie for KTM-IR was produced for 12 hrs. Two-way ANOVA was employed for comparison of drug-blood concentration profiles for standard and test treatment over a period of time, $P<0.05$.

Plasma sample analysis:

Blood was collected in a heparinized microcentrifugation tube; plasma was immediately separated and stored at −22°C until analyzed. Plasma samples were extracted with 0.9 mL methanol by vortex mixing for 3–4 min and then centrifuged at 13,000 rpm for 30 min at 20°C temperature. Supernatant (0.8 mL) was collected, evaporated to dryness, and further reconstituted in 750 μL of mobile phase, the vortex was mixed for 3–4 min and then centrifuged at 13,000 rpm for 15 min. Aliquots of 100 μL were injected in high performance liquid chromatography (HPLC), with UV spectrophotometeric detection (Shimadzu HPLC (SPD-10 AVP, Japan)) at 313 nm. The chromatographic column used was Lichrosphere 100 RP-18e (250×4, 5 μm, Merck, Germany) and mobile phase constituted of acetonitrile:water in 40:60 ratio, adjusted to pH 3.0±0.01 with 85% orthophosphoric acid. The flow rate was 1 mL/min. The analytical method for drug concentration determination in plasma samples by HPLC was developed and validated. The method was validated for linearity and a precision and a calibration curve produced.

RESULTS AND DISCUSSION

Analytical Method Validation Data

The analytical method of UV spectroscopy was validated, a calibration curve was developed for ketorolac tromethamine in the range 2–20 μg/mL ($r^2=0.9999$) and precision determined in terms of reproducibility (RSD=0.009). A calibration curve for ketorolac was developed in the range 1–14 μg/mL ($r^2=0.9997$) and precision determined in terms of reproducibility (RSD=0.009). An analytical method for drug quantification in plasma samples by HPLC was developed and validated. The method was linear in range 2.5–100 μg/mL ($r^2=0.9991$) and precision determined in terms of reproducibility (RSD = 0.248).

In Vitro Drug Release Evaluation

Modified Franz diffusion cell was designed to study the in vitro release behavior of test formulations. Cumulative amount of drug released per cm sq vs. time, across the synthetic membrane is shown in Fig. 1. The release profile obtained for batch KTM-IR was considered the fastest release that can be achieved, as the support membrane was the only release-controlling parameter. Efficiency of test formulations was determined by comparing their ability to retard the release beyond that done by support membrane. Cumulative amount of drug released per cm sq in 12 hours (M_{12}) was 77.93, 59.66, 2.22, and 1.27 mg for formulation KTM-IR, KTM-SR-01, KTM-SR-02, and KTM-SR-03, respectively giving a ranking of KTM-SR-01<KTM-SR-02<KTM-SR-03, for drug release-sustaining capacity. The cumulative amount of drug released was significantly different from the three test formulations, compared to the aqueous drug solution, $P<0.05$.

In vitro evaluation is a useful preliminary screening tool, however the test formulations may vary in their performance under in vivo conditions due to

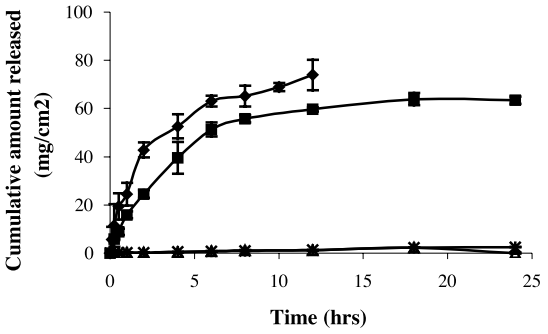

Figure 1. In vitro drug release profile of formulation KTM-IR (◆), KTM-SR-01 (■), KTM-SR-02 (▲) and KTM-SR-03 (×), (mean ± S.D.).

parameters like 1) blood flow, 2) exposed surface area of formulation, and 3) effect of formulation constituents on intramuscular tissue physiology.

In Vivo Evaluation

Pharmacodynamic Evaluation

Parenteral sustained-release formulations have been studied for their pharmacodynamic and pharmacokinetic performance[15,17] to prove their efficacy, as the in vitro conditions may not exactly simulate the in vivo environment. Ketorolac tromethamine belongs to the class of NSAIDs and, hence, its slow-release formulations may be assessed by determining the

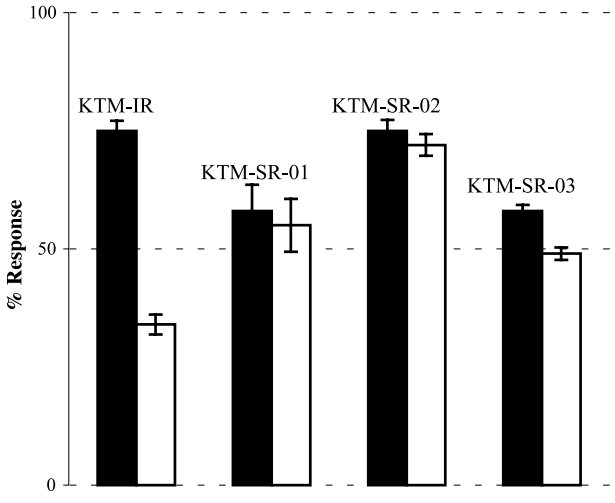

Figure 2. Comparison of percentage analgesic response in writhing test produced by KTM-IR, KTM-SR-01, KTM-SR-02, and KTM-SR-03 after 15 min (■) and 4 hrs (□) of i.m. administration (mean ± S.E.M).

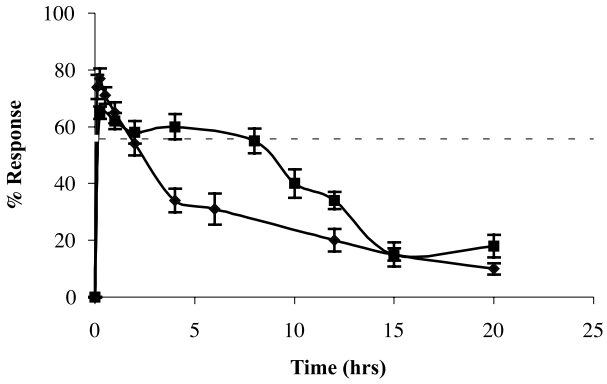

Figure 3. Percentage analgesic response produced by KTM-IR (◆) and KTM-SR-01 (■) (mean ± S.E.M), n = 6. (*View this art in color at www.dekker.com.*)

analgesic response at prolonged time periods in a suitable animal model. As an initial pharmacodynamic screening tool, the standard and test formulations were injected to mice at a dose of 7.5 mg/kg and response was measured at two time points i.e., 15 min and four hrs after administration (Fig. 2). The percentage response vs. time profile for aqueous KTM solution (KTM-IR) at a dose of 7.5 mg/kg[5] was generated (Fig. 3). The profile of KTM-IR suggested that maximum response is produced after approximately 15 min of administration and reduced to less than 50% after four hrs. For achieving a therapeutically optimum sustained-release formulation it is essential that the formulation should produce an onset of action comparable to that of conventional formulation, and, at the same time, prolong the action significantly. Formulations KTM-SR-01 and KTM-SR-03 showed significantly different response to that of KTM-IR at

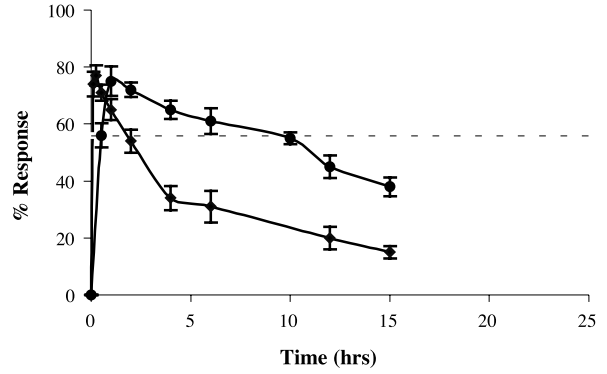

Figure 4. Percentage analgesic response produced by KTM-IR (◆) and KTM-SR-02 (●) (mean ± S.E.M), n = 6. (*View this art in color at www.dekker.com.*)

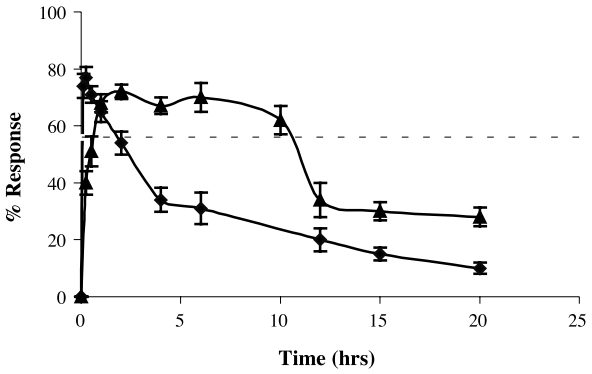

Figure 5. Percentage analgesic response produced by KTM-IR (◆) and KTM-SR-03 (▲) (mean±S.E.M), n=6. (*View this art in color at www.dekker.com.*)

15 min, whereas KTM-SR-02 produced a similar response to that of the standard, $P<0.05$. The analgesic response after four hrs of administration was significantly higher for all three test formulations in comparison to the standard, $P<0.05$.

After initial study at conventional dose level, a dose for human sustained-release formulations was calculated. Administration of 30 mg IM conventional ketorolac tromethamine injection, every six hrs produces steady state concentration levels of Css_{max} 3.11±0.87 μg/mL and Css_{mim} 0.93±0.26 μg/mL.[18] Theoretical dose calculation and concentration vs. time profiles were generated according to zero order release kinetics using the superposition method[19] with Css_{max} and Css_{min} desired set at 2.5 and 1.14 μg/mL, respectively. For a once-a-day sustained-release formulation a dose of 85 mg was calculated. This gave a ratio of 30:85 for a conventional vs. a sustained-release formulation in humans. The dose for mice was increased in the same ratio taking 7.5 mg/kg bw as the conventional dose. This gave a dose of 21.25 mg/kg bw for the sustained-release formulation dose. Subsequently, for the pharmacodynamic and pharmacokinetic evaluation of sustained-release formulations, KTM-SR-01, KTM-SR-02, and KTM-SR-03 were administered to animals at dose level of ketorolac tromethamine 21.25 mg/kg bw.

Pharmacodynamic response obtained for KTM-SR-01, KTM-SR-02, and KTM-SR-03 (dose: 21.25 mg/kg bw) was compared to that of aqueous drug solution (KTM-IR, dose: 7.5 mg/kg bw), shown in Figs. 3, 4, and 5, respectively. The maximum response produced by KTM-IR is considered as peak analgesic response. A T-70% response is the time period for which the analgesic level is superior or equal to 70% of peak analgesia produced by aqueous drug solution. The dotted line in the figures is the cutoff for desired analgesic response, i.e., 70% response of peak analgesia. The performance of slow-release formulations can be assessed by parameters such as half-value duration (HVD, plasma level for classical HVD), plateau time, or T-70% peak response (C_{max} for classical T-70%).[15,20] These were used as markers for comparison of performance of various formulations. The ratio of T-70% response of test formulation and aqueous drug solution was calculated and is listed in Table 2. Formulations KTM-SR-02 and KTM-SR-03 were almost comparable in their performance and better than KTM-SR-01, based on these results further pharmacokinetic evaluation was carried out only on formulations KTM-SR-02 and KTM-SR-03. The percent of analgesic response vs. time profile for standard and test formulations were significantly different, $P<0.05$.

Pharmacokinetic Evaluation

A single dose of aqueous drug solution (KTM-IR, dose: 7.5 mg/kg) was administered intramuscularly to mice, C_{max} was attained in approximately 15 min (Fig. 6) and the concentration reduced significantly

Table 2. Comparison of the pharmacodynamic characteristics obtained from single dose administration of formulations.

Batch code	T 70% response of peak analgesia (hrs)	Ratio of T 70% response of peak analgesia of test formulation and T 70% response of peak analgesia of aqueous solution
KTM-IR	2	–
KTM-SR-01	8	4
KTM-SR-02	10	5
KTM-SR-03	11	5.5

between the second and fourth hour. Similar response was observed in the pharmacodynamic evaluation of KTM-IR (dose; 7.5 mg/kg bw) where the peak analgesic effect was seen at 15 min, which then reduced to less than 50% at the fourth hour (Fig. 3). The reported terminal half life of ketorolac in mice is 3.8 hrs.[7]

Hence, by correlating the pharmacodynamic response with the pharmacokinetic profile from these animal studies, C_{max}±25% was taken as the desired Css_{max} and Css_{min} drug blood concentrations, which were 51.39 μg/mL and 30.0 μg/mL respectively (shown as dotted lines in Figs. 6 and 7) to be maintained for effective analgesic response.

The drug blood concentration vs. time profile obtained for single dose test formulations, KTM-SR-02 and KTM-SR-03 (dose: 21.25 mg/kg bw) were compared with that of aqueous drug solution, KTM-IR (dose; 7.5 mg/kg bw). The pharmacokinetic profile of standard and test formulations were significantly different, $P<0.05$. The test formulation KTM-SR-02 (Fig. 6) produced C_{max} of approximately 65 μg/mL, which was higher than the desired Css_{max}. It was followed by a drug-blood concentration phase within the desired Css_{max} and Css_{min} levels for approximately nine hrs, beyond which the drug concentration falls below the Css_{min} desired. In comparison, KTM-SR-03 (Fig. 7) produced higher drug-blood levels, with maxima of approximately 100 μg/mL and maintained the drug-blood concentration levels within the desired Css_{max} and Css_{min} levels for a shorter time period. Overall KTM-SR-02 maintained drug-blood concentration above the desired Css_{min} for 11 hrs as compared to 8 hrs for KTM-SR-03. Hence, the test formulation KTM-SR-02 behaved in the most favorable manner, proving the sustaining property of the formulation.

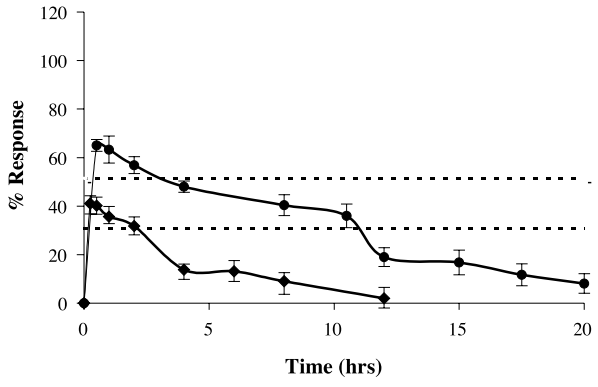

Figure 6. Drug blood concentration vs. time profile of KTM-IR (◆) and KTM-SR-02 (●) (mean±S.D.), n=4.

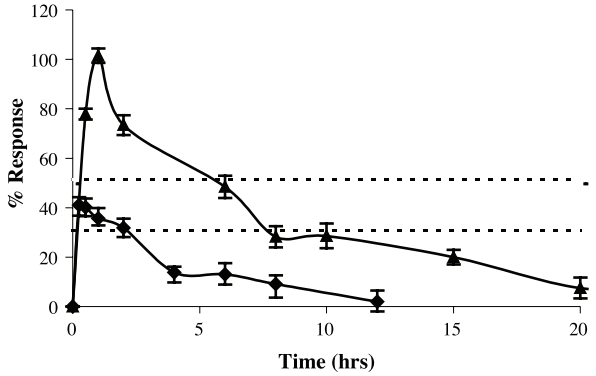

Figure 7. Drug-blood concentration vs. time profile of KTM-IR (◆) and KTM-SR-03 (▲) and (mean±S.D.), n=4.

CONCLUSION

One of the cardinal issues of parenteral preparations is that the excipients incorporated should be biocompatible and biodegradable. Formulations based on polyvinylpyrrolidone, glyceryl monooleate, and castor oil were evaluated. Preliminary screening of the excipients was done by in vitro drug-release studies. The drug release profiles and cumulative drug released were compared to predict the drug-release sustaining capacity of formulations. Glyceryl monooleate and castor oil had notable sustaining behavior in comparison to polyvinylpyrrollidone. Pharmacodynamic studies were performed for initial screening of the excipients in the in vivo environment. The analgesic response produced in the mouse writhing test was compared with the conventional formulation for the onset and duration of analgesic effect. The pharmacodynamic profiles for sustained-release formulation were generated. Ratio of T-70% response of test formulation and aqueous drug solution indicated that glyceryl monooleate and castor oil formulations were similar in their prolonged effect and superior compared to the polyvinylpyrrolidine-based formulation.

Pharmacodynamic/pharmacokinetic correlation was established in an animal model for the conventional dose of ketorolac tromethamine. Based on this correlation the desired blood levels, i.e., Css_{max} and Css_{min}, were derived for evaluation of sustained-release formulations. Pharmacokinetic profiles suggest KTM-SR-02 to be superior to KTM-SR-03, as it maintained the desired blood levels for a longer time period.

From the excipents evaluated, sustained-release response was maximum for glyceryl monooleate followed by castor oil and the least by polyvinylpyrrolidone. The water soluble excipients, though showed

release-retarding property in vitro but could not maintain it in the in vivo environment. Glyceryl monooloeate produced the most favorable release profile of drug-blood concentration vs. time. Glyceryl monooleate can form a depot system, which can control the release based on diffusional exchange of water from the surrounding medium into the matrix that follows square root of time-dependent drug-release kinetics.[13] However, it is essential that the cubic phase formed remains in equilibrium and the drug incorporated does not disrupt the formation of cubic lattice system in vivo. This could be a possible explanation for the fast release observed in the early period of formulation administration. Various works have been published on the incorporation of drugs such as lidocaine, clotrimazole, and vitamin E in these systems.[14] Hence the formulation of glyceryl monooleate can be developed for injectable intramuscular sustained-release drug delivery of ketorolac tromethamine.

REFERENCES

1. Dahl, J.B.; Kehlet, H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br. J. Pharmacol. **1991**, *66*, 703–712.
2. Dahl, J.B. Postoperative analgesia; review. Acta Anaesthesiol. Scand. **2000**, *44*, 1–13.
3. Gillis, J.C.; Brogden, R.N. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs **1997**, *53*, 139–188.
4. DeAndrade, J.R.; Maslanka, M.; Maneatis, T.; Bynum, L.; Burchmore, M. The use of ketorolac in the managment of postoperative pain. Orthopedics **1994**, *17*, 157–166.
5. Domer, F. Characterization of the analgesic activity of ketorolac in mice. Eur. J. Pharmacol. **1990**, *177*, 127–135.
6. United States Pharmacopeia 24/ National Formulary 19. United States Pharmacopeial Convention, Rockville, MD, 1999; 946.
7. Mroszczak, E.J.; Lee, F.W.; Combs, D.; Sarquist, F.H.; Huang, B.L. Ketorolac tromethamine absorption, distribution, metabolism, excretion, and pharmacokinetics in animal and humans. Drug Metab. Dispos. **1987**, *15*, 618–626.
8. Loftsson, T.; Fridriksdottir, H.; Gudmundsdottir, T.K. The effect of water-soluble polymers on aqueous solubility of drugs. Int. J. Pharm. **1996**, *127*, 293–296.
9. URL:http://www.basf.de/en/dispersionen/products/pvp (accessed June 2000).
10. Malhotra, M.; Majumdar, D.K. In vitro transcorneal permeation from oil based ocular drops and ophthalmic ointment. Indian J. Exp. Biol. **1997**, *35*, 1324–1330.
11. Chang; Hung-Chih; Li; Lukchiu; Tian; Youqin. Butorphanol sustained release formulations. Unites States Patent 6,197,344, March 6, 2001.
12. Engstrom, S.; Lindahl, L.; Wallin, R.; Engblom, J. A study of polar lipid drug carrier systems undergoing a thermoreversible lamellar-to-cubic phase transition. Int. J. Pharm. **1992**, *86*, 137–145.
13. Wyatt, D.M. A cubic-phase delivery system composed of glyceryl monooleate and water for sustained release of water-soluble drugs. Pharm. Technol. **1992**, *16*, 116–122.
14. Shah, J.C.; Sadhale, Y.; Chilukuri, D.M. Cubic phase gels as drug delivery systems. Adv. Drug Deliv. Rev. **2001**, *47*, 229–250.
15. Malonne, H.; Fontaine, J.; Moes, A. In vitro/in vivo characterisation of a Tramadol HCl depot system composed of monoolein and water. Biol. Pharm. Bull. **2000**, *23*, 627–631.
16. Vogel, H.G.; Vogel, W.H. Analgesia, antiinflammatory and antipyretic activity. In *Drug Discovery and Evaluation*; Springer, 1997; 360–420.
17. Benita, S.; Friedman, D.; Weinstock, M. Pharmacological evaluation of an injectable prolonged release emulsion of physostigmine in rabbits. J. Pharm. Pharmacol. **1986**, *38*, 653.
18. *Toradol® IV/IM Complete Product Information*; Roche U.S. Pharmaceuticals, 2002.
19. Ritschel, W.A. Biopharmaceutic and pharmacokinetic aspects in the design of controlled release peroral drug delivery systems. Drug Dev. Ind. Pharm. **1989**, *15*, 1073–1103.
20. Steinijans, V.W. Pharmacokinetic characterisation of controlled-release formulations. Eur. J. Drug Metab. Pharmacokinet. **1990**, *15*, 173–181.

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